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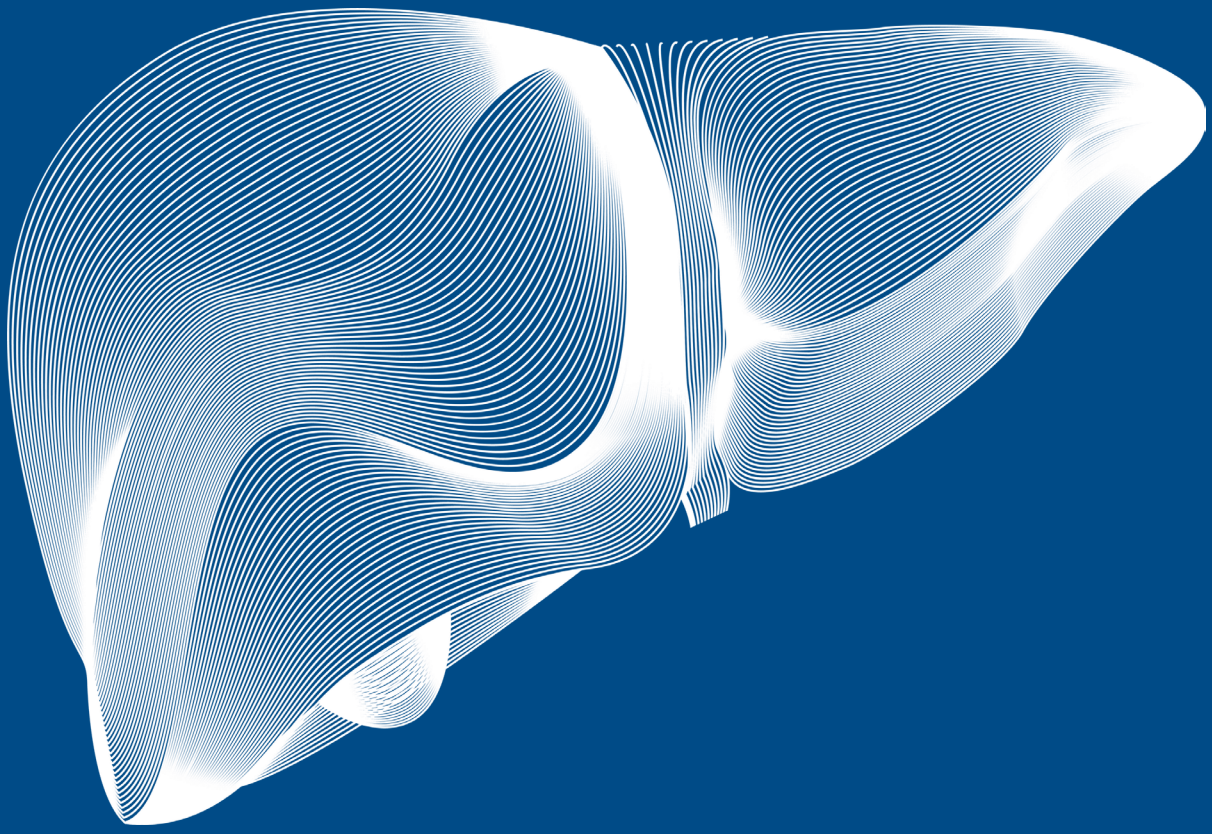
EASL CONGRESS

7-10 May 2025

Amsterdam, the Netherlands



ABSTRACT BOOK

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JOURNAL OF HEPATOLOGY

The Home of Liver Research

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7–10 May 2025, Amsterdam, the Netherlands

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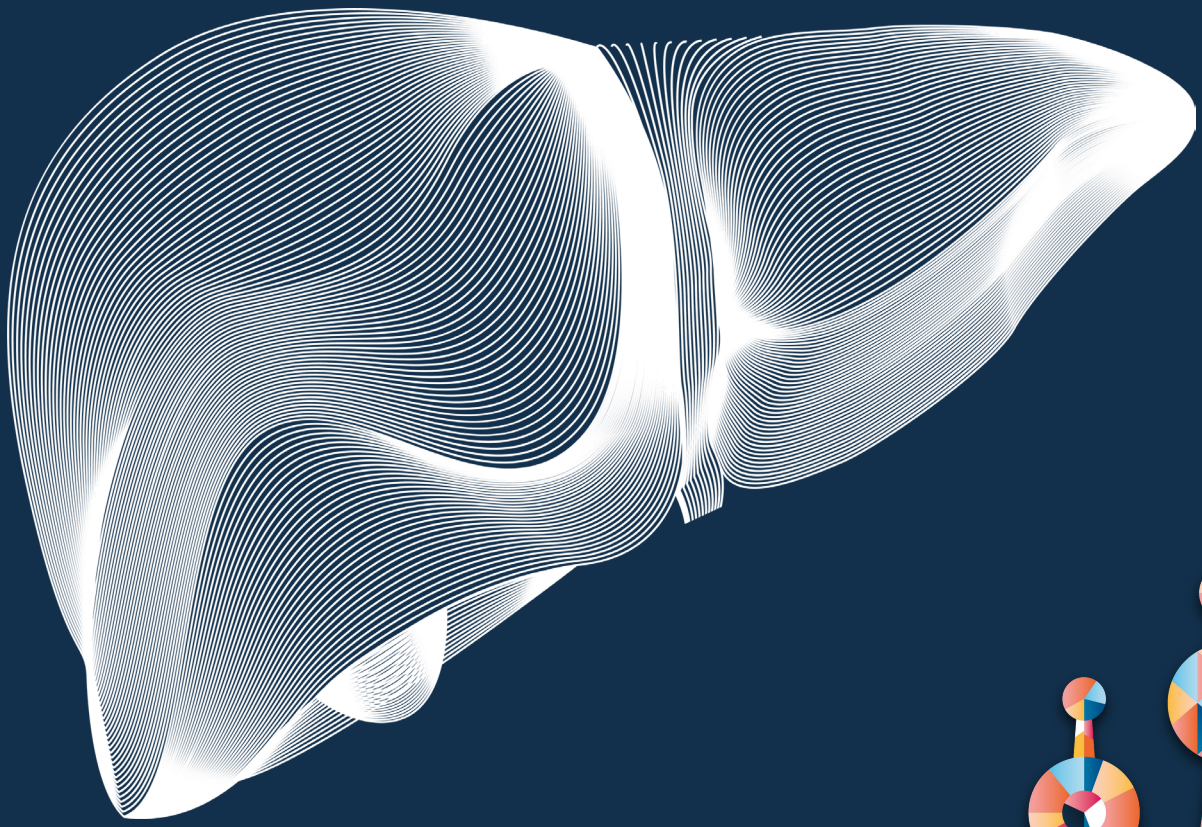
Barcelona Spain
27–30 May 2026



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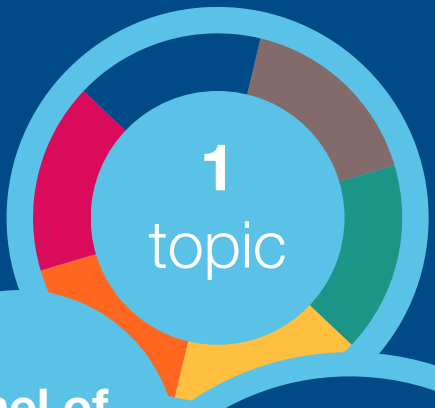
CONTENTS

Registration of Clinical Trials
The *Journal of Hepatology* endorses the policy of the WHO and the International Committee of Medical Journal Editors (ICMJE) on the registration of clinical trials. Therefore, any trial that starts recruiting on or after July 1, 2005 should be registered in a publicly owned, publicly accessible registry and should satisfy a minimal standard dataset. Trials that started recruiting before that date will be considered for publication if registered before September 13, 2005.
More detailed information regarding clinical trials and registration can be found in New Engl J Med 2004; 351:1250–1251 and New Engl J Med 2005; 352:2437–2438.

EASL DeepDive

Exploring Key Topics in Hepatology



Panel of 4 experts

Target audience: all healthcare professionals interested in liver diseases

EASL DeepDive is a free educational webinar series offering an in-depth exploration of specific topics in hepatology and liver research, ensuring that medical professionals stay updated on the latest developments and best practices in the field.

Goal

Deepen the knowledge of healthcare professionals on critical aspects of liver diseases.

Format

Live 60-min, interactive Q&A, free registration

Assessment

Quiz test pre and post webinar

Accreditation

1 EACCME® credit for live attendance

Access

On-demand content available on EASL Campus

Watch previous webinars

EASL CAMPUS

HEALTHY LIVERS HEALTHY LIVES

A global coalition for action across the clinical, public health and policy level

Our Vision

A world free of liver diseases

Our Mission

To mobilise action for liver diseases

Our Goal

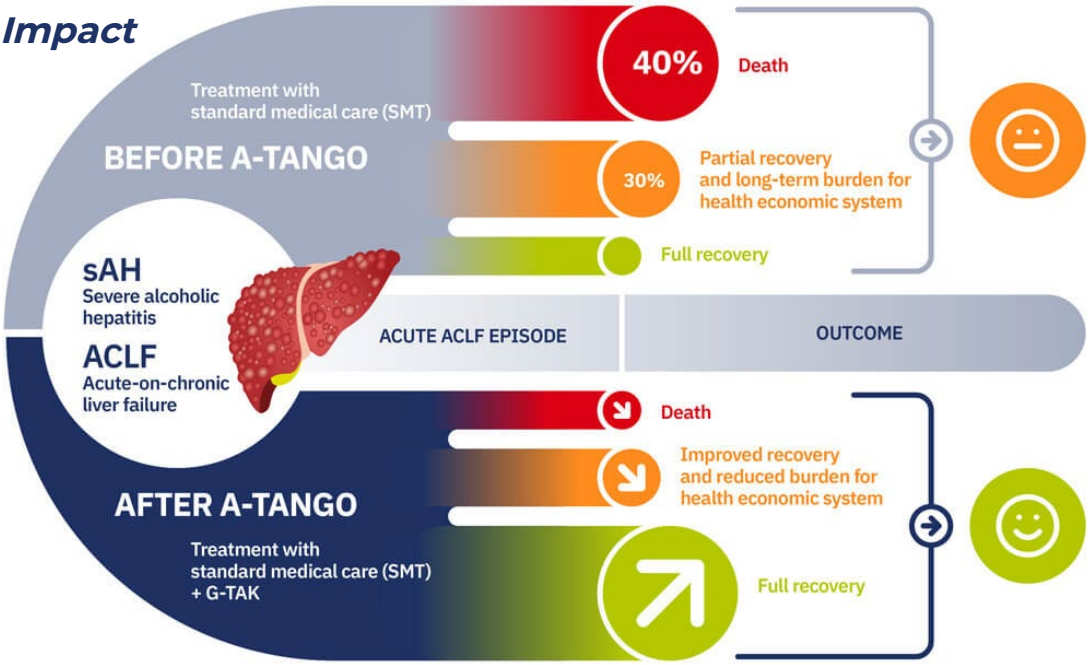
Reducing the prevalence of liver diseases worldwide

READ MORE

A-TANGO

Featuring G-TAK, a novel combinatorial therapy for acute-on-chronic liver failure (ACLF)

Expected Impact



- More than **10 million people** suffer from **decompensated cirrhosis** worldwide.
- Effective treatment of ACLF is an urgent and unmet need.
- A-TANGO performs **Phase II clinical studies of G-TAK,** a novel and innovative therapeutic strategy that aims to **reduce inflammation** and **improve hepatocyte proliferation.**
- A-TANGO also strives to identify **reliable biomarkers** for better patient stratification and increased survival.

13 partners, one goal: Helping cirrhosis patients in Europe and beyond

kick-off
1st March 2021

project duration
5.0 years

grant amount
6.0 million €

a-tango.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 945096.

DECISION

decision-for-liver.eu

DEcompensated CIrrhoSIs: identification of new cOmbiNatorial therapies based on systems approaches

Key facts

- **Project start**: 1st April 2020
- **Duration**: 5.5 years
- **Members**: 21 institutions from 10 European countries
- **EC funding**: € 6 million

AIM 1
Understanding at systems level

- Using **high-throughput technologies** to understand decompensated cirrhosis at systems level
- Re-analyzing standardized biobank samples from **2,200 patients** with decompensated cirrhosis by characterizing
  - **epigenetics »** manuscript in preparation
  - **transcriptomics »** presented at EASL 2025 and manuscript submitted
  - **metabolomics »** presented at EASL 2024 and manuscript submitted
  - **microRNA »** manuscript in preparation
  - **extracellular vesicles »** presented at EASL 2024

AIM 2
New combinatorial therapy

COMBAT-Trial: proof-of-concept, phase II randomized controlled clinical study

- **Goal**: Evaluate safety and tolerability of a novel combinatorial therapy (human albumin and enoxaparin) in patients with decompensated cirrhosis discharged from the hospital; comparison to standard medical treatment
- First patient enrolled in July 2024

PROSPECT study: prospective, multicenter observational cohort study on post-discharge outcomes in patients with cirrhosis and AD

- **Goal**: Test the prognostic accuracy of novel biomarkers identified within DECISION
- First patient enrolled in March 2025

AIM 3
Pre-clinical models

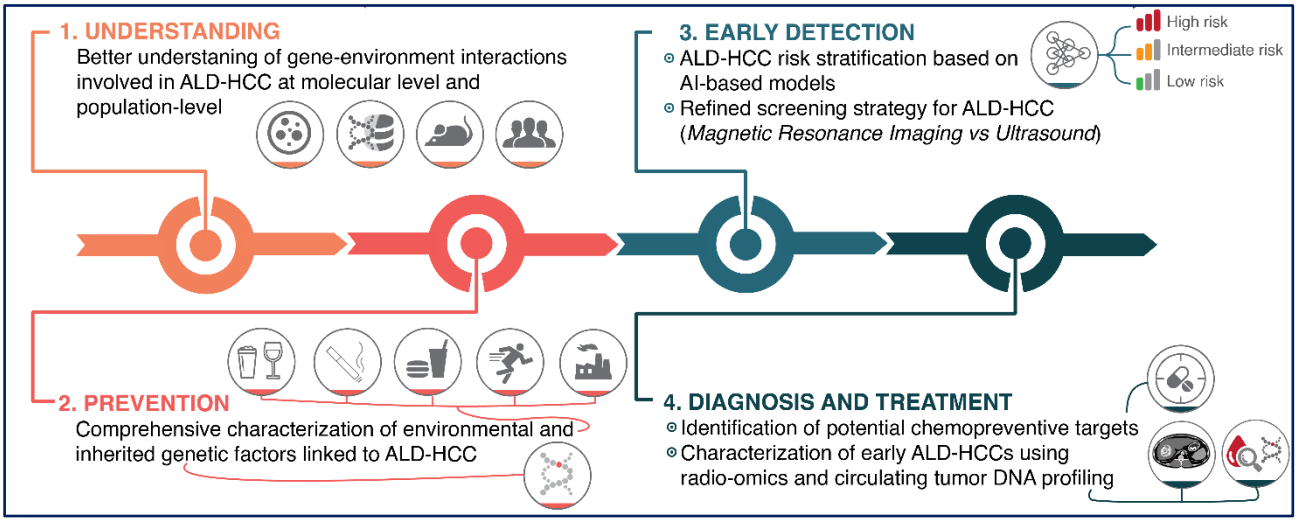
- Existing rat models for acute decompensation of cirrhosis leading to ACLF lack full replication of human disease heterogeneity
  » We therefore aim to refine existing animal models
- Publications:
  - Development & characterization of **novel rodent ACLF models**
    » manuscript in preparation
  - Acceleration of an advanced **NASH model** by acute and toxic effects of Phenobarbital
    » published: *Kraus N, Uschner FE et al. Cells (2024)*

AIM 4
Prognostic and response tests

- Novel and robust **stratification method** identifies three clusters of patients with acute decompensation of cirrhosis (AD)
  » published: *Palomino-Echeverria S et al. J Transl Med (2024)* and *Ortega-Lagerreta A, Palomino-Echeverria S et al. PLOS Comp Bio (2024)*
- Potential tool for healthcare providers to enhance patient monitoring or preventative measures using existing electronic health record data and method could guide future clinical trial design
- Further results will be published soon

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 847949.

GENIAL is a pioneering initiative targeting **alcohol-related liver cancer** (**ALD-HCC**). Our primary goal is to identify **genetic** and **environmental** factors contributing to ALD-HCC risk and unravel how their **interactions** drive alcohol-related liver carcinogenesis. By pinpointing individuals at risk, GENIAL will pave the way for innovative **prevention strategies** and potential **chemopreventive targets** to tackle this devastating disease. Moreover, GENIAL is dedicated to **educating** and empowering the entire EU community with vital knowledge for effective disease prevention and **early detection**.



The GENIAL Project is funded by the European Union within the Horizon Europe programme under grant agreement No 101096312.

innovative health initiative · efpia · EuropaBio · MedTech Europe from diagnosis to cure · Vaccines Europe · COCIR Advancing Healthcare

AIM LIVER

A biomarker-based platform for early diagnosis of chronic liver disease to enable personalized therapy

Academia and industry are collaborating on one of the largest project's ever in the field of liver diseases

AIM

To design and validate an AI-powered screening platform using biomarkers for the early diagnosis of liver diseases in the general population, and to establish connections to care through personalized interventions

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Co-funded by the European Union

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101132901. The JU receives support from the European Union's Horizon Europe research and innovation programme and EFPIA, COCIR, MedTech Europe, Vaccines Europe and EuropaBio. Funded by the European Union, the private members, and those contributing partners of the IHI JU. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the aforementioned parties. Neither of the aforementioned parties can be held responsible for them

LIVER SCREEN

Funded by the European Union

Screening for liver fibrosis population-based study across European Countries

A project that will change the paradigm of diagnosis of chronic liver diseases

AIM:

To assess the prevalence of liver fibrosis in the general population using Transient Elastography, with the objective of establishing criteria for screening for liver fibrosis in the population.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847989

MICROBiome-based biomarkers to PREDICT decompensation of liver cirrhosis and treatment response

MICROB-PREDICT

Project duration
6 1/4 years

Start
01 January 2019

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Grant amount
15 million €

10 Countries
22 Partners

www.microb-predict.eu

MICROB-PREDICT investigates

the human microbiome to identify predictors and mechanisms associated with the development of decompensation of cirrhosis and progression to acute-on-chronic liver failure (ACLF).

- → New microbiome-based tests for better stratification of cirrhosis patients
- → Personalized prediction and prevention of decompensation and ACLF
- → Clinical trial to predict response to treatment
- → Modern, effective nanobiosensors as clinical tools with improved specificity
- → More personalized treatment
- → Increased survival times
- → Decreased costs for the health systems

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

THRIVE

TUMOUR-HOST INTERACTIONS IN LIVER CANCER
OF CHILDHOOD AND ADULTS

THRIVE is a pioneering EU initiative that aims to **enhance** the **outcome of paediatric & adult liver cancer patients** by:

advancing the **understanding** of HCC	identifying **biomarkers** for current therapies	**developing novel treatments** to overcome resistance

THRIVE Consortium

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Helen Reeves - UNEW, UK
Quentin Anstee - NUTH, UK
Jessica Zucman-Rossi - UPCITE, France
Manel Esteller - IJC-CERCA, Spain
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EASL JOURNAL OF HEPATOLOGY

THURSDAY 08 MAY

GENERAL SESSION I

GS-001

Diagnostic performance of imaging and serum based MASLD biomarkers: robust validation in the prospective LITMUS imaging study

Michael Pavlides[1,2], Yasaman Vali[3], Ferenc Mozes[4], Kristy Wonders[5], Salma Akthar[4], Guruprasad Aithal[6], Rocío Aller[7], Michael Allison[8], Johanna Arola[9], Rajarshi Banerjee[10], Annalisa Berzigotti[11], Jerome Boursier[12], Clifford Brass[13], Elisabetta Bugianesi[14], Jeremy Cobbold[15], Harvey O. Coxson[16], Susan Davies[8], Ann Driessen[17], Kevin Duffin[18], Richard L. Ehman[19], Mattias Ekstedt[20], Céline Fournier-Poizat[21], Annette Gouw[22], Paul Hockings[23], Prodromos Hytiroglou[24], Michael J. Kalutkiewicz[25], Morten Karsdal[26], Carolin Lackner[27], Diana Julie Leeming[26], Jeremy Magnanensi[28], Miljen Martic[29], Stefan Neubauer[4], Valérie Paradis[30], Kay Pepin[25], Juan Manuel Pericàs[31], Salvatore Petta[32], Vlad Ratziu[33], Manuel Romero-Gómez[34], Jörn M. Schattenberg[35], Moritz Schneider[23], Detlef Schuppan[36], Elizabeth Shumbayawonda[10], Beate Straub[36], Joanne Verheij[37], Mette Kjaer[38], Dina Tiniakos[39], Maria Manuela Tonini[40], Richard Torstenson[41], Hannele Yki-Järvinen[42], Theresa Tuthill[43], Carla Yunis[44], David Wenn[45], Patrick Bossuyt[3], Quentin Anstee[46]. *[1]Translational Gastroenterology and Liver Unit, University of Oxford, Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, United Kingdom; [2]Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, United Kingdom; [3]Amsterdam University Medical Centre, Amsterdam, Netherlands; [4]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom; [5]Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom; [6]NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, United Kingdom; [7]Department of Medicine, Dermatology and Toxicology, Universidad de Valladolid, Spain; Gastroenterology Unit, Hospital Clínico Universitario de Valladolid, 47003, Valladolid, Spain; [8]Cambridge Liver Unit, Cambridge NIHR Biomedical Research Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [9]University of Helsinki, Helsinki University Hospital, and Minerva Foundation Institute for Medical Research, Helsinki, Finland; [10]Perspectum, Oxford, United Kingdom; [11]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [12]Service d'Hépato-Gastroentérologie, Centre Hospitalier Universitaire d'Angers, Angers, France; & Laboratoire HIFIH UPRES EA3859, Université d'Angers, Angers, France; [13]Resolution Therapeutics, 9 Westway, East Hampton, New York, United States; [14]Department of Medical Sciences, Division of Gastro-Hepatology, City of Health and Science of Turin, University of Turin, Turin, Italy; [15]Translational Gastroenterology and Liver Unit, University of Oxford, Oxford, United Kingdom; [16]Boehringer Ingelheim Pharma GmbH & Co. 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Background and aims: There is an urgent need for reliable non-invasive biomarkers to accurately grade and stage metabolic dysfunction associated steatotic liver disease (MASLD). Several imaging and serum-based biomarkers have been described but direct, independent assessments are lacking. The prospective LITMUS Imaging Study aimed to evaluate the diagnostic accuracy of biomarkers in a large multicentre cohort.
Method: Participants with MASLD were prospectively recruited from centres across Europe and the USA into the LITMUS Imaging Study cohort. Clinical data, blood samples, liver stiffness measurements (LSM) by VCTE and MRE, steatosis measurement (CAP and MRI-

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PDFF), cT1, and other MRI biomarkers were acquired within six months of biopsy and processed at centralised facilities by technicians blinded to all clinical data. Individual imaging biomarkers, composite imaging scores (FAST, Agile3+/4, MAST, cTAG, MEFIB), and blood-based biomarkers (FIB4, CK18-M30, CK18-M65, PROC3, ADAPT, ELF™, NIS2+®) were then assessed against paired histologic data. Histological slides were centrally scored by expert pathologists using the NASH-CRN system. Target conditions were "at-risk MASH" (MAS≥4 with at least 1 in each component + ≥F2), advanced fibrosis (≥F3), and cirrhosis (F4). Performance was assessed as the area under the receiver operating characteristic curve (AUC) with an AUC>0.80 and p-value ≤0.05 as the minimally acceptable performance criterion (MAC) for biomarkers to replace liver histology.

Results: A total of 357 participants were included (mean age 55, male 55%, mean BMI 33.8 kg/m^2, T2DM 50%). Fibrosis stages were F0-4: 12%, 16%, 25%, 32%, 15% respectively. For at-risk MASH, NIS2+® had the highest diagnostic accuracy (AUC 0.82) but did not achieve statistical significance above MAC. Other biomarkers performed as follows: CAP (AUC 0.64), LMS-cT1 (0.66), PDFF (0.66), FAST (0.73), MAST (0.76). For advanced fibrosis, MAC was significantly exceeded by MRE (AUC 0.91) and AGILE3+ (AUC 0.84); and for cirrhosis by MRE (AUC 0.91), VCTE (AUC 0.87), AGILE 3+ (AUC 0.89), and AGILE4 (AUC 0.88). For advanced fibrosis/cirrhosis respectively the performance of other biomarkers was: FIB4 (AUC 0.74/0.78), VCTE (0.81), PROC3 (0.60/0.69), ADAPT (0.76/0.80), ELF (0.74/0.78), MEFIB (0.72/0.76).

Conclusion: This comprehensive study identifies suitable markers for fibrosis assessment while highlighting the challenges for diagnosing "at-risk MASH." For fibrosis endpoints, elastography-based imaging markers achieved MAC for advanced fibrosis (MRE, Agile 3+) and cirrhosis (MRE, VCTE, Agile3+, Agile4). For detecting at-risk MASH, no marker exceeded MAC in this cohort. Serum biomarkers like NIS2+ outperformed imaging; CAP, PDFF and LMS-cT1 all performed similarly, with FAST and MAST performing marginally better. Further studies on prognostic performance are ongoing.

GS-002

Safety and efficacy of inebilizumab in IgG4 related disease in participants with pancreatic, biliary, and hepatic involvement: results from the phase 3 MITIGATE trial

Emma Culver[1], John Stone[2], Arezou Khosroshahi[3], Wen Zhang[4], Nicolas Schleinitz[5], Kazuichi Okazaki[6], Yoshiya Tanaka[7], Matthias Lohr[8], Qian Huang[9], Xinxin Dong[9], Melissa Rosen[9], Sue Cheng[9], Daniel Cimbora[9]. *[1]Translational Gastroenterology and Liver Unit, John Radcliffe Hospital, and Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; [2]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, United States; [3]Division of Rheumatology, Emory University School of Medicine, Atlanta, United States; [4]Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Science, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, China; [5]Departement de Medecine Interne Hôpital de la Timone, AP-HM, Aix-Marseille Université, Marseille, France; [6]Department of Internal Medicine, Kansai Medical University Kori Hospital, Osaka, Japan; [7]The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; [8]Department of Clinical Science, Intervention, and Technology, Karolinska Institutet, Stockholm, Sweden; [9]Amgen Inc., Thousand Oaks, United States*
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Background and aims: Pancreatic and hepatobiliary disease are frequent manifestations of IgG4 Related Disease (IgG4-RD), an immune-mediated, relapsing, fibroinflammatory disease that results in tissue damage and loss of organ function. Inebilizumab (INEB) is an anti-CD19 antibody that results in rapid and durable B cell depletion. MITIGATE (NCT04540497) is an international, randomised, blinded, placebo (PBO)-controlled Phase 3 trial evaluating the safety and efficacy of INEB as treatment for IgG4-RD.

Method: A post hoc subgroup analysis of MITIGATE trial results was conducted to evaluate safety and efficacy outcomes in participants who had baseline disease activity in the pancreas, bile ducts, or liver. Eligible participants had a history of at least 2 organs involved and had experienced an IgG4-RD flare that required glucocorticoid treatment during the screening period. Participants were randomised 1:1 to INEB or PBO and were treated on day 1, day 15, and week 26 of the 1-year randomised controlled period (RCP). Steroids were tapered to discontinuation at the end of RCP week 8. Other immunosuppressive therapy for IgG4-RD was prohibited during the study.

Results: Among 135 enrolled participants, 52% had historic involvement of the pancreas, 32% of the bile ducts, and 7% liver. At study baseline, disease activity was seen in the pancreas, bile ducts, and liver in 51 (38%), 28 (21%), and 5 (4%) participants, respectively. INEB reduced the risk of flare (primary endpoint of the study) relative to PBO in the pancreas group (HR = 0.03, nominal p = 0.005). In the bile duct group, 0/13 INEB-treated and 12/15 PBO-treated participants experienced a flare. In the liver group, 0/2 INEB-treated and 3/3 PBO-treated participants experienced a flare. Annualised flare rates were reduced by INEB relative to PBO in all groups (rate ratio of 0.04 in the pancreas group, nominal p = .0015; no flares in the INEB-treated bile duct or liver groups). The proportion of participants achieving flare-free, treatment-free complete remission were higher with INEB vs. PBO (odds ratios 10.8 and 35.8 for the pancreas and bile duct groups, respectively). Steroid use was substantially reduced with INEB vs. PBO in the pancreas and bile duct groups (nominal p < .001). Adverse event (AE) incidences in the pancreas, bile duct, and liver groups were similar to the overall study population. The most frequent (>10%) AEs in any group of the INEB arm were lymphopenia, COVID-19, pyrexia, back pain, upper respiratory tract infection, and urinary tract infection. Serious AEs included hyponatraemia and fibroadenomatoid mastopathy (benign), each occurring in one participant. Sclerosing cholangitis was observed in one PBO-treated participant. No deaths occurred during the study.

Conclusion: Analysis of IgG4-RD patients with pancreas and hepatobiliary involvement from the MITIGATE trial demonstrates the benefit and safety of CD19-targeted B cell depletion by INEB in this cohort.

GS-003

Circulating CD8 T cells are sentinels for intrahepatic T cell responses during HBV infection

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Background and aims: Chronic hepatitis B (CHB) is characterized by scarcity and dysfunction of virus-specific CD8 T-cells in the liver and circulation. As such, immune therapies such as therapeutic vaccination (TherVacB) aim to generate virus-specific T-cells to control infection. This study sought to identify whether circulating HBV-specific CD8 T-cells reflect the intrahepatic T-cell response, thereby offering an insight into the T cell response in the liver, and to identify

biomarkers on circulating HBV-specific CD8 T cells that predict immune control in patients.
Method: Using pre-clinical models of HBV as well as patient samples during acute-resolving infection, chronic infection or functional cure following nucleos(t)ide analogue (NA) withdrawal, we studied the dynamics of virus-specific T-cell response by flow cytometry and paired single-cell RNA and single-cell TCR sequencing.
Results: Using single-cell transcriptomic and protein-level analysis of CD8 T-cells in the liver of preclinical models, we defined signatures that discriminate between lymphoid-tissue derived HBV-specific CD8 T cells compared to those HBV-specific CD8 T cells, which had seen their antigen in the liver. Intrahepatic HBV-specific CD8 T cells were characterized by expression of CXCR6 and, during acute-resolving infection, were potent effector cells, whereas CD8 T cells during persistent infection were dysfunctional. Strikingly, scRNAseq analysis revealed close similarity between circulating and intrahepatic HBV-specific CD8 T cells. Of note, the ability to predict T cell immunity in infected organs was restricted to hepatotropic infections, as circulating virus-specific CD8 T cells did not reflect the T cells response in the lung following influenza A virus infection. Paired scRNAseq and scTCRseq of HBV-specific CD8 T cells in acute, acute-resolved and chronic infection, and in patients achieving functional cure following NA discontinuation identified immune signatures on T cells with an activated, liver-signature which predicted immune control.
Conclusion: Our results identify distinct markers on HBV-specific CD8 T cells that are equally present on circulating and intrahepatic CD8 T cells and predict immune control of infection. The proprietary biomarker set allows the study of intrahepatic HBV-specific CD8 T cells by targeted analysis of circulating HBV-specific CD8 T cells and enables monitoring of immune therapies in CHB patients using peripheral blood, rather than liver biopsies.

GS-004

Development of portal hypertension after non-cirrhotic non-tumoral recent portal vein thrombosis (RPVT). A long-term follow-up study

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Background and aims: RPVT may lead to portal hypertension (PH). The study aims to evaluate the incidence and risk factors for PH development (portosystemic collaterals (PSCS), gastroesophageal varices (GEV), PH-related bleeding, ascites, or hepatic encephalopathy (HE)) after RPVT.
Method: Multicentric retrospective study of patients with RPVT between 2000 and 2020 that had a diagnostic imaging to quantify thrombosis extension and another imaging at least one year later to evaluate recanalization. Portal vein trunk, superior mesenteric and splenic veins were considered as main veins for thrombosis classification. Complete recanalization (CR) was defined as a fully patent portal venous system, and partial (PR) when thrombosis decreased > 50% of all affected veins or at least the PV.
Results: 485 patients were included, 214 (44.1%) females; mean age: 50 (16–88). RPVT was an asymptomatic finding in 38 (8%) and symptomatic in 447 (92%: n = 427 with abdominal pain). 123 patients presented with ascites (25%). 179 patients (37%) had a hereditary/acquired prothrombotic factor (74 myeloproliferative neoplasm (MPN)), 156 (32%) a local factor and 150 (31%) were considered idiopathic. 472 (97%) patients received anticoagulant treatment. CT-Scan was the diagnostic test in 466 patients and angio-MRI in 19. Thrombosis only affected intrahepatic portal vein branches (IPVB) in 130; one main vein in 77 (PV in 52); two in 120 (PV in 118); and three in 158. Median follow-up was 67 months (42–106). 262 patients (54%) achieved recanalization (CR in 148; 30.5%). The cumulative incidence (CI) of PR+CR or of CR at 1, 2, 3, 4, and 5 years was 36, 44, 47, 50, and 54% or 22, 26, 28, 31, and 34%, respectively. 219 patients (45%) developed signs of PH (more than 1 in 140): 188 PSCS at imaging, 153 GEV, 24 PH-related bleeding, 32 ascites, and 7 HE. CI of PH was 34, 41, 44, 46, and 48% at 1, 2, 3, 4, and 5 years. PH development probability

decreased after 36 months of RPVT. To maximally reduce the risk of misclassifying patients not developing PH, in the analysis of risk factors we only included those patients having a follow-up of at least 36 months. Thus, 426 patients were included (median follow-up: 76 months (50–114)); 219 of those (51%) developed PH. Ascites at diagnosis, MPN etiology, number of thrombosed veins, and degree of recanalization were associated with PH development. One, 2, 3, 4, and 5 years CI of PH in patients without recanalization; with PR or with CR was 50, 58, 63, 64, and 67%; 31, 43, 44, 46, and 48% and 8, 12, 13, 16, and 17%, respectively. Interestingly, 58 patients despite not having recanalization after a median follow-up of 80 months had not developed PH. In 35 of those, only IPVB were affected. By contrast, 20 patients achieving CR developed PH of whom only 3 can be explained by later splanchnic rethrombosis.
Conclusion: CI of PH after RPVT was 48% at 5 years. Ascites at diagnosis, associated MPN, a major number of affected veins and the degree of recanalization were independent risk factors for PH development.

GS-005

Outcomes by liver function in patients with unresectable hepatocellular carcinoma treated with nivolumab plus ipilimumab vs lenvatinib or sorafenib in the CheckMate 9DW trial

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Background and aims: In an interim analysis of the phase 3 CheckMate 9DW study (median follow-up, 35.2 months [mo]) in patients (pts) with unresectable hepatocellular carcinoma (uHCC), first-line (1L) nivolumab plus ipilimumab (NIVO + IPI) demonstrated statistically significant overall survival (OS) benefit vs lenvatinib or sorafenib (LEN/SOR; median OS [mOS] [95% CI]: 23.7 [18.8–29.4] mo vs 20.6 [17.5–22.5] mo; HR 0.79; 95% CI 0.65–0.96; p = 0.018). NIVO + IPI had a higher objective response rate vs LEN/SOR (ORR: 36% vs 13%; p < 0.0001) per blinded independent central review (BICR), durable responses (median duration of response [mDOR] per BICR: 30.4 mo vs 12.9 mo), and manageable safety. Since impaired liver function is a common characteristic of pts with uHCC, we evaluated outcomes by liver function in CheckMate 9DW.
Method: Adult pts with previously untreated HCC not eligible for curative surgical or locoregional therapies, Child-Pugh score 5–6, and ECOG performance status 0–1 were randomized 1:1 to receive NIVO 1 mg/kg + IPI 3 mg/kg Q3W (≤4 cycles; then NIVO 480 mg Q4W) or investigator's choice of LEN 8 mg or 12 mg QD or SOR 400 mg BID until disease progression or unacceptable toxicity. NIVO was given for a maximum of 2 years. The primary endpoint was OS; secondary endpoints included ORR and DOR per BICR using RECIST v1.1. Baseline liver function was evaluated using albumin-bilirubin (ALBI) score (0.66 × log10[bilirubin (µmol/L)] −0.085 × [albumin (g/L)]); ALBI subgroups were classified by score: grade 1, ≤−2.60; grade 2, >−2.60 to ≤−1.39; and grade 3, >−1.39.
Results: Of 668 randomized pts, 396 were classified as ALBI grade 1, 271 as grade 2, and 1 as grade 3 (grades 2 and 3 combined for analysis). Baseline disease characteristics were similar across treatment arms in both the grade 1 and grade 2/3 ALBI subgroups. In pts with ALBI grade 1, mOS (95% CI) was 35.4 (23.9–not estimable [NE]) mo with NIVO + IPI vs 23.2 (21.4–28.3) mo with LEN/SOR (HR 0.75; 95% CI 0.57–0.98); 24-mo OS rates (95% CI) were 58% (50–64) vs 47% (39–54), respectively. ORR (95% CI) was higher with NIVO + IPI vs LEN/SOR (37% [30–45] vs 14% [10–20]) with higher complete response (CR) rates (8% vs 3%) and durable responses (mDOR [95% CI]: 30.4 [20.0–NE] mo vs 12.9 [8.4–NE] mo). In pts with ALBI grade 2/3, mOS (95% CI) was 16.9 (12.6–23.0) mo with NIVO + IPI vs 14.0 (11.1–16.6) mo with LEN/SOR (HR 0.75; 95% CI 0.57–0.99); 24-mo OS rates (95% CI) were 39% (31–47) vs 27% (19–35), respectively. ORR (95% CI) was higher with NIVO + IPI vs LEN/SOR (35% [27–43] vs 11% [6–18]) with higher CR rates (6% vs 0%) and durable responses (mDOR [95% CI]: 26.8 [16.8–NE] mo vs 11.1 [5.2–NE] mo). Safety was generally consistent with the overall population across ALBI subgroups.
Conclusion: NIVO + IPI showed a favorable benefit-risk profile vs LEN/SOR across ALBI subgroups. These results support NIVO + IPI as a potential 1L treatment option for pts with uHCC, regardless of liver function.

GS-011

Linerixibat significantly improves cholestatic pruritus in primary biliary cholangitis: results of the pivotal phase 3 GLISTEN trial

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Background and aims: Cholestatic pruritus is common, debilitating and undertreated in patients with primary biliary cholangitis (PBC). Here, we describe the results of GLISTEN (NCT04950127), a Phase 3 study investigating the efficacy and safety of the ileal bile acid transporter inhibitor linerixibat for pruritus in PBC.

Method: In this double-blind, randomised, placebo-controlled study, patients with PBC and moderate-to-severe pruritus received oral linerixibat 40 mg or placebo twice daily. Pruritus severity and pruritus-related sleep interference were assessed using a 0–10 numerical rating scale. The primary endpoint was change from baseline in worst itch over 24 weeks. Secondary endpoints included: at Week 2, change in worst itch; over 24 weeks, change in sleep interference; at Week 24, proportion of responders (≥ 2-, ≥ 3-, ≥ 4-point reduction in worst itch) and analysis of responses to 2 patient global impression items (itch severity and change). Safety endpoints included adverse event (AE) reporting.
Results: 238 patients were randomised; 95% were female, itch severity was mean (standard deviation [SD]) 7.34 (1.54), 52% had alkaline phosphatase < 1.67 times upper limit of normal, and 47% were receiving stable therapy for pruritus. Pruritus improvement over 24 weeks was significantly greater with linerixibat than placebo: least-squares (LS) mean change -2.86 versus -2.15, adjusted mean difference -0.72; p = 0.001. At Week 24, the observed mean (SD) difference from baseline in pruritus was -3.66 (2.50) with linerixibat and -2.82 (2.32) with placebo. The effect of linerixibat was rapid and superior to placebo at Week 2: LS mean change -1.78 versus -1.07, adjusted mean difference -0.71; p < 0.001. Linerixibat also significantly improved pruritus-related sleep interference over 24 weeks versus placebo: LS mean change 2.77 versus -2.24, adjusted mean difference -0.53; p = 0.024. At Week 24, more patients on linerixibat than placebo achieved a ≥ 2-point (68% vs 64%), ≥ 3-point (56% vs 43%) or ≥ 4-point (41% vs 29%) reduction in pruritus and a higher proportion of linerixibat than placebo-treated patients reported their pruritus was very much improved (55% vs 37%) or absent (21% vs 9%). AEs reported more frequently with linerixibat than placebo were predominantly gastrointestinal (GI), including diarrhoea (61% vs 18% of patients) and abdominal pain (18% vs 3% of patients); 4% of patients in the linerixibat group discontinued treatment due to diarrhoea.
Conclusion: In patients with PBC and moderate-to-severe pruritus, linerixibat rapidly and significantly improved pruritus and pruritus-related sleep interference versus placebo. While GI AEs were more common with linerixibat than placebo, they rarely led to treatment discontinuation.
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FRIDAY 09 MAY

GENERAL SESSION II

GS-006
A multicentre randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

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Background and aims: The evidence for the efficacy of non-selective beta-blockers (NSBB) compared with variceal band ligation (VBL) in the primary prevention of variceal bleeding is uncertain. Carvedilol may be more effective than VBL in primary prevention, but data are lacking. The CALIBRE trial aimed to compare carvedilol versus VBL for this indication.
Method: CALIBRE was an investigator-initiated, multicentre, pragmatic, randomised controlled, open-label trial conducted in 60 hospitals in the UK. Investigators randomly assigned participants using a web-based system in a 1:1 ratio to either treatment with 12.5 mg carvedilol once daily or VBL. Inclusion criteria were cirrhosis and medium to large oesophageal varices that had not bled. Patients on NSBB or who had previous VBL were excluded. The primary outcome is any variceal bleeding within one year of randomisation. Secondary outcomes include time to first variceal bleed, mortality within one year of randomisation, transplant-free survival, other complications of cirrhosis (new onset ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, hepatic encephalopathy), quality of life, cost-effectiveness and adverse events. Analyses were performed using the intention-to-treat principle, and the main analyses included all randomised participants. A qualitative sub-study was conducted to understand the acceptability of the trial and trial interventions in relation to recruitment and patient and clinician treatment preference. Recruitment closed early, mainly due to the impact of the pandemic. The trial is registered on the International Trials Registry (ISRCTN73887615).
Results: 265 participants from 52 sites were randomised to carvedilol (n = 133) or VBL (n = 132) between 22 January 2019 and 31 August 2022. 5/133 participants (3.8%) in the carvedilol arm vs 10/132 participants (7.6%) in the VBL arm experienced variceal bleeding (risk ratio 0.50 (95% CI; 0.17–1.41, p = 0.189); risk difference –0.038 (95% CI; –0.094–0.017), p = 0.178). Serious adverse events related to treatments were noted in one participant in each treatment arm, and there were no treatment-related deaths. Of the secondary outcomes, there were no statistically significant differences. Carvedilol was cheaper and resulted in slightly more quality-adjusted life years than VBL. Qualitative research on selected participants demonstrated no clear preference for NSBB or VBL in advance of treatment. Clinicians preferred to use carvedilol as first-line treatment.
Conclusion: Although underpowered, CALIBRE showed no evidence of a difference between carvedilol 12.5 mg daily and VBL in the primary prevention of variceal bleeding in patients with cirrhosis and medium to large-sized oesophageal varices. No untoward safety concerns were noted.

GS-007-YI
Novel "3-in-1" blood metabolomic test for the early diagnosis and risk stratification of primary sclerosing cholangitis and cholangiocarcinoma

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease that confers high risk of developing cholangiocarcinoma (CCA). Up to 20% of patients with PSC develop CCA during their lifetime, which constitutes the primary cause of premature death in this population. Current diagnostic modalities for the early detection of PSC and CCA are suboptimal and new predictive and diagnostic non-invasive approaches are urgently needed. Here, we aimed to investigate serum metabolite biomarkers for PSC and PSC-CCA.
Method: This multicentre international study included a total of 434 serum samples from 13 centres in eight countries worldwide. The cohort comprised patients with PSC (n = 216); PSC without clinical evidences of malignancy at sampling who developed CCA during follow-up (between 2 months and 8 years before diagnosis; PSC-to-CCA; n = 28); PSC with concomitant CCA (PSC-CCA; n = 97); ulcerative colitis (UC; n = 14); and healthy individuals (n = 79), divided in discovery (60%) and validation cohorts (40%). Serum metabolomics was evaluated by ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS) and the accuracy of the single candidate metabolite biomarkers was further assessed. Machine learning was used to generate the best diagnostic and predictive algorithms.
Results: Fifty metabolites associated with PSC diagnosis independent of age, biological sex and the presence of liver cirrhosis or UC. A model combining 13 metabolites differentiated patients with PSC from healthy controls with 98% accuracy both in the discovery and validation cohorts, respectively. Furthermore, 57 metabolites were altered in patients with PSC-CCA compared with PSC, independent of age, biological sex, presence of cirrhosis and anatomical CCA subtype. A model combining 13 of these metabolites accurately confirmed the presence of CCA in patients with PSC in the discovery and validation cohorts, with area under the curve (AUC) values of 0.91 and 0.90, respectively, particularly identifying patients with early tumor stages (0-II; AUC = 0.930), being superior to CA19.9 (AUC = 0.646). Noteworthy, the diagnostic capacity of this model was retained (AUC = 0.92) when considering only patients with low serum CA19-9 levels (i.e. false-negative test result). Finally, a model including seven metabolites allowed the prediction of CCA development in patients with PSC before any clinical evidence of cancer, with a positive predictive value (PPV) of 83% and 73% in the discovery and validation cohorts, respectively.
Conclusion: The "3-in-1" metabolomic test is a useful non-invasive tool that allow the diagnosis of PSC and early PSC-CCA, as well as to predict CCA development. Implementation in clinical practice may improve risk stratification and follow-up in patients with PSC, facilitating personalized surveillance, early diagnosis and prioritize therapeutic decisions.

GS-008-YI
Elexacaftor-Tezacaftor-Ivacaftor Era and cystic fibrosis liver disease progression: a 10-year national study

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Background and aims: The impact of Elexacaftor-Tezacaftor-Ivacaftor (ETI) on cystic fibrosis liver disease (CFLD) progression to liver-related complications is unknown. Consequently, current guidelines neither recommend for nor against ETI use in people with cystic fibrosis (pwCF) with CFLD (1). This study aimed to compare the burden of CFLD progression in the pre-ETI and post-ETI eras at a national level.
Method: Using the French National Discharge Database (2014–2023), we conducted a retrospective longitudinal cohort study of pwCF aged 12 years or older. The primary exposure was defined as censoring after ETI's introduction in France in December 2019. Outcomes included CFLD progression and liver transplantation without prior CFLD progression. Mortality was a secondary outcome. pwCF were censored after lung transplantation. Incidence rates and Kaplan-Meier curves were used to measure CFLD progression, and adjusted hazard ratios (aHR) were calculated, accounting for competing mortality risks.
Results: The cohort included 9,997 pwCF [median age 19 years (IQR 14–29), 52.6% male], with 20% (n = 1,993) censored in the pre-ETI era and 80% (n = 8,004) in the ETI era. The incidence of CFLD progression was 3.2 per 1,000 person-years overall: 20.7 pre-ETI and 1.14 post-ETI ($p < 0.001$). Five-year probabilities of CFLD progression were 11.4% (95% CI, 9.1%–13.7%) pre-ETI and 0.27% (0.15%–0.4%) post-ETI ($p < 0.001$). All liver-related events, including non-bleeding gastroesophageal varices and HCC, declined significantly in the ETI era ($p < 0.001$). The 5-year transplant-free mortality probabilities were 18.5% (95% CI, 15.7%–21.2%) pre-ETI and 0.57% (95% CI, 0.39%–0.76%) post-ETI ($p < 0.001$). The burden of CFLD progression was partially offset by competing mortality risks before and after ETI ($p < 0.001$ with Gray's test). The aHRs for CFLD progression and for liver and lung transplant-free mortality were 0.083 (0.034–0.202; $p < 0.001$) and 0.011 (0.006–0.021; $p < 0.001$), respectively.
Conclusion: CFLD outcomes and mortality significantly improved following the introduction of ETI in France. CFLD should not be considered a contraindication to ETI therapy for pwCF.

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GS-009
Latest liver stiffness measurements predict liver-related outcomes in primary biliary cholangitis patients with discordant biochemical and liver stiffness responses

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Background and aims: Biochemical response in serum alkaline phosphatase (ALP) is prognostic in patients with primary biliary cholangitis (PBC). Liver stiffness measurement (LSM) was increasingly used to prognosticate patients with PBC. It was unclear how discordant biochemical and LSM changes should be best interpreted. Here, we aim to determine the clinical outcomes of PBC patients with discordant biochemical and LSM responses.

Method: In this large international multicenter study from GLOBAL-PBC, we included patients with at least two reliable LSMs by vibration-controlled transient elastography performed at least 6 months apart. Patients with prior hepatic decompensation (HD), liver transplantation (LT), hepatocellular carcinoma or less than 3 months follow-up were excluded. *Biochemical response* was based on the Paris-2 criteria. *LSM response* was defined as stable or any reduction in LSM. Sensitivity analysis was performed using different LSM reduction threshold by percentages (10%, 20% or 30%) and biochemical responses (ALP normalization or Deep response). We performed landmark analysis by setting the time of the *latest LSM (LSMc)* as time zero to the occurrence of first HD (*primary outcome*), LT and liver-related death (*secondary outcomes*) using Cox regression analysis, allowing for non-linear associations with restricted cubic splines.

Results: From 4,096 PBC patients with LSM, analysis cohort consist of 1,793 PBC patients with serial LSMs performed. Over a median follow-up of 22 (IQR: 12–39) months from LSMc, 3.3% of patients developed HD. Biochemical and LSM response were achieved in 51% and 52%, respectively. Patients achieving biochemical responses by either the Paris-2 criteria (51%), normal ALP (39%), or deep response (25%) had a lower risk of developing HD ($p < 0.05$ for all). While LSM response was not predictive of HD, LSM reduction by 10%, 20% and

30%, and LSMc <10 kPa were independently associated with a lower risk for HD (p < 0.05 for all). LSMc alone has a C-statistic of 0.87 to predict HD. LSMc≥10kPa strongly predicted HD (HR:14.5, 95%CI 6.9–30.6). The risk of developing HD increases proportionally with the "rule-of-five" based on LSMc. Discordant biochemical and LSM response occurred in up to 52% of PBC patients. While biochemical or LSM response in isolation was not predictive of HD in the setting of discordant biochemical and LSM response, LSMc >10 kPa is predictive of first HD (HR; 37.4, 95%CI: 4.8–289.7), LT or death (HR: 2.6, 95%CI: 1.3–5.4).

Conclusion: In this large multinational study, discordant between biochemical and LSM responses are common in PBC. The latest LSM >10 kPa is the strongest predictor the first liver-related outcomes in patients with PBC, irrespective of prior biochemical response or LSM trajectory. With the increasing use of repeated LSMs, the use of LSMc alone considerably simplifies prognostication of patients with PBC.

GS-010

Outcomes of 48 weeks of therapy and subsequent 24-week post-treatment period with tobevibart (VIR-3434) and elebsiran (VIR-2218) with or without pegylated interferon alfa-2a in chronic hepatitis B virus infection. Findings from the MARCH study

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Background and aims: Tobevibart (VIR-3434) and elebsiran (VIR-2218) with or without pegylated interferon alfa-2a (IFN) are under evaluation in participants with chronic hepatitis B virus (HBV) infection in the Phase 2 MARCH study. Tobevibart is an investigational engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg, while elebsiran is an investigational small interfering ribonucleic acid (siRNA) targeting the HBx region of the HBV genome. Here, we present available end of treatment (EOT) data after 48 weeks of therapy, and 24 weeks post-EOT functional cure rate (FCR) results will be available at time of presentation.

Method: Participants with chronic HBV infection on nucleos(t)ide-reverse transcriptase inhibitors (NRTIs) received 44–48 weeks of tobevibart alone, a combination of tobevibart and elebsiran, or a regimen including tobevibart, elebsiran, and IFN. Tobevibart, elebsiran, and IFN were administered subcutaneously at 300 mg every 4 weeks (Q4W), 200 mg Q4W, and 180 µg weekly, respectively. Key endpoints included the evaluation of treatment-emergent adverse events (TEAEs), HBsAg seroclearance (<0.05 IU/mL) at the EOT, and FCR at 24 weeks post-EOT in participants with HBsAg seroclearance who had discontinued NRTI treatment.

Results: EOT results for all participants in the tobevibart (n = 20) and tobevibart + elebsiran (n = 51) cohorts, and in 27 out of 50 participants in the tobevibart + elebsiran + IFN cohort were previously reported. HBsAg seroclearance rates at EOT were 0/20 (0%), 8/51 (15.7%), and 6/27 (22.2%) for the tobevibart, tobevibart + elebsiran, and tobevibart + elebsiran + IFN cohorts, respectively. Higher HBsAg seroclearance rates were observed in participants with lower baseline HBsAg. Specifically, in participants with baseline HBsAg < 1000 IU/mL, seroclearance at EOT was observed in 7/18 (38.9%) in the tobevibart + elebsiran cohort and 5/11 (45.5%) in the tobevibart + elebsiran + IFN cohort. TEAEs were predominantly grade 1–2, with grade ≥ 3 TEAEs observed in 0, 2 (3.9%), and 9 (33.3%) participants in the respective groups. Serious TEAEs related to study drugs were reported only in the tobevibart + elebsiran + IFN group, including one case of leukopenia attributed to IFN and one case of hepatitis attributed to all three study drugs; both events improved without lasting consequences. Follow-up is ongoing, and FCR results at 24 weeks post EOT for participants with HBsAg seroclearance who have discontinued NRTIs will be presented.

Conclusion: The combination tobevibart and elebsiran, with or without the addition of IFN, can achieve HBsAg loss, especially in participants presenting with lower baseline HBsAg. TEAEs were predominantly mild to moderate, and no new safety concerns emerged. These positive outcomes and the overall risk-benefit profile are supportive of the further clinical development in treating chronic HBV infection.

GS-012

Efruxifermin improves fibrosis in participants with compensated cirrhosis due to MASH: results of a 96-week, randomized, double-blind, placebo-controlled, phase 2b trial (SYMMETRY)

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a leading cause of cirrhosis, which can lead to liver failure, hepatocellular cancer, need for transplant, or death. There are no approved treatments for cirrhosis due to MASH. Efruxifermin is a bivalent fibroblast growth factor 21 (FGF21) analogue in development for treatment of MASH. The SYMMETRY trial assessed the efficacy and safety of efruxifermin for 96 weeks in participants with cirrhosis due to MASH.

Method: This phase 2b, randomized, placebo-controlled, double-blind trial enrolled participants with biopsy-confirmed compensated cirrhosis (F4 fibrosis) due to definitive MASH (78%) or cryptogenic cirrhosis presumed secondary to MASH (22%). Participants were randomly assigned (1:1:1) to once-weekly subcutaneous efruxifermin (50 or 28 mg) or placebo. The primary outcome was at least 1-stage fibrosis improvement (cirrhosis reversal) without MASH worsening at Week 36 and at study end (Week 96).

Results: A total of 181 participants were randomized and dosed with study drug (age: 61 yrs, 67% female, BMI 36 kg/m2, 80% T2D). Among participants with a Week 36 biopsy (N = 154), the proportion with cirrhosis reversal without MASH worsening was 24% for 50 mg efruxifermin and 22% for 28 mg efruxifermin vs 14% for placebo (both p = ns). Among those with a Week 96 biopsy (N = 134), the proportion of participants with cirrhosis reversal without MASH worsening was 39% for 50 mg efruxifermin (p-value vs placebo = .009) and 29%

for 28 mg efruxifermin (p = .131) vs 15% for placebo. For the intent-to-treat population (N = 181), with missing data imputed as nonresponse, the proportion of participants with cirrhosis reversal without MASH worsening at Week 96 was 29% for 50 mg efruxifermin (p = .031) and 21% for 28 mg efruxifermin (p = .194) vs 11% for placebo. Of those with definitive MASH at baseline and a Week 96 biopsy (N = 106), the proportion of participants with MASH resolution at Week 96 was 55% for 50 mg efruxifermin (p = .001) and 59% for 28 mg efruxifermin (p < .001) vs 18% for placebo. Efruxifermin was also associated with improvements in non-invasive markers of liver fibrosis (ELF, LSM) and liver injury (ALT, AST), as well as improvements in lipoproteins and insulin sensitivity (HOMA-IR, C-peptide, adiponectin). Gastrointestinal adverse events were more common with efruxifermin, and most were transient and mild or moderate in severity.
Conclusion: This is the first randomized controlled trial to show pharmacological reversibility of cirrhosis due to MASH. Histology of serial biopsied revealed that longer treatment with 50 mg efruxifermin for 96 weeks resulted in more participants with cirrhosis reversal. These improvements were corroborated by improvements in non-invasive markers of liver fibrosis and injury, as well as metabolic health, suggesting that treatment with efruxifermin may have a positive impact on liver outcomes.

Late-breaker Orals

LBO-001

Norucholic acid for the treatment of primary sclerosing cholangitis: 96-week analysis of a pivotal phase 3 trial

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic inflammatory, fibro-obliterative cholestatic liver disease lacking effective medical therapy. The semi-synthetic bile acid derivative norucholic acid (NCA) is resistant to amidation, allowing it to undergo cholehepatic shunting. This results in bicarbonate-rich hypercholeresis and cholangiocyte protection, as well as potential direct anti-inflammatory and immunomodulatory effects. Here, we report the results from the pivotal phase 3 trial of NCA in PSC over 96 weeks (NCT03872921).
Method: In this randomized, placebo (PBO)-controlled, double-blind (DB) phase 3 trial, adult PSC patients with ALP >1.5 × upper limit of normal (ULN) were randomized 2:1 to 1500 mg NCA once daily or to PBO. Randomization was stratified by concomitant ursodeoxycholic acid (UDCA) use. Overall treatment duration is 192 weeks, with analysis of the primary endpoint at 96 weeks, followed by an ongoing 96-week DB extension phase. The combined primary endpoint at week 96 was partial normalization of ALP to <1.5 × ULN without worsening of fibrosis stage by Ludwig staging at week 96 compared to baseline in the full analysis set (FAS). Here, we report the results of the primary analysis after 96 weeks.
Results: A total of 301 patients were included in the FAS population (NCA: 205; PBO: 96 patients), with 213 (70.8%) completing to week 96. Baseline data were similar between treatment groups, with slightly more severe disease in the NCA group (Ludwig stage 3-4: 50.5% (NCA) vs. 37.9% (PBO); modified Nakanuma stage 3-4: 72.1% (NCA) vs. 55.8% (PBO); median ALP: 320 U/L (NCA) vs. 290 U/L (PBO)). Concomitant UDCA use was reported for 78.7% of patients. At week 96, the percentage of patients achieving the primary endpoint was 15.1% for NCA versus 4.2% for PBO (p = 0.0048). Among patients without concomitant UDCA, significantly more reached the primary endpoint with NCA versus none with placebo (23.4% vs. 0.0%, n = 47 vs. n = 18; p = 0.0267). Improvement by at least 1 Ludwig stage was observed for 25.2% of NCA patients versus 10.5% in the PBO group (p = 0.0217). Conversely, only 20.3% of NCA patients worsened by at least 1 Ludwig stage compared with 40.4% in the PBO group (p = 0.0069). The percentage of patients with partial normalization of ALP without worsening of modified Nakanuma stage was 15.1% for NCA vs. 5.2% for PBO (p = 0.0086), confirming the superiority of NCA by a second histological score. Sustained biochemical improvement in the levels of multiple liver enzymes was observed with NCA but not PBO. The study drug was well tolerated, with similar rates of patients with serious adverse events between both treatment groups.
Conclusion: In this pivotal phase 3 trial in adult patients with PSC, treatment with 1500 mg/day NCA for 96 weeks was safe and superior to placebo for the primary combined endpoint, indicating beneficial effects of NCA for halting disease progression.

LBO-002

Treatment with resmetirom for up to two years led to improvement in liver stiffness, fibrosis biomarkers, fibrosis scores and portal hypertension risk in 122 patients with compensated MASH cirrhosis

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Background and aims: Resmetirom, a selective thyroid hormone receptor beta agonist, is an approved therapy for metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis based on improvement in both NASH and fibrosis. MASH cirrhosis with clinically significant portal hypertension (CSPH) leads to major adverse liver outcomes. This analysis aimed to assess the effect of resmetirom over two years of treatment in 122 patients with MASH cirrhosis, with and without CSPH, as defined by Baveno VII criteria.
Method: A total of 122 patients with Child Pugh A MASH cirrhosis (based on MASH F4 on historic biopsy >66% or clinical diagnosis) were treated with 80 mg resmetirom for up to 2 years (MAETRO-NAFLD-1 (NCT04197479) year 1; open-label extension trial (NCT04951219) (year 2)). Patients were assessed for baseline CSPH (Baveno VII) with FibroScan vibration-controlled transient elastography (VCTE), platelet count and confirmed using magnetic resonance elastography (MRE). Non-invasive biomarkers and imaging were analysed at baseline and out to 2 years. Results are presented as mean change or % change from baseline.
Results: Baseline characteristics included age 61.3 (9.1) (mean (SD)), female 56%, Hispanic 27%, BMI 35.3(7.6)kg/m^2, T2D 65%. Median, (Q1, Q3): VCTE, 20.1 (17.1,31.3) kPa; CAP, 327 (292,370)dB/m; FIB4, 2.4 (1.7,3.8), MRE, 5.2 (4.4,6.3) kPa; ELF, 10.7 (10.0,11.5); MRI-PDFF, 8.6% (6,11.5); Agile3$^+$, 0.96(.89,.93); Agile 4, 0.64(0.40,0.84). Resmetirom statistically significantly improved the following: mean change from baseline: VCTE, -6.1(1.4) kPa at year 1; -6.7(1.3) kPa at year 2; at year 2: MRE -0.57(.14) kPa; procollagen-3 N-terminal peptide (P3NP), -1.6 (.57) ng/ml; Agile3+, -.06(.01); Agile4, -.09(.02); % change from baseline: MRI-PDFF -33%; ALT,-25%; AST,-21%; GGT,-45%; LDL,-20%, ApoB, -22%, triglycerides, -30%. At year 1 and 2, respectively, 46% and 52% had a ≥ 25% decrease in VCTE; 12% and 9% had ≥25% increase in VCTE. At baseline, 63% of patients were categorized as probable/definitive CSPH (Baveno VII), and at 1 and 2 years, respectively, 20% and 28% of CSPH positive patients no longer met criteria for CSPH. 35% of patients with confirmed F4 at baseline (liver biopsy F4 and/or platelets <140/MRE ≥ 5 with VCTE ≥ 15) showed a transition from F4 to F3 at year 2 (VCTE<15 and ≥25% decrease from baseline). Discontinuation rate was 8%. Mild gastrointestinal disorders were the most common adverse events.
Conclusion: At 2 years of treatment, resmetirom demonstrated significant improvements in non-invasive biomarkers, liver stiffness on imaging and portal hypertension risk in patients with MASH cirrhosis. Resmetirom was safe and well-tolerated in this population. These findings highlight the potential of resmetirom to demonstrate clinical benefit in MAESTRO-NASH OUTCOMES, an ongoing 845 MASH cirrhosis patient clinical outcome study.

LBO-003

Efficacy and safety of long-term human albumin therapy in cirrhotic patients with acute decompensation and ascites: top-line results of the PRECIOSA trial

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Background and aims: Previous single-country randomized controlled trials suggested that long-term albumin (LTA) administration may improve clinical outcomes in patients with decompensated cirrhosis and ascites. PRECIOSA evaluated the efficacy and safety of LTA therapy to improve transplant-free survival (TFS), mortality, and disease-related complications in cirrhotic patients with existing or prior ascites and acute decompensation from 14 countries across North America and Europe.
Method: PRECIOSA was a phase 3, randomized (1:1), multicenter, active-controlled, parallel-group, open-label study (NCT03451292). Patients were randomized to standard medical treatment (SMT) plus Albutein® 20% (1.5 g/Kg body weight, maximum 100 g, every 10 ± 2 days for up to 12 months (Treatment) or SMT alone (Control). The primary endpoint was 1-year TFS assessed in the intent-to-treat population, powered to at least 80% to detect a hypothesized hazard ratio (HR) of 0.6 (2-sided α of 5%) comparing Treatment to Control. Secondary and exploratory endpoints included 1-year mortality, 3- and 6-month TFS and mortality, and incidence of disease-related complications. Safety assessments included treatment emergent serious adverse events (TESAEs) and suspected adverse drug reactions (SADRs).
Results: 410 patients were randomized to the Treatment (n = 203) or Control (n = 207) groups. Demographic and baseline characteristics were similar between groups. Alcohol was the dominant etiology for cirrhosis in both groups. The LTA dosing regimen raised and maintained higher serum albumin concentrations, on average 0.5 g/dL to 0.65 g/dL, in the Treatment group compared to the Control group during study treatment. HRs [95% CI; p-value] for TFS and mortality by 3 months were 0.58 [0.34, 0.99; p = 0.044] and 0.65 [0.37, 1.17; p = 0.15], by 6 months 0.73 [0.50, 1.08; p = 0.11] and 0.68 [0.44, 1.05; p = 0.08], and by 1 year 0.80 [0.58, 1.10; p = 0.17] and 0.77 [0.53, 1.10; p = 0.15], respectively. The incidences of all disease-related complications were lower in the Treatment group, most notable by odds ratio [95% CI] for spontaneous bacterial peritonitis (0.28 [0.09, 0.86]) and hepatorenal syndrome (0.24 [0.09, 0.64]). TESAEs were numerically lower in the Treatment group (77 in 52 patients) compared to the Control group (127 in 70 patients). SADRs to Albutein 20% were infrequent (20 in 14 patients). No new adverse reactions related to LTA administration were identified.
Conclusion: The LTA therapy studied in PRECIOSA showed clinically meaningful improvements in TFS, mortality, and disease-related complications for cirrhotic patients with existing or prior ascites and acute decompensation; however, the hypothesized primary endpoint was not met. The LTA dosing regimen showed favorable safety and tolerability profile with no new adverse reaction risks beyond that on label for Albutein 20% to limit adoption of the therapy.

LBO-004

Final results of MYR301: a randomised phase 3 study evaluating the efficacy and safety of up to 144 weeks of bulevirtide monotherapy for chronic hepatitis delta and 96 weeks of posttreatment follow-up

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Background and aims: Bulevirtide (BLV) 2 mg/day (d) is approved in Europe, Australia, and Russia for treatment of compensated chronic hepatitis delta (CHD). In MYR301, a Phase 3 study evaluating BLV monotherapy for 2 to 3 years, BLV treatment was safe and effective through 144 weeks (W). We present final MYR301 results through follow-up at 96W after end of treatment (EOT; FU96).
Method: Patients with CHD and compensated liver disease (N = 150) were randomised to immediate treatment with BLV 2 or 10 mg/d for 144W or to 48W of delayed treatment (DT) followed by BLV 10 mg/d for 96W (DT to 10 mg) and 96W posttreatment FU. Efficacy endpoints included virologic response (VR; undetectable hepatitis delta virus [HDV] RNA or ≥ 2 $\log_{10}$ IU/mL decline from baseline [BL]), combined response (CR; VR and alanine aminotransferase [ALT] normalisation), ALT normalisation, undetectable HDV RNA, and hepatitis B surface antigen (HBsAg) loss. The primary analysis was intention to treat, with missing data considered failures.
Results: BL characteristics were previously reported and similar across groups. Most patients (92%) remained in the study at EOT; 72% and 57% completed FU48 and FU96, respectively. CR rates in the 2, 10, and DT to 10 mg groups, respectively, declined from 57%, 54%, and 56% at EOT to 24% in each group at FU96. HDV RNA undetectability rates in these groups were 29%, 50%, and 52% at EOT and 20%, 22%, and 20% at FU96. Of the 64 patients across all groups with undetectable HDV RNA at EOT and available FU data, 23 (36%) had sustained undetectable HDV RNA through FU96, and 41 patients had viral relapse, which occurred in 38 (93%) by FU24 and none after FU48. Sustained posttreatment undetectable HDV RNA was more frequent in patients with longer on-treatment continuous HDV RNA undetectability at EOT: 9/10 (90%) for ≥ 96 weeks, 11/22 (50%) for ≥ 48 to < 96 weeks, and 3/32 (9%) for 0 to < 48 weeks. Posttreatment HBsAg loss occurred in 3 patients. In the posttreatment period, 14/142 (10%) patients had ALT > 10 × the upper limit of normal (ULN), which occurred by FU24 in most (10/14, 71%). Posttreatment hepatic serious adverse events (SAEs) were reported in 20/142 (14%) patients: 7 had ALT > 10 × ULN, 15 had HDV rebound (HDV RNA increased ≥ 2 $\log_{10}$ IU/mL from EOT), and 4 had liver-related hospitalisation (including 1 case of oesophageal varices haemorrhage); 1 additional patient experienced nonserious ascites. The hepatic SAEs resolved in 17/20 (85%) patients, ≥ 16 of whom restarted BLV.
Conclusion: In patients with CHD treated with BLV monotherapy for 96W or 144W, response rates decreased after treatment discontinuation. However, a subset of patients maintained undetectable HDV RNA for 2 years posttreatment, which was associated with longer duration of continuous on-treatment undetectability. Posttreatment viral relapse occurred only in the first year after EOT and may be associated with hepatitis flares.

LBO-005

High prevalence of undiagnosed liver fibrosis in the adult european population driven by metabolic risk factors and alcohol consumption. results from the prospective liverscreen cohort in 30,541 subjects

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Background and aims: Findings from small-scale, single-country cohorts suggest that undiagnosed liver fibrosis resulting from chronic liver disease is common in the general population. However, the exact prevalence and main risk factors remain incompletely understood. We aimed to investigate the prevalence of undiagnosed liver fibrosis in a prospective large-scale multi-national European cohort and determined the association between liver fibrosis and metabolic risk factors and/or alcohol consumption.
Method: From May 2018 to December 2024, we enrolled 30,541 participants older than 40 years, without known liver disease, from the general population in 9 European countries. We collected demographic and clinical data and standard lab parameters. Liver fibrosis was assessed by liver stiffness measurement (LSM) using vibration controlled transient elastography (Fibroscan®, Echosens, France). Since LSM <8 kPa rules out significant fibrosis, only subjects with LSM ≥8 kPa, and/or ALT ≥ 1.5 the upper normal limit were referred for evaluation of liver disease. The primary outcome was the prevalence of LSM≥8 kPa.
Results: Mean age was 58 years, 57% were women, and 89% were Caucasian. Most subjects had metabolic risk factors, including overweight/obesity (40%/26%), dyslipidemia (53%), arterial hypertension (35%), and type 2 diabetes [T2D] (10%). We observed hazardous alcohol consumption in 18%, defined by SDU ≥ 14-21/w for women-men or AUDIT-C ≥ 5, and high-risk consumption in 3.4%, defined by SDU ≥ 35-42/w or AUDIT-C ≥ 8. The prevalence of LSM ≥ 8 kPa was 4.6%, and that of LSM ≥ 10 or 15 kPa was 2.5% and 0.8%, respectively. The prevalence of LSM ≥ 8 kPa was 1.3% in subjects without metabolic risk factors, and 2.3%, 5.2%, 9.8% and 21.6% in subjects with one, two, three or four risk factors, respectively. Hazardous alcohol consumption increased this prevalence further (1.7%, 4.5%, 8.1%, 14.9%, and 28.5%, respectively). Steatosis (CAP ≥ 275 dB/m) was present in 32% and was associated with LSM ≥ 8 kPa (8.8% vs 2.6% in subjects with and without steatosis respectively). In multivariate analysis, the strongest predictors of LSM ≥ 8 kPa were obesity, T2D, and high-risk alcohol consumption (OR 3.8, 3.0, and 2.5, respectively). Chronic liver disease with liver fibrosis was confirmed in 31% of subjects referred for evaluation (with liver biopsy in 67% of these cases). Etiology was mainly due to MASLD, ALD or MetALD while only a very small number was related to other etiologies.
Conclusion: In this large-scale European cohort, we found a remarkably high prevalence of undiagnosed liver fibrosis mainly related to steatotic liver disease driven by metabolic risk factors and/or high-risk alcohol consumption. Efforts should be made to identify liver fibrosis early to apply specific therapies that could reverse liver fibrosis. Funded by the European Commission H20/20 program, call SC1-BHC-30-2019. Project number: 847989

LBO-006
Belapectin at 2 mg/kg/LBW reduces varices development in MASH cirrhosis with portal hypertension: results from the NAVIGATE trial

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Background and aims: There are no approved treatments for metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis. Belapectin, a galectin-3 inhibitor, previously showed reduced hepatic venous pressure gradient (HVPG) and varices development in MASH cirrhosis without baseline varices (Chalasani et al., Gastroenterology 2020). The Phase 2b/3 NAVIGATE trial (NCT04365868) evaluated the efficacy and safety of belapectin in subjects with MASH cirrhosis and portal hypertension but without baseline varices.
Method: NAVIGATE is a randomized, placebo-controlled trial in subjects with MASH cirrhosis and portal hypertension using the

latest guidelines. Subjects were stratified based on type 2 diabetes mellitus (T2DM) status and randomized to intravenous belapectin at 2 mg/kg or 4 mg/kg lean body weight (LBW) or placebo every 2 weeks for 18 months. Endoscopic evaluations at baseline and end of treatment were assessed for new-onset varices. Endoscopies were centrally reviewed in a blinded manner. The composite primary endpoint was defined as subject with new varices, intercurrent events, and/or missing endoscopic assessments (EGDs) in intent-to-treat (ITT) population. The incidence of new varices was assessed in per-protocol (PP) population, defined as subject who underwent EGDs at both baseline and the end of therapy (EOT).

Results: Total of 357 subjects were randomized (n = 119 per cohort), two with baseline varices were excluded from ITT analysis; 70 did not complete EOT endoscopy. Baseline characteristics were comparable across groups (mean age: 60 years, 64.8% female, 90.7% White, 29.9% Hispanic, platelet count: 131.4k/μL, liver stiffness: 24.8 kPa, 67% with T2DM, 21.7% on GLP-1 receptor agonists, 42.5% on statins). Neither belapectin dose achieved statistical significance for the composite primary endpoint in ITT (2 mg: 37.8%, 4 mg: 43.2%, placebo: 47.5%). In ITT, the 2 mg/kg group had a 43.2% lower incidence of new varices than placebo (10.1% vs. 17.8%, p = 0.13). In PP, the 2 mg/kg group showed a significant 50% reduction in new varices compared to placebo (11.3% vs. 22.3%, p = 0.04). The 4 mg/kg dose showed no significant effect. Liver stiffness progression (≥30% increase) occurred in 13.7% of the 2 mg/kg group vs. 19.8% in placebo. Liver stiffness progression of ≥30% at 18 months was observed in 13.7% of subjects in the 2 mg/kg belapectin group compared to 19.8% in the placebo group. Both doses of belapectin were well tolerated, with adverse events (AEs), serious AEs (SAEs), and treatment discontinuations comparable across cohorts.

Conclusion: Belapectin at 2 mg/kg/LBW significantly reduced varices development in the PP population at 18 months, replicating prior Phase 2 findings. Long-term 36-month follow-up data will provide further insights. These results support continued investigation of belapectin in a Phase 3 trial for MASH cirrhosis with portal hypertension.

WEDNESDAY 07 MAY

Interprofessional Forum: Nurses and AHPs

OS-001-YI

A palliative care approach for cirrhosis patient: feasibility and preliminary results from a prospective Danish multi-center study

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Background and aims: Cirrhosis is linked to a high symptom burden, hospitalization and mortality, and reduced quality of life for patients and relatives. Despite these challenges, palliative care remains underutilized due to stigma, misperceptions, and a healthcare focus on curative treatment. While evidence suggests palliative care benefit other patient groups, more research is needed to develop and evaluate interventions. This study aimed to assess the feasibility, acceptability, and preliminary outcomes of a palliative care intervention for patients with cirrhosis and their relatives.

Method: This study was a prospective multicenter study including four Danish hospitals. The intervention was developed by a multidisciplinary team comprising hepatologists, specialized nurses, researchers from the participating centers, palliative care specialists, and a psychologist. The intervention included (1) education and training of all healthcare professionals involved and monthly online supervision sessions with palliative care specialists, and (2) a palliative care intervention based on advance care planning and the actions taken as part of the conversations. The goal was to identify, assess, and treat mental, physical, social, or spiritual symptoms and problems. The effects were measured in interviews and with the PRO PAL symptom burden questionnaire, the hospital anxiety and depression scale (HADS), the Euro Quality of Life (EQ-5D-5L), and the Zarit Burden (ZCB). Feasibility across eight general areas (acceptability, demand, implementation, practicality, adaption, integration, expansion, limited-efficacy testing) was evaluated using a mixed-methods approach.

Results: Sixty-eight patients (75% male, mean age 65 years, 88% with alcohol-related etiology, MELD 13) were invited to participate. Of these, 42 agreed, 25 asked a relative to join, and 12 completed a 6-month follow-up. Patients and relatives found the intervention positive and informative and that it provided clarity regarding disease progression and emotional support at qualitative assessments and provided. The patient-reported outcomes (PRO PAL, HADS, EQ-5D-5L) remained unchanged, but the caregiver burden decreased (ZCB score 25 vs.16). Healthcare professionals reported that the collaboration and supervision were beneficial and deemed the intervention feasible. The education and training program was well received. The patient who declined to participate lacked resources or felt no need for the intervention.

Conclusion: This study demonstrates that a structured palliative care intervention for patients with cirrhosis and their relatives is feasible and acceptable, and preliminary results demonstrate a significant improvement in caregiver burden. Results will inform adjustments and a larger evaluation study with 240 patients, including the effects on healthcare utilization.

OS-002-YI

Identifying training needs to improve detection and management of metabolic dysfunction-associated steatotic liver disease in primary care settings: a qualitative interview study with healthcare professionals

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent liver disease globally. People with MASLD have an increased risk of overall mortality when compared to the general population, however MASLD often goes undetected until it reaches an advanced stage. Raising awareness and motivation of healthcare professionals (HCPs) to detect MASLD, and arming them with the appropriate knowledge and skills to manage it is crucial. Due to high prevalence and common risk factors, primary care is ideally placed to identify and manage the majority of patients

with MASLD. However, previous research suggests that many primary HCPs do not have a full understanding of what MASLD is, how it can be detected, or how it should be managed. The aim of this study was to identify the training needs of primary HCPs for improving detection and management of MASLD.
Method: A qualitative interview study was conducted with primary HCPs in the Tees Valley region (UK). Interviews were audio-recorded, transcribed verbatim and data were thematically analysed using the Theoretical Domains Framework (TDF).
Results: 25 primary HCPs were recruited from 16 practices across Teesside (IMD deciles 1–7) between March and June 2024. The mean age of participants was 41 (± 8 years) and 15/25 participants were female. Participants were GPs (n = 16), practice nurses (n = 6), and clinical pharmacists (n = 3). Mean length of time in post was 4 years (range: 1 month-20 years). Preliminary themes generated from the data represent barriers and/or enablers to detecting and managing MASLD in primary care. Themes concerning detection (n = 10) included: 'understanding MASLD aetiology and symptomatology', including distinguishing MASLD from other diseases; 'assigning roles and responsibilities to MASLD detection and escalation'; and 'detection leads to a 'Pandora's Box' of unanswered questions' - i.e., lack of management approaches reduced motivation to detect MASLD. Themes concerning management (n = 9) included: 'competence in providing MASLD-specific lifestyle advice'; 'establishing clear referral pathways to secondary care'; and 'believing that MASLD is reversible' - i.e., motivation for MASLD management is evident when primary HCPs are aware that MASLD can be managed or reversed.
Conclusion: Several barriers and enablers to the detection and management of MASLD in primary care were identified. Findings suggest that training targeting the knowledge, skills and beliefs of primary HCPs could facilitate increased detection and management of MASLD. However, it was highlighted that specific pathways (i.e. clarification of HCP roles in MASLD detection and management; streamlining care pathways between primary and secondary care) and resources (i.e. MASLD-specific management options) should also be addressed to facilitate integration of detection and management of MASLD in primary care.

OS-003
A quality improvement project: multidisciplinary nutrition approach to improve the nutritional and functional status of pre-liver transplant patients

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Background and aims: Pre-liver transplant patients are at high risk of malnutrition and its associated complications, which can lead to increased hospitalisation and elevated infection rates. The progressive nature of liver diseases exacerbates malnutrition, potentially impacting eligibility for transplant. The aim of this quality improvement project is to improve nutrition and functional status of chronic liver disease patients planned for liver transplant using a multidisciplinary approach.
Method: Participants who were potential candidates for liver transplant were recruited over two distinct periods in inpatient and outpatient settings (Cohort 1: 2020–2021 and Cohort 2: 2022–2023). Standard care was provided to participants in Cohort 1. Key factors contributing to the decline in nutritional and functional status of pre-liver transplant patients were identified using data from Cohort 1 and illustrated with an Ishikawa diagram, which mapped potential causes and areas for improvement. A multidisciplinary approach was piloted in Cohort 2, involving a structured nutrition protocol that included the use of a nutrition screening tool at outpatient clinic, closer follow-up and timely referrals to a dietitian, nutrition education and collaboration with physiotherapists to improve functional status. Parameters measured include mid-arm muscle circumference, handgrip strength, and liver frailty index (LFI) at initial assessment, 3 months, and 6 months to monitor changes over time.
Results: 24 patients in Cohort 1 and 17 patients in Cohort 2. Comparing Cohort 2 to Cohort 1, we found an increase in mid-arm muscle circumference and handgrip strength at 6 months in Cohort 2 by 40% and 22%, respectively. Participants in Cohort 2 showed a significant increase in handgrip strength (3.2 kg ± 1.2, p = 0.0141) and mid-arm muscle circumference (9.9 mm ± 3.4, p = 0.0105) when measured at 6 months against initial assessment. We found a reduction in prevalence in frailty from 18.5% to 4.3% using the LFI after multidisciplinary intervention in Cohort 2. The proportion of participants in robust status increased by 5.2% in Cohort 2, demonstrating a significant improvement in overall functional status following intervention.
Conclusion: These findings demonstrate that a multidisciplinary approach combined with a structured nutrition protocol led to significant improvements in both nutritional and functional status among pre-liver transplant patients. However, larger-scale studies are needed to explore additional clinical outcomes in both pre- and post-transplant patients.

OS-004
Development and implementation of an innovative allied health professional (AHP)-led group education programme for patients with metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and aims: MASLD affects up to 30% of adults worldwide and is a common cause of cirrhosis, HCC and liver failure. With few pharmacological agents available, lifestyle changes are the cornerstone of treatment. Clinical guidelines recommend structured education programmes however these are uncommon in practice. We developed and implemented an AHP-led structured group education programme for patients with MASLD. We aimed to assess patient engagement and experiences of attending the groups and evaluate whether attendance led to weight loss.
Method: Patients with MASLD attending hepatology clinics at a tertiary liver unit were offered 3x 1-hour sessions either face-to-face (F2F) or online. Sessions were designed/delivered by Dietitians and Physiotherapists specialising in MASLD. Content included what MASLD is, how lifestyle change can improve outcomes and signposting to appropriate resources. Patient Related Experience Measures (PREMs) and clinical outcomes were collected.
Results: 152 patients were invited to attend the groups between Oct 23 – Oct 24. 21/152 self-referred, and a further 80/152 agreed to attend after a follow-up call. 51/152 declined, mainly due to session timing. 68/152 attended (46 F2F; 22 online) within the study period (mean age 60y; 54% male; BMI 38 kg/m2). To date, mean weight change at 3-months was −3.8 kg (−3.6%); 42% achieved >3% weight loss, 33% >5% and 11%>10%. Patients attending F2F achieved mean weight loss −2.7 kg (−2.8%) (−11.3 to +3.8 kg); patients attending online achieved −6.8 kg (−5.2%) (−23.0 to +0.5 kg). PREMs reported overall satisfaction with the programme (mean score: 9.6/10); the sessions provided "more information than a Doctor's consultation can". Patients were likely to recommend the "informative and motivational" course to friends/family (mean score: 9.9/10) and it helped patients "to think more about what I eat and to do more exercise little by little.".

Conclusion: The group education programme was feasible to deliver and well received by patients. On average attendees lost weight which will likely improve liver health and reduce cardiometabolic risk. Most patients invited to the programme booked to attend; a minority of patients self-referred, however the addition of a follow-up call significantly increased uptake highlighting the crucial role of administrative support in facilitating patients joining the groups. Offering additional sessions, particularly outside of working hours, may improve accessibility.

THURSDAY 08 MAY

Liver tumours: Experimental and Pathophysiology

OS-005-YI

Crosstalk between senescent cancer cells and the TME reveals myeloid cell centric therapeutic targets in HCC

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Background and aims: The liver tumor microenvironment (TME) plays a key role in hepatocellular carcinoma (HCC), representing an attractive therapeutic target. Senescence-inducing therapy (SIT) can be enforced in tumor cells to restrict their proliferative capacity, while promoting non-cell autonomous effects on the TME. Senescent cancer cells (SCCs) reprogram the TME through their senescence-associated secretory phenotype (SASP) and expression of immuno-modulatory surface receptors. XL413-mediated CDC7 inhibition is a novel senescence-inducing therapy (SIT) in *Tp53*-deficient HCC, promoting tumor-associated macrophage (TAM) expansion in the TME. In this project, we aim to characterize the interaction between SCCs and the liver TME to combine SIT with immunomodulation strategies in HCC.
Method: Through multi-omic analyses encompassing scRNAseq, flow cytometry and multiplex immunofluorescence we have characterized the changes in SIT-treated *Tp53*-deficient HCC tumors. To gain insight on the spatial niches in SIT-treated tumors and characterize the interactions between SCCs and TAMs, we have performed visium spatial transcriptomics. Our findings have been further validated in *in vivo* mouse studies where we have explored the combination of SIT and targeted immunomodulation in *Tp53*-deficient HCC.
Results: The anti-tumorigenic functions of CDC7i *in vivo* encompassed a dynamic induction of senescence in cancer cells associated with a spatiotemporal reorganization of the surrounding microenvironment. These effects involve the structural and functional remodelling of the tumor vasculature accompanied by an expansion of chronically exhausted T cells and TAMs. In SIT-treated tumors, we detected TAM subsets with antigen-presenting, angiogenic and immunosuppressive features. Interestingly, combining CDC7i and pan-macrophage depletion prolonged HCC mouse survival while changing the tumor vasculature. Importantly, spatial transcriptomic analysis highlighted the heterogeneity of senescent cancer cells *in vivo* which correlated with a distinct spatial organization of TAM clusters. Indeed, different senescent cancer cell subsets localized in distinct tumor niches and displayed unique inflammatory profiles and interactions with TAM populations.
Conclusion: These data highlight, for the first time, the importance of distinct TAM clusters in shaping the senescence-educated liver TME, while offering new myeloid centric targets to enhance SIT efficacy.

OS-006

Oleic acid-PPARgamma-FATP1 loop fuels cholangiocarcinoma colonization in lymph node metastases through lipid metabolic reprogramming

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Background and aims: Lymph node metastasis is one of the most significant risk factors for patients with cholangiocarcinoma (CCA), but the mechanisms underlying the colonization of metastatic cancer cells within the lymph nodes, which are rich in fatty acids, remain unclear. We aim to elucidate the mechanisms by which CCA cells survive and colonize lymph nodes, and to identify and validate potential therapeutic targets.
Method: Metabolomics and single-cell RNA sequencing (scRNA-seq) were employed to identify differential metabolites and pathways between the primary lesions and paired lymph node metastases of CCA, characterizing the specific metabolic reprogramming that occurs within the lymph node microenvironment of CCA. Orthotopic CCA and lymph node CCA inoculation mouse models were constructed to investigate the progression of CCA in both primary and metastatic lesions. Proteomics was utilized to identify key targets that fuel CCA colonization in lymph node microenvironment. ChIP-qPCR, dual-luciferase reporter assays, and fatty acid oxidation (FAO) assays were applied to explore the mechanisms by which the identified target promotes CCA colonization in lymph node microenvironment, whose therapeutic vulnerability was validated in patient-derived organoids and mouse models.
Results: Our metabolomic and scRNA-seq analyses revealed an enrichment of oleic acid (OA) in lymph node metastases of CCA and the activated peroxisome proliferator-activated receptor gamma (PPARgamma)-regulated lipid metabolism reprogramming in CCA cells within lymph node microenvironment. Differential proteomic analysis of in vivo models illustrated the sequential up-regulation of long-chain fatty acid transport protein 1(FATP1) in CCA cells in lymph node microenvironment in a time-dependent manner. Immunohistochemical analysis identified the higher expression of FATP1 in lymph node metastases from CCA patients, which correlates with worse prognosis and further progression. Cellular experiments, patient-derived organoids, and lymph node CCA inoculation mouse models demonstrated that OA facilitates lipid accumulation and FAO in CCA cells, thereby promoting cell proliferation in a FATP1-dependent manner. Dual-luciferase reporter assays and ChIP-qPCR confirmed the transcriptional regulation of PPARgamma, which is activated in CCA cells within the lymph node microenvironment, on the expression of FATP1. Furthermore, both in vitro and in vivo models showed that knockdown of FATP1 or treatment with its specific inhibitor, FATP1-IN-1, significantly inhibits lipid metabolism in CCA, reducing its proliferative and colonizing capabilities within the lymph node microenvironment.
Conclusion: Our findings reveal the role of the oleic acid-PPARgamma-FATP1 positive feedback loop in fueling CCA colonization in lymph nodes, where FATP1 is a promising therapeutic target for alleviating CCA lymph node metastatic burden and reducing further progression.

OS-007

E2F1-driven metabolic dysregulation is involved in hippo pathway-driven cholangiocarcinoma progression

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Background and aims: Cholangiocarcinoma (CCA) comprises a heterogeneous group of biliary tumors with a poor prognosis, exhibiting an increasing incidence and mortality over the past decades. It is often diagnosed at an advanced stage, typically with metastasis, limiting access to curative-intent surgery. Metabolic reprogramming is a hallmark of cancer, and lipid metabolism plays an important role in cholangiocarcinogenesis. The cell cycle regulators E2F1 and E2F2 have been identified as modulators of energy metabolism in hepatocellular carcinoma, but their role in CCA remains unknown. This study aimed to: 1) investigate whether E2F1 and E2F2, and/or their targets, are involved in the development of CCA, and 2) determine whether they contribute to the reprogramming of lipid metabolism associated with CCA progression.
Method: Gene expression data from two CCA patient cohorts were analyzed, along with human CCA cell lines and primary cultures of normal human cholangiocytes (NHC). The *sleeping beauty* technique was employed to generate murine models of CCA (hepatic overexpression of *Akt1*/NOTCH1 intracellular cytoplasmic domain (*Nicd1*), *Akt1/Yap*, or of *Akt1/Taz*) in WT, *E2f1*$^{-/-}$, and *E2f2*$^{-/-}$ mice. The impact of pharmacological inhibition of E2F activity or its targets on cell and tumor viability, proliferation, mitochondrial respiration, and fatty acid oxidation was evaluated.
Results: *E2F1* and *E2F2* levels were elevated in human CCA samples and in cellular and murine models of CCA. Both *E2f1*$^{-/-}$ and *E2f2*$^{-/-}$ mice developed liver lesions similarly to WT mice when overexpressing *Akt1/Nicd1*. However, *E2f1*$^{-/-}$ mice were protected against the development of CCAs induced by the Hippo signaling (*Akt1/Yap* and *Akt1/Taz*), whereas no protection was observed in *E2f2*$^{-/-}$ mice. YAP and TAZ, coactivators of the Hippo pathway, interact with E2F1 to drive the transcription of several target genes, including MCM proteins, which are helicases involved in DNA replication. *Mcm2-7* expression was decreased in the liver of *E2f1*$^{-/-}$ mice resistant to CCA induction by *Akt1/Yap* or *Akt1/Taz*, compared to WT or *E2f2*$^{-/-}$mice. Furthermore, *MCM2-7* expression was elevated in human CCA tumors and correlated positively with *E2F1* levels. Pharmacological inhibition of E2F or MCM activity significantly reduced mitochondrial respiration, fatty acid oxidation, cell viability, proliferation, and spheroid and organoid growth in CCA cells.
Conclusion: E2F1 is essential for the progression of CCA subtypes characterized by Hippo pathway activation, cooperating with YAP/TAZ for the transcription of MCM2-7 helicases. Pharmacological inhibition of E2F/MCM activity decreases mitochondrial lipid metabolism and slows CCA progression, representing a potential therapeutic strategy.

OS-008
Microenvironment-responsive bispecific T-cell receptor-engineered T cells against hepatocellular carcinoma

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Background and aims: Clinical efficacies of Adoptive Cell Transfer (ACT) therapy including T-cell receptor (TCR)-engineered T cells (TCR-T) and Chimeric Antigen Receptor-engineered T cells (CAR-T) are hindered by the immunosuppressive tumor microenvironment (TME) in Hepatocellular Carcinoma (HCC). Cancer associated fibroblasts (CAFs) are a pivotal contributor of the immune suppressive TME in HCC. CAFs secret collagen and other immune suppressive factors to establish physical and immune barriers within the tumor to limit the function of immune cells in the tumor. We hypothesize that treatment targeting both malignant cells and CAF will overcome the therapy resistance from the TME in ACT therapy. Here, we report an engineered bispecific TCR-T targeting both HCC and CAF cells in the tumor in order to improve therapeutic efficacy.
Method: We developed bispecific T cells, called TRuC/TCR-T, that combines aspects of T cell receptor fusion constructs (TRuC) comprising an anti-FAP single-chain variable fragment (ScFv)-based binding domain fused to CD3ε subunit against CAFs and α-fetoprotein (AFP)-specific TCR against HCC. The therapeutic efficacy of TRuC/TCR-T is tested in two models (1) HLA-A201 restricted AFP specific TCR to treat HepG2 xenograft in NOD-SCID mice, (2) To further explore immune landscape after treating with TRuC/TCR-T cells, here we report a new type model of murine TCR-T cell therapy for HCC. Utilizing a H2-Kb restricted AFP specific TCR to treat DEN/Cl4C induced spontaneous HCC in C57BL/6 mice. T cells were injected when the TME is considered to be establish.
Results: The TRuC/TCR-T cells elicit strong cytotoxicity to both HCC cells and CAFs in vitro. In vivo, the TRuC/TCR-T significantly reduced tumor size in the xenograft model. Moreover, TRuC/TCR-T cells injection significantly reduced liver tumor burden in mice treated with DEN/Cl4C with negligible toxicity. TRuC/TCR-T cells depleted the tumor stroma within the tumor residue, suggesting a critical role of TRuC/TCR design in overcoming physical and immune barriers via increase T cells infiltration to tumors. Furthermore, TRuC/TCR-T cells exhibited low tonic activation signals in vivo, and better activation response when encounter to its specific antigen.
Conclusion: Our data suggest that TRuC/TCR-T can respond within the immunosuppressive TME and is a novel and effective therapeutic candidate in treating HCC.

OS-009
Tumor size-dependent endothelial switch modulates CD8+ T cell immune surveillance in liver cancer

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Background and aims: Effector CD8+ T cells eliminate antigen-expressing hepatocytes by extending cytoplasmic protrusions through endothelial fenestrations, bypassing the need to migrate into the tissue. However, the impact of anatomical, hemodynamic, and environmental factors acquired by tumors during growth on the immune surveillance capacity of CD8+ T cells remains poorly understood.
Method: To investigate this, we developed a mouse model of hepatocellular carcinoma (HCC) that mimics key features of the human disease. This model enables longitudinal visualization and non-invasive assessment of CD8+ T cell behavior and antitumor potential, leveraging advanced imaging techniques, flow cytometry, single-cell RNA sequencing, and spatial transcriptomics.
Results: Our findings revealed a marked reduction in the antitumor potential of effector CD8+ T cells as tumor lesions reached a size beyond 100 mm³. In "non-responder" lesions, CD8+ T cells exhibited impaired antigen recognition and activation, whereas in "responder" lesions (≤10 mm³), T cells efficiently recognized and attacked tumor cells. Mechanistic analysis revealed that non-responder lesions were characterized by the replacement of liver sinusoidal endothelial cells (LSECs) with capillarized endothelial cells (cECs) lacking fenestrations. Single-cell RNA sequencing of endothelial cells from non-responder lesions revealed the upregulation of immunomodulatory genes (e.g., *Cxcr4, Esm1,* and *Cd200*) and the downregulation of LSEC-specific genes (*Gata4, Lyve1,* and *Maf*) as well as leukocyte adhesion molecules (*Vcam1* and *Icam1*). Notably, the non-responder endothelial cell signature closely resembled that of endothelial cells in human HCC. In both mouse and human cancers, activated CD8+ T cells localized near LSECs but were absent from areas dominated by cECs. Finally, pharmacological restoration of endothelial fenestrations in non-responder lesions significantly enhanced antigen recognition by CD8+ T cells and reinstated their antitumoral activity.
Conclusion: These findings uncover a size-dependent endothelial switch in liver cancers that impairs CD8+ T cell-mediated immune surveillance. Restoring endothelial fenestrations in non-responder tumors offers a promising strategy to enhance tumor immune surveillance, not only by endogenous T cells but also by engineered therapies such as CAR T cells or TCR-redirected T cells.

MASLD: Clinical and therapeutical aspects

OS-010-YI

Informing management of patients at increased risk of hepatic decompensation by two-step non-invasive assessment - a multicentre cohort study of 12,950 patients with metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and aims: While affecting 30% of the general population, MASLD only leads to hepatic decompensation in a minority of patients. We aimed to determine cut-offs of non-invasive tests for selecting this high-risk population for timely management and interventions.
Method: The vibration-controlled transient elastography (VCTE)-Prognosis Study was a longitudinal study at 16 centres from the US, Europe and Asia (prospective data at 14 centres). Adult patients with MASLD who underwent liver stiffness measurement (LSM) by VCTE and fibrosis-4 index (FIB-4) were included. We excluded patients who developed hepatic decompensation or hepatocellular carcinoma

before or within the first 3 months of follow-up. Cumulative incidence was estimated by the Aalen-Johansen method and converted to annual incidence.
Results: Of 12,950 patients (mean age 51.7 [SD 13.9] years; 5,316 [41.1%] female; 4,429 [34.2%] diabetes; median LSM 5.9 [IQR 4.6–8.3] kPa; median BMI 27.2 [IQR 24.7–30.4] kg/m^2),174 (1.3%) patients developed hepatic decompensation at a median follow-up of 47.7 (IQR 23.3–72.3) months. FIB-4 was below the low cut-off (1.3 for <65 years and 2.0 for ≥65 years) for 8,582 (66.3%) patients, with an annual incidence of hepatic decompensation at 0.04% (95% CI 0.02%-0.07%). If LSM by VCTE was performed in 4,368 patients with FIB-4 above the low cut-off, 2,398 (54.9%), 498 (11.4%), 352 (8.1%), 350 (8.0%), 265 (6.1%), 182 (4.2%), and 323 (7.4%) had LSM of <8, 8–10, 10–12, 12–15, 15–20, 20–25, and ≥25 kPa, respectively. Their annual incidence (95% CI) of hepatic decompensation was: <8 kPa: 0.05% (0.02%–0.12%); 8–10 kPa: 0.14% (0.03%–0.47%); 10–12 kPa: 0.40% (0.15%–0.88%); 12–15 kPa: 0.88% (0.45%–1.53%); 15–20 kPa: 2.46% (1.56%–3.58%); 20–25 kPa: 1.77% (0.93%–2.94%); and ≥25 kPa: 4.27% (3.28%–5.35%). Aligned with Baveno VII's rule of 5, the annual incidence of hepatic decompensation exceeded 0.2% with LSM ≥10 kPa and 1% with LSM ≥15 kPa. While FIB-4 below the low cut-off consistently classified patients with a low risk of hepatic decompensation in different patient subgroups based on age, sex, body mass index (BMI), and the presence of diabetes (annual incidence ranged from 0.025% to 0.14%), heterogeneity existed on the cut-off of LSM as the second assessment. The cut-off of LSM ≥15 kPa pointed to an annual hepatic decompensation incidence of ≥1% in patients aged <65 years, females, those with BMI ≥30 kg/m^2, and those with diabetes, while a lower cut-off of 12 kPa was required in those aged ≥65 years, males, with BMI <30 kg/m^2, or without diabetes targeting an annual incidence of ≥1%.
Conclusion: FIB-4 below the low cut-off safely excludes the majority of patients at risk of hepatic decompensation. In patients with elevated FIB-4, LSM ≥15 kPa predicts an increased risk of hepatic decompensation, while a lower cut-off of LSM ≥12 kPa predicts an increased risk in those aged ≥65 years, males, with BMI <30 kg/m^2, or without diabetes.

OS-011-YI
Comparison of diagnostic accuracy and utility of 10 non-invasive tests for clinically significant liver disease among a general population with metabolic dysfunction

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Background and aims: Screening for liver health in the general population requires accurate non-invasive tests (NITs). A head-to-head comparison of NITs for early detection of clinically relevant liver disease among large general population cohorts with metabolic dysfunction – the target population for screening - has not yet been performed.
Method: Among a pooled population from the Rotterdam Study and NHANES with metabolic dysfunction aged 18–80 years, 10 NITs were investigated: AST to platelet ratio (APRI), Cirrhosis Outcome Risk Estimator (CORE), fibrosis-4 index (FIB-4), Fibrotic NASH index (FNI), FORNS, Hepamet Fibrosis Score (HFS), LiverRisk score (LRS), Metabolic dysfunction associated fibrosis score-5 (MAF-5), NAFLD fibrosis score (NFS) and steatosis associated fibrosis estimated (SAFE). The diagnostic accuracy (area under curve, AUC) was assessed for the detection of increased liver stiffness measurement (LSM ≥8 kPa, LSM ≥12 kPa), MASH (FibroScan AST score ≥0.35), advanced fibrosis (Agile 3+ ≥0.679) or cirrhosis (Agile 4 ≥0.565). Subgroup analysis included stratification by age group, level of obesity and diabetes mellitus status. Sensitivity analysis included an assessment of (1) test characteristics at the threshold corresponding with 80% sensitivity and (2) diagnostic yield when 20% of the at-risk population with the highest NIT score was selected for further work-up.
Results: We analysed 11,404 participants. MAF-5 had the highest AUC for increased LSM (LSM ≥ 8/12 kPa, AUC 0.80/0.87) and advanced fibrosis (AUC 0.90). FNI and MAF-5 were most suited for MASH (AUC 0.93 and 0.92). SAFE and NFS performed best for cirrhosis (AUC 0.92 and 0.91). At the NIT cut-off to obtain at least 80% sensitivity for LSM ≥ 8 kPa, the corresponding MAF-5 cut-off resulted in fewer referrals compared to FIB-4 (42% vs 77%) and had higher specificity (62% vs 24%); the MAF-5 was also superior for detecting LSM ≥ 12 kPa and advanced fibrosis. Age-dependent scores yielded lower sensitivity amongst younger individuals e.g., by referring 20% of the population with the highest NIT-scores, the FIB-4, SAFE, NFS, FORNS and HFS yielded < 10% sensitivity for LSM ≥ 8 kPa amongst individuals aged 18–35y while the FNI and MAF-5 obtained 40% and 71%, respectively.
Conclusion: Of the 10 investigated NITs, the MAF-5 was most suited for ruling in and ruling out all conditions except cirrhosis, for which SAFE yielded the highest accuracy. The performance of FIB-4 was overall low, implying that referral pathways for significant liver disease in low prevalence populations can be improved when more accurate NITs such as MAF-5 are employed.

OS-012
Efimosfermin alfa once monthly treatment improves collagen biomarker profiles and rapidly induces histological fibrosis regression in subjects with MASH stage F2-F3 fibrosis in a 24-week phase 2 trial

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Background and aims: Efimosfermin alfa (formerly BOS-580) is a once monthly subcutaneous administered long-acting FGF21 analogue that has demonstrated significant MASH resolution without worsening of fibrosis and fibrosis improvement ≥1 stage without worsening of MASH compared to placebo at week 24 in subjects with biopsy-confirmed stage F2/F3 fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH) in a Phase 2 trial. The effects of efimosfermin on collagen biomarkers and the changes in extracellular matrix (ECM) remodeling were also evaluated during the trial (NCT04880031).
Method: Subjects (N = 84) were randomized 1:1 to receive once monthly efimosfermin 300 mg or placebo and underwent pre- and post-treatment liver biopsy. Serum samples were collected at baseline and weeks 4, 12 and 24. Pro-C3, Pro-C6, and CTX-III collagen fragments were measured according to standard methods and analyzed for absolute and relative changes over time. To determine if there were any differences in response based on fibrosis stage, changes in these biomarkers at week 24 were compared between the total study population and those with stage F2 and F3 fibrosis at baseline. Changes in collagen biomarkers stratified by their baseline

levels were also assessed. Pro-C3/CTX-III ratio was calculated to assess the overall balance between fibrogenesis and fibrolysis.
Results: Levels of profibrogenic biomarkers Pro-C3 and Pro-C6 were significantly reduced at week 4 after treatment with once monthly efimosfermin and remained low through the end of the study. Pro-C3 declined by 44.6% at week 24, and Pro-C6 achieved a maximum reduction of 11.2% at week 4. CTX-III, a profibrolysis biomarker of ECM degradation, also demonstrated steady decline over time, with a maximum decrease of 9.2% at week 24. Efimosfermin treatment was equally effective at reducing collagen biomarkers in subjects with MASH stage F2 or F3 fibrosis. Subjects with baseline levels at or above the median value in the treatment groups generally showed a greater decline compared to those with baseline values below the median. The Pro-C3/CTX-III ratio was significantly lower at all timepoints compared to placebo, with a maximum decrease of 33.9% at week 24, suggesting an overall shift towards clearance of fibrosis in response to efimosfermin treatment.
Conclusion: Efimosfermin treatment rapidly induces fibrosis regression in subjects with MASH stage F2/F3 fibrosis as evidenced by significant improvements in ECM remodeling during a 24-week Phase 2 trial. Efimosfermin showed improvements in collagen biomarkers regardless of baseline MASH stage F2 or F3 fibrosis. Consistent with histology data, decreases in the Pro-C3/CTX-III ratio show a shift in the overall balance between fibrogenesis and fibrolysis towards fibrosis clearance in the efimosfermin treated subjects with MASH stage F2/F3 fibrosis.

OS-013

Optimizing non-invasive screening to reduce biopsy screen failure in clinical trials for metabolic dysfunction-associated steatotic liver disease

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Background and aims: The target patient population studied in pre-cirrhotic clinical trials for metabolic dysfunction-associated steatotic liver disease (MASLD) is "at-risk MASH," defined histologically as MAS score of ≥4 and fibrosis stage ≥ F2. Improving the ability to accurately pre-select cases for biopsy using non-invasive tests (NITs) could significantly reduce screen-failure rates that commonly exceed 80% of patients screened. In the multi-center LITMUS Study, we evaluated NIT-based pre-screening strategies to reduce the histological screen failure rates (SFR) in future trials.
Method: We analyzed data on 19 NITs acquired across 13 countries in Europe and the US (2018–2023). For each NIT, we identified a threshold to minimize biopsy-based screen failures when recruiting at-risk MASH patients. We split the LITMUS Study Cohort into development and evaluation sets by recruitment country. The development set was used to find thresholds for each marker corresponding to a SFR ≤33% while maximizing sensitivity. The evaluation set then assessed marker performance using these thresholds. To evaluate potential inequities, we compared true positive and false negative cases by age, gender, Body Mass Index (BMI), and diabetes status. Imbalances between these groups were quantified using standardized differences (SD), with values ≥0.2 indicating a meaningful impact on distribution.
Results: The evaluation of the diagnostic screening performance of the markers in the evaluation set, using the thresholds selected in the development set, showed that several markers could reduce histological SFR to 33% in trials. The best screening performance for at-risk MASH was observed for SomaSignal with a number needed to test (NNT) to find one true positive of four tested. This was followed by NIS2+ (NNT = 5), NIS4 (NNT = 7), FAST (NNT = 8), TSP2 (NNT = 8), and CK18-M65 (NNT = 8). All the other markers resulted in a NNT greater than 8. Using the selected thresholds to evaluate a potential imbalance in the distribution of age, gender, BMI, and diabetes between true positives and false negatives showed variable results for different markers. Notable differences (SD ≥ 0.2) for several markers were observed in the proportion of patients with type 2 diabetes.
Conclusion: NIT-based pre-screening strategies could lead to substantial efficiencies in recruitment of trials targeting at-risk MASH: reducing the number of cases biopsied to identify each eligible patient. Given the high SFR in current trials, such preselection could facilitate trial recruitment and accelerate drug development. These results also have implications to guide risk-stratification in routine clinical practice. Our analysis of demographic differences between true positives and false negatives highlighted the need to consider such factors in non-invasive screening tools.

OS-014-YI
Bariatric surgery identifies a protective amino acid in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Bariatric surgery is one of the most effective interventions to ameliorate metabolic dysfunction-associated steatotic liver disease (MASLD). However, MASLD persists in 7–12% after the surgery. To elucidate the underlying metabolism, we investigated which plasma metabolites associate with 1) severity, 2) improvement and 3) persistence of MASLD after bariatric surgery. We asked whether the identified metabolites replicate in a mouse model of MASLD. Finally, we investigated whether the identified metabolites predict incident MASLD-related clinical outcomes in the UK Biobank (UKB).
Method: We assigned 84 bariatric surgery patients (mean age 52.8 years, 70.2% women) into three groups based on baseline liver histology. The control group (n = 28) had normal livers, the MASL group (n = 26) had steatosis and the MASH group (n = 30) had steatohepatitis and/or fibrosis ≥ F2. After an average of 7.7 years, we invited the patients for a follow-up visit, where liver stiffness (LS) was measured using transient elastography. At both baseline and follow-up, 249 plasma metabolites were quantified using nuclear magnetic resonance. We fed C57BL/6J mice (n = 18) either the Gubra Amylin NASH (GAN) diet or chow for 16 weeks, after which we extracted their livers for histology and metabolomics. In the UKB (N = 101,153), we conducted multivariable Cox regressions to evaluate whether baseline plasma metabolites predict liver disease, cardiovascular disease and type 2 diabetes during a median of 13.8-year follow-up.
Results: The control, MASL and MASH groups had similar age, sex and BMI. At follow-up, body weights were decreased by 20.1% ($p < 0.0001$) similarly in all groups. Thirteen plasma metabolites distinguished the groups at baseline, of which four improved after bariatric surgery ($p < 0.05$). LS was high (>8 kPa) after bariatric surgery in 10.7% of patients. Only one of the four metabolites differentiated patients with high LS from those without ($p < 0.05$). This metabolite – an amino acid – associated inversely with hepatic and adipose tissue insulin resistance ($p < 0.05$). The concentration of the amino acid decreased by 47.3% in the GAN-fed mouse livers compared to controls and correlated inversely with severity of MASLD ($p < 0.001$). In the UKB, the amino acid protected against incident MASLD, alcohol-related liver disease, cirrhosis, and hepatocellular carcinoma (HR 0.50–0.76, $p < 0.0001$) as well as cardiovascular events (HR 0.92, $p < 0.0001$) and type 2 diabetes (HR 0.72, $p < 0.0001$).
Conclusion: We identified a distinct amino acid which: 1) associates with reduced histological severity of MASLD, 2) increases after bariatric surgery, 3) is lower in patients with high LS after bariatric surgery compared to those without, 4) decreases in a mouse model of MASLD, and 5) predicts reduced risk of MASLD-related clinical outcomes. These data suggest that this amino acid may protect against MASLD.

Public Health

OS-015
The burden of HDV chronic infection and the gaps in HDV screening across Europe: an urgent need to strengthen diagnostic strategies at pan-european level

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Background and aims: Hepatitis D virus (HDV) infection is often underdiagnosed, despite the severity of the related liver disease. Here, we investigate the rates of HDV screening and the prevalence of HDV RNA among antiHDV+ individuals in routine care across Europe and parts of the Middle East, as well as the characteristics of individuals with active HDV infection.
Method: We collected data from 15,200 HBsAg+ people attending 16 tertiary centres during 2021–2023: Northwestern Europe (NWE: UK, Switzerland, Luxembourg, Germany, Sweden; N = 3596, 23.6%), Southern Europe (SE: Spain, Italy, Slovenia, Croatia; N = 3203, 21.1%), and Eastern Europe (EE: Romania, Serbia, Slovakia; N = 4136, 27.2%) and the Middle-East (ME: Israel, Turkey; N = 4265, 28.1%).
Results: Participants were predominantly males (59.5%), HBeAg-negative (90.7%) with a median (IQR) age of 49 (39–60) years and only 28.6% received nucleos(t)ide analog treatment. The rate of HDV screening varied widely across regions: 23.9%, EE; 59.3%, NWE; 71.5%, ME; 79.1%, SE. Overall, HDV seroprevalence was 5.9% (523/8801) with the highest rate of anti-HDV positivity in EE (9.9%), followed by ME (7.0%), NWE (5.8%) and SE (3.3%). By country, anti-HDV positivity peaked in Romania (10.4%), Turkey (8.7%), Germany (7.9%) and Italy (6.8%). Compared to individuals with HBV infection, people with anti-HDV had significantly higher HBsAg (median [IQR]: 3225 [591–9784] vs 2568 [242–11163] IU/ml, p < 0.001), lower HBV-DNA (3.1 [2.2–3.9] vs 2.4 [1.6–3.7] log IU/ml, p < 0.001) and a more advanced liver disease (Ishak score >4: 25.7% vs 4.6%, HCC: 5.9% vs 1%, p < 0.001 for both). HIV coinfection was also more common (10.8% vs 4.1%, p < 0.001). Overall, among 523 individuals with anti-HDV, 82.6% were tested for HDV-RNA and 46.9% showed active HDV infection with a median (IQR) HDV-RNA of 5.7 (4.2–7.1) log IU/ml and ALT of 92 (58–171) U/L. Strikingly, large regional variations were noted in both HDV-RNA detection (ME: 39.6%, NWE: 40%, SE: 56.1% and EE: 71.6%, p = 0.0002) and HDV-RNA levels (median [IQR] log IU/ml: 6.4 [4.9–7.2] in ME, 5.4 [3.9–6.7] in EE, 5.4 [4.0–7.4] in NWE and 4.0 [3.2–4.7] in SE, p = 0.001).
Remarkably, among 344 participants tested for HDV-RNA despite anti-HDV negativity, a total of 7 (2%) from EE (N = 5), SE (N = 1) and Africa (N = 1) had detectable HDV-RNA with median levels of 5.4 (5–6) log IU/ml.
Conclusion: Despite the substantial burden of HDV infection and related liver disease, there remain significant gaps in HDV screening across Europe, particularly in specific regions. Notably, we observed a small but appreciable proportion with HDV RNA despite lack of anti-HDV, underscoring the need for greater standardisation of HDV diagnostics. Overall, the data supports the urgent need to improve and harmonize HDV screening measures and promote the access to antiviral treatment at pan-European level.

OS-016
Cirrhosis death rates are increasing rapidly among young Americans – analysis of national death certificate data

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Background and aims: In the United States (US), there has been a concerning increase in the prevalence of obesity, diabetes, unhealthy alcohol use, and incident chronic hepatitis C virus infections among younger individuals. We aimed to assess trends in cirrhosis mortality among Americans younger than 35 years old.
Method: The National Vital Statistics System provides a publicly available database of vital statistics based on death certificates from the entire US. Using this data source, we identified deaths with an underlying cause from cirrhosis (K70.3, K71.7, K72.9, K74.3, K74.4, K74.5, K74.6) or complications of cirrhosis (I85.0, I86.4, K76.6, K76.7, R18) among individuals younger than 35 from 1999–2022. We extracted the number of deaths and calculated annual mortality rates overall and stratified by gender. As a comparison group, we assessed deaths among individuals ≥65 years. We additionally examined trends of cirrhosis deaths with a contributing cause from alcohol-associated liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD) and viral hepatitis. Using the NCI Joinpoint program, we assessed statistically significant changes in average percentage change (APC) and the overall average annual percentage change (AAPC) in death rates.
Results: The median crude mortality rate from 1999–2022 was significantly higher in individuals ≥65 years (median 31.7 per 100,000 population) compared to those <35 (median 0.3 per 100,000). The average annual percentage change in death rates was significantly higher in individuals <35 years (AAPC 5.2, 95% CI 4.5, 5.9) vs ≥65 years (AAPC 0.7, 95% CI 0.6, 0.8). Joinpoint analysis demonstrate that, among individuals <35 years, death rates were stable from 1999–2008 (APC −1.7, 95% CI −6.0, 0.3), increased from 2008–2018 (APC 7.0, 95% CI 3.5, 9.4), and further accelerated from 2018–2022 (APC 17.3, 95% CI 12.5, 26.6). Recent increases were less pronounced among those ≥65 years (from 2019–2022 APC 4.4, 95% CI 2.9, 6.3). Among those younger than 35 years, the AAPC was lower among females (APC 4.8, 95% CI 4.1, 5.6) compared to males (APC 5.3, 95% CI 4.6, 6.1), but this difference was not statistically significant. The Joinpoint analysis demonstrated a steady, statistically significant increase in death rate APC in younger females from 2011–2022 (APC 10.7, 95% CI 9.0, 13.2) while males had a significant increase from 2006–2018 (APC 5.7, 95% CI 3.6,8.3) and further acceleration from 2018–2022 (APC 20.6, 95% CI 15.1, 30.2). Deaths from ALD-associated cirrhosis among individuals age <35 years increased from 1999–2022

(AAPC 10.9, 95% CI 8.9, 13.6). The joinpoint analysis could not be performed for MASLD or viral hepatitis due to small numbers.
Conclusion: Cirrhosis death rates have increased more rapidly among younger individuals and these increases accelerated from 2018–2022, particularly among younger males. Increased alcohol use in recent years has likely contributed to recent rises in cirrhosis death rates among Americans under age 35.

OS-017

Long-term air-pollution exposure is associated with metabolic-dysfunction steatotic liver disease and liver fibrosis in the general population

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Background and aims: Chronic liver disease has emerged as a critical global health challenge, primarily driven by the obesity epidemic. Air pollution, the leading contributor to the global burden of disease, has been linked to metabolic dysfunction-associated steatotic liver disease (MASLD). This study examines the associations between different air pollutants, MASLD, and liver fibrosis in the general population.
Method: This study is embedded within The Rotterdam Study, an ongoing prospective cohort study in a suburban area of the city of Rotterdam, The Netherlands. We included participants with available ultrasound and reliable liver stiffness measurement (LSM) data. Exclusion criteria were viral hepatitis, excessive alcohol consumption (≥50 grams daily for females and ≥60 grams daily for males) and prevalent heart failure. MASLD was defined as steatosis with at least one metabolic dysfunction according to clinical practice guidelines, and liver fibrosis was defined as an LSM ≥8 kPa. Annual air pollutant concentrations of PM2.5, NO_2, ozone, and black carbon were determined at participants' residential addresses using land-use regression models. Average pollutant levels for the previous 1, 5, and 10 years were calculated for each participant. Cross-sectional associations between each pollutant and liver outcomes were assessed using logistic regression models, adjusted for age, age², sex, smoking, alcohol consumption, waist circumference, insulin resistance, and education level.
Results: We analyzed data from 4,185 participants (median age: 66 years [IQR 61–73], 44% male). The prevalence of MASLD was 34% (n = 1,409), while liver fibrosis was present in 5.7% (n = 239) of participants. Risk of MASLD was associated with black carbon (aOR 1.92; 95%CI 1.26–2.92), NO_2 (aOR 1.03; 95%CI 1.01–1.05), and PM2.5 (aOR 1.12; 95%CI 1.02–1.23) for up to 5 years of exposure. Significant associations with liver fibrosis were observed for PM2.5 (aOR 1.19; 95%CI 1.00–1.41) at 5 years and black carbon (aOR 2.31; 95%CI 1.10–5.27) at 10 years of exposure. No significant associations were found for ozone with MASLD or liver fibrosis at any exposure duration, neither for annual means or during warm seasons.
Conclusion: In this population-based study, we demonstrated that long-term exposure to air pollutants may increase the risk of liver disease. Specifically, NO_2, PM2.5, and black carbon at 5 years, were associated with MASLD, but only PM2.5 and black carbon were linked to the long-term risk of liver fibrosis. These results suggest that air pollution control policies may play a role in mitigating chronic liver disease risks at the population level.

OS-018

Impact of weekend warrior physical activity on all-cause mortality in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Recent EASL-EASD-EASO guidelines on metabolic dysfunction-associated steatotic liver disease (MASLD) recommend more than 150 minutes of moderate to vigorous physical activity (MVPA) per week. However, it is unclear if concentrating MVPA into 1–2 days per week ("weekend warrior" pattern) offers comparable benefits as spreading activity throughout the week. We aimed to evaluate whether the weekend warrior activity pattern is associated with lower odds of MASLD and reduced mortality in MASLD patients.
Method: We conducted cross-sectional and prospective analyses of data from NHANES (2003–2006) linked to mortality records from the National Death Index (through 2019). Using accelerometer data, participants were classified into 3 groups: weekend warrior (>150 minutes of MVPA with ≥50% of total MVPA accomplished over 1–2 days), active (>150 minutes of MVPA, not meeting weekend warrior criteria), and inactive (≤150 minutes of MVPA weekly). U.S. Fatty Liver Index (FLI) ≥30 with at least one cardiometabolic risk without other liver disease and excessive alcohol use was defined as probable MASLD. Logistic regression and Cox models were adjusted for age, sex, race, income, and total amount of physical activity.
Results: Among 2,490 participants (mean age: 48.5 years; 47.4% male; 73.4% White; 55.8% with obesity), 32.3% had MASLD, 27.4% and 14.1% were classified as active and weekend warriors, respectively. Both the weekend warrior and active groups had significantly lower odds of MASLD [Odds Ratio (OR): 0.34 (95% CI: 0.24–0.50) and OR: 0.48 (95% CI: 0.37–0.63)], type 2 diabetes [OR: 0.43 (95% CI: 0.21–0.90) and OR: 0.34 (95% CI: 0.19–0.61)], and obesity [OR: 0.36 (95% CI: 0.24–0.55) and OR: 0.48 (95% CI: 0.37–0.62)], compared to the inactive group. Among individuals with MASLD, after a median follow-up of 14.3 years (11,242 person-years), mortality rates (per 1,000 person-years) were highest in the inactive group (27.69), compared to active (6.68) and weekend warrior (6.66) groups. Adjusted Cox models demonstrated significantly lower all-cause mortality in the active [Hazard Ratio (HR): 0.48 (95% CI: 0.23–0.98)] and the weekend warrior group [HR: 0.34 (95% CI: 0.13–0.91)] compared to the inactive group ($p < 0.05$).
Conclusion: The weekend warrior pattern of physical activity is equally protective against MASLD and all-cause mortality as the other active pattern. This study supports recommendations for meeting physical activity guidelines to improve long-term outcomes in MASLD and highlights the potential to personalize training programs to fit individual schedules and lifestyles.

OS-019

A large multicentre hepatitis B cohort study in the United Kingdom highlights high rates of comorbidity associated with liver disease outcomes

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Background and aims: The chronic hepatitis B (CHB) population is ageing in some countries, with a rising burden of comorbidities reported from multiple settings. This study aims to assess the prevalence of comorbidities in a UK HBV cohort and their impact on liver disease outcomes including development of cirrhosis, decompensation, and hepatocellular carcinoma (HCC).

Method: We analysed an ethnically diverse cohort of >23,800 people living with HBV from nine secondary care centres in England, established by the National Institute for Health and Care Research (NIHR) Health Informatics Collaborative using electronic health records. Comorbidities were identified by ICD-10 codes, and associations with liver-related outcomes were evaluated using univariable and multivariable logistic regression models, adjusting for age, sex, ethnicity, and antiviral treatment.

Results: Among 14,149 adults eligible for analysis (median age: 45 years [IQR: 34–58]; 55.2% male), the most prevalent comorbidities were hypertension (HTN, 27.8%), diabetes mellitus (DM, 16.6%), cardiovascular disease (CVD, 16.0%), chronic kidney disease (14.9%), non-liver malignancy (12.7%), chronic pulmonary disease (12.3%), hyperlipidaemia (11.1%), obesity (10.7%), depression (7.8%), hepatic steatosis (7.0%), HCV coinfection (6.7%), HIV coinfection (3.8%), rheumatic disease (3.3%), alcohol-related liver disease (ArLD, 3.2%), and peptic ulcer disease (PUD, 2.8%). Moderate/severe liver disease and complications were observed in 27.0% of patients, including fibrosis/cirrhosis (10.2%), ascites (5.1%), portal hypertension (4.6%), HCC (4.1%), and varices (4.0%). Males had higher rates of comorbidities and liver complications than females, except for bone-related conditions (all $p < 0.001$). Fibrosis/cirrhosis was significantly associated with HCV coinfection, ArLD, PUD, and hepatic steatosis, with odds ratios (ORs) (95% CIs) of 4.6 (3.9–5.4), 3.0 (2.3–3.7), 2.8 (2.2–3.6), and 2.2 (1.9–2.7), respectively, as well as metabolic conditions including HTN, DM, and obesity (ORs ranging from 1.3 to 1.7). ArLD (OR 18.6, 95%CI 14.8–23.4), PUD (OR 4.0, 95%CI 3.1–5.1), and HCV coinfection (OR 3.1, 95%CI 2.5–3.7) were linked to complications of ascites, varices, or portal hypertension, with HTN, DM, CVD, hepatic steatosis, and obesity also significantly associated (ORs ranging from 1.2 to 1.7). HCC was significantly associated with HCV coinfection, ArLD, obesity, HTN, and DM, with ORs (95% CIs) of 4.4 (3.5–5.6), 3.6 (2.6–4.9), 2.0 (1.4–2.6), 1.5 (1.2–1.6), and 1.4 (1.1–1.7), respectively.

Conclusion: This large multicentre study highlights the prevalence of comorbidities in HBV and their association with liver disease outcomes. The findings emphasise the need for holistic monitoring and intervention strategies, particularly the management of metabolic syndrome and hepatic steatosis in CHB due to their high prevalence and impact.

Rare Liver Diseases

OS-020

Reviewing the utility of genetic cholestasis testing in adults with cholestatic liver disease

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Background and aims: Cholestatic liver diseases are a wide range of pathologies involving an impairment in the formation or secretion of bile. The more common adult cholestatic diseases are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), however a significant portion of patients have an undefined cholestatic disease. In this group, the role of genetic mutations in genes previously thought to be autosomal recessive is being increasingly recognized in the last few years, including but not limited to *ABCB4*, *ABCB11* and

ATP8B1. We sought to review the genetic cholestasis testing experience in our cholestatic liver disease program.
Method: Clinical, demographic and laboratory data were collected retrospectively from patients' medical records attending a tertiary liver programme that had results from a genetic cholestasis panel between 2016–2024. Genetic cholestasis panels were performed by Prevention Genetics or Eurofins Clinical Diagnostics EGL Genetics, with variant screening in a total of 77 different genes.
Results: A total of 166 patients underwent genetic cholestasis testing, with 82 patients (49.4%) found to have variants likely associated with the primary cause of disease. Pathogenic sequence variants were found in *ABCB4* (13.9%), *ATP8B1* (2.4%), and *ABCB11* (0.6%). Additional pathogenic variants were identified in *CFTR* (12.7%), *PKHD1* (4.8%), *HNF1B* (1.8%) and *NOTCH* (1.2%). Of the 82 patients with identified pathogenic variants, 35.4% were tested due to a cholestatic abnormality after ruling out PBC and PSC, 18.3% had cholestatic abnormalities with sclerosing cholangitis visible on MRI, and 14.6% had personal history of intrahepatic cholestasis of pregnancy (ICP). Patients with identified pathogenic variants were 54.3% female, with an average age of 41.6 years at the time of genetic testing; only 16 (19.5%) had a family history of liver disease. At last follow-up, 49 patients (59.8%) were treated with UDCA, and 19 (23%) required an anti-pruritic agent. While most patients had a normal biliary tree or non-specific findings on MRI, 19 patients (23%) had sclerosing cholangitis. Twenty-six patients (31.7%) had undergone cholecystectomy. Ten patients (12%) had evidence of intrahepatic stones, 6 with ABCB4 mutations and 4 with CFTR mutations. Interestingly, 40 patients (49%) had positive immune serology (mostly anti-nuclear antibody or smooth-muscle antibody).
Conclusion: The yield of genetic testing in the appropriate clinical setting is high, reaching approximately 50%. Findings of sclerosing cholangitis on imaging do not preclude genetic mutations and should be considered in the absence of inflammatory bowel disease. Interpretation of the results is still unclear in some of the cases, and further research is required to better understand the clinical impact of various genetic mutations.

OS-021
Fontan-associated liver disease: clinical and epidemiological impact on a large cohort in the UK, a retrospective multicenter study

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Background and aims: Fontan-Associated Liver Disease (FALD) is the consequence of liver exposure to the Fontan circulation. As surgical outcomes improve, FALD prevalence is rising. While paediatric FALD onset is increasingly recognized, data remain limited. This study aims to assess FALD prevalence, its impact on survival, and indentify risk factors for disease severity.
Method: This retrospective cohort study included three UK centers: Evelina Children's Hospital, Great Ormond Street Hospital, and King's College Hospital. Patients with univentricular heart who completed the Fontan sequence between 1987 and 2024 were enrolled. MELD-XI and VAST scores assessed the disease severity.
Results: A total of 729 patients underwent Fontan surgery at a median age of 3.9 years (IQR 3.2–4.8). Liver assessment was performed in 390 patients (53.5%). The median follow-up time was 12.8 years (IQR 9.4–18), and the median age was 13.1 years (IQR 8.2–18.06). Liver assessment rates post-Fontan were 32.4% within 5 years, 44.2% at 5–10 years, 73.2% at 10–15 years, rising to 100% beyond 25 years. FALD prevalence increased over time: 10.9% at 0–5 years, 23.3% at 5–10 years, 63.7% at 10–15 years, 82.6% at 15–20 years, 91% at 20–25 years, and 100% at 25–40 years. Radiological findings included hepatomegaly (23.2%), caudate hypertrophy (17.8%), heterogeneous (32.2%) and coarse (44.6%) parenchyma, FNH-like nodules (27.5%), cirrhosis (40.9%), and splenomegaly (28.2%). Hepatocellular carcinoma prevalence was 0.14%. Cirrhosis was present in 18.2% of liver imaging within 5 years, 29.9% at 5–10 years, 37.7% at 10–15 years, and 83.3% beyond 25 years. Liver stiffness (n = 127) showed no significant change over time nor correlation with MELD-XI or VAST. A positive correlation was found between follow-up time and higher VAST and MELD-XI scores ($p < 0.0005$ and 0.0001), both significantly rising from the 10–15 years interval ($p < 0.001$). Older age at Fontan, cardiac isomerism, and male sex correlated with MELD-XI ($p = 0.003$, 0.004 and 0.036). Univariate Cox regression identified liver injury prior to Fontan surgery (HR 3.74, $p = 0.041$), VAST (HR 2.93, $p < 0.0005$) and MELD-XI (HR 1.17, $p = 0.015$) as mortality predictors. Multivariable analysis confirmed VAST (HR 3.15, $p < 0.0005$) and MELD-XI (HR 1.21, $p = 0.013$) independent role. ROC analysis identified VAST ≥ 1 (AUC 0.84) and MELDXI ≥ 10 (AUC 0.92) as mortality predictors.
Conclusion: FALD results in advanced liver disease in nearly all patients over time. MELD-XI and VAST scores predict mortality in FALD. Pre-Fontan liver injury is associated with increased mortality. Liver stiffness is not a reliable marker of FALD progression. Although disease severity increases significantly in the 10–15 years post-Fontan interval, a notable subset of patients develops FALD and cirrhosis earlier, when liver assessment rates are low. We therefore advocate for the initiation of liver assessments in all patients within the first decade post-Fontan to enable timely monitoring and management of hepatic complications.

OS-022
Patient-level analysis of intrahepatic z-alpha-1 antitrypsin burden in patients with alpha-1 antitrypsin deficiency-associated liver disease following fazirsiran treatment

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease characterized by Z-alpha-1 antitrypsin (Z-AAT) aggregates in the liver, which may lead to AATD-associated liver disease (AATD-LD). Periodic Acid–Schiff staining with diastase (PAS-D) and liquid chromatography–mass spectrometry (LC–MS) are methods to assess intrahepatic Z-AAT burden, which is a biomarker of AATD-LD. This study aimed to leverage data from two phase 2 trials of fazirsiran (an investigational small interfering RNA therapy for AATD-LD) to understand the onset and magnitude of changes in PAS-D and LC–MS-based Z-AAT burden in patients with AATD-LD, which has not previously been fully characterized.
Method: Baseline and post-baseline (range 24–96 weeks) liver biopsy samples from patients enrolled in the phase 2 AROAAT-2001 (NCT03945292)/-2002 (NCT03946449) trials who received fazirsiran or placebo were included. PAS-D composite score (range: 0–9) and its histologic components were centrally read and adjudicated by three histopathologists. Intrahepatic Z-AAT (total, soluble and insoluble) protein burden was analysed by LC–MS. Further methodological details are described in Strnad *et al. NEJM*, 2022 and Clark *et al. Gastroenterology*, 2024.

Results: Of 41 patients from the AROAAT-2001 (n = 25)/-2002 (n = 16) trials, baseline median (interquartile range) PAS-D composite score was 8.0 (5.0, 8.0), total intrahepatic Z-AAT was 39.4 (26.4, 83.8) nmol/g, soluble intrahepatic Z-AAT was 20.8 (15.9, 28.6) nmol/g and insoluble intrahepatic Z-AAT was 18.4 (8.2, 53.1) nmol/g. Compared with baseline, all patients treated with fazirsiran (n = 32) had markedly reduced intrahepatic Z-AAT burden when measured using PAS-D and LC–MS; reductions occurred as early as Week 24 and were sustained to Week 96. In five patients with two available post-fazirsiran liver-biopsy assessments, there were continuous and sustained reductions in PAS-D score and LC–MS-based total intrahepatic Z-AAT burden; in patients who received placebo (n = 9), intrahepatic Z-AAT burden was largely unchanged after treatment. Overall, 15/19 (78.9%) and 1/9 (11.1%) patients treated with fazirsiran 200 mg or placebo, respectively, had a ≥ 4-point reduction in PAS-D composite score. All patients treated with fazirsiran 200 mg, and no patients treated with placebo, had a ≥ 70% reduction in LC–MS-based total intrahepatic Z-AAT protein burden.
Conclusion: A robust and sustained reduction of intrahepatic Z-AAT burden in patients with AATD-LD following fazirsiran treatment was demonstrated using two independent analytical approaches (PAS-D and LC–MS). Current findings will be validated in an ongoing phase 3 trial (NCT05677971) in which the effect of fazirsiran on the reversal of liver fibrosis in patients with AATD-LD will be evaluated.
Study/writing funding: Takeda Development Center Americas, Inc.

OS-023

Single-cell spatial transcriptomic map of biliary atresia

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Background and aims: Biliary atresia is characterised by neonatal obliteration of the extrahepatic biliary tree. 50% of children require liver transplantation at under 5 years, despite Kasai portoenterostomy. Multiple aetiological factors are implicated in the initial hit to the biliary system (e.g. polygenic, viral). In the liver, cholangiocytes proliferate in an fibroinflammatory niche known as the 'ductular reaction'. These fibroinflammatory foci may expand to eventually result in end-stage cirrhosis. The epithelial-mesenchymal-immune interactions governing regulation of fibroinflammation across the disease course are not known. It is not clear why some children need early transplant 'rapid progressors' and some remain stable long-term. Here, our overall aim was to understand the interactions governing fibroinflammation across the spectrum of biliary atresia at single-cell resolution. Specifically, we aimed to identify differences at the time of Kasai that predict need for early transplantation.
Method: We performed CosMx single-cell transcriptomic profiling (1000 genes) on liver at time of Kasai from 4 patients with non-syndromic biliary atresia. 2 patients were 'rapid progressors' - transplant under 2 years old; and 2 were 'slow progressors' requiring transplant at 12–15 years old. All patients had moderate (3/6) fibrosis at the time of Kasai. CellChat was used to calculate cell-cell interaction signalling networks. Markers were replicated using a meta-analysis of RNA sequencing data from 182 BA cases, 92 disease-free controls, and 19 cholestatic non-BA controls. Results were validated using multiplex immunofluorescence.
Results: Single-cell spatial profiling identified 269,825 individual cells, after quality-control. Liver at the time of Kasai demonstrated proliferative cholangiocytes, surrounded by portal fibroblasts (expressing IGFBP7, CXCL12, and CD74), accompanied by SPP1 +TREM2+GPNMB+ macrophages. 'Rapid progressors' had more GPNMB+ macrophages, monocytes, and fibroblasts but fewer cholangiocytes. Sinusoidal endothelia from rapid progressors had higher expression of ICAM1 (51% vs. 29%, p.adj= 9.7 × 10–96) and CCL2 (43% vs. 24%, p.adj= 6.2 × 10–78). Cholangiocytes from rapid progressors had higher ANKRD1 expression (36% vs. 21%, p.adj= 3.4 × 10–131), which is down-stream of the pro-fibrotic transcription factor YAP. In addition, CellChat found SPP1-ITGAV/ITGB1, MIF-CD74, CXCL12-CD44/ACKR3, to be key cell- communication factors in the fibroinflammatory niche at Kasai.
Conclusion: At time of Kasai, patients who would go on to need early transplant was predicted by presence of a pro-inflammatory endothelial phenotype with increased monocytes and fewer, but dysfunctional cholangiocytes.

OS-024

Proteomic newborn screening for Wilson disease in Washington state

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Background and aims: Wilson disease (WD) is an autosomal recessive condition caused by mutations in the *ATP7B* gene, which encodes the copper-transporting ATPase 2 that plays a crucial role in cellular copper homeostasis. The prevalence is widely accepted as 1 in 30,000 individuals in most populations with a carrier frequency of 1 in 90, although variations in the estimation have been reported. While early diagnosis with effective treatment is critical to preventing long-term complications such as liver cirrhosis and permanent brain damages, the wide array of clinical phenotypes and variations of manifestations among patients present significant challenges for early diagnosis. We recently demonstrated that quantification of ATP7B peptide in the dried blood spots (DBS) using LC-MS/MS is a promising methodology for newborn screening (NBS). NBS is considered the most successful public health program to identify infants with treatable disorders for early intervention with favorable outcomes.
Method: A novel proteomic-based multiplex assay to detect two surrogate peptides of ATP7B protein from DBS using high-throughput LC-MS/MS was developed and validated for analytical and clinical precision following the Clinical and Laboratory Standards Institute (CLSI) guidelines. Initial diagnostic cutoffs were set by running 1,056 newborn samples. Additionally, 30,024 newborn samples have been screened using the multiplex analysis from 2022 to 2024. 57 samples with peptide concentrations above but near the cutoff were sent out for sequencing as part of a false negative study to determine if borderline samples were being missed as negative.
Results: The analytical validation study results show that LOB, LOD and LOQ were lower than the diagnostic cutoffs. The reproducibility study results show that our immuno-SRM assay can produce consistent results over days or between different users/instruments. The assay was successfully validated by detecting all 32 genetically confirmed true WD positive blinded samples from a total of 3,294 newborn samples across 3 study sites. One true presumptive positive case of WD has been found along with three false positive cases from the pilot study samples. The positive predictive value was estimated to be 25%, and the false positive rate to be 0.001%. No false negatives were detected from the 57 borderline samples except two samples, each with one pathogenic and one variant of uncertain significance.
Conclusion: Our novel proteomic assay has the sensitivity and precision required to quantify low abundance proteins from dried blood spots. The assay also yields reproducible results in different test sites, making it the appropriate screening candidate for countries across the globe. The pilot study demonstrates the feasibility and

effectiveness of utilizing the proteomic assay for newborn screening of Wilson disease.

Viral hepatitis Basic Science and Liver Immunology

OS-025
Characterizing the molecular mechanism of hepatitis B virus cccDNA loss following mitosis

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Background and aims: The persistence of covalently closed circular DNA (cccDNA) in infected hepatocytes represents the primary barrier to hepatitis B virus (HBV) eradication. Effective elimination of cccDNA is therefore critical for achieving an HBV cure. Recent findings suggest that the proliferation of HBV-infected hepatocytes may lead to cccDNA depletion, but the underlying mechanism remains unclear. We hypothesize that during mitosis, the breakdown of the nuclear envelope exposes cccDNA to cytoplasmic components, leading to its degradation.
Method: Cell division was induced in HBV-infected cells and cells transfected with HBVcircle, a cccDNA mimic, by passaging the cells. cccDNA loss was monitored, and the effect of cell cycle inhibitors on this process was assessed. HBVcircle was incubated with nuclear or cytoplasmic lysates to identify components responsible for cccDNA degradation. The degradation activity was further characterized using heat inactivation, proteinase K, EDTA, EGTA, and nuclease inhibitors. LC-MS analysis was conducted to identify candidate nucleases. siRNA screening and CRISPR-mediated knockout were employed to validate the involvement of a specific cytoplasmic DNA nuclease (CDN). Functional studies included prokaryotic expression and purification of CDN and its overexpression in HBV-infected cells with a nuclear localization sequence (NLS).
Results: cccDNA loss was observed following cell division in both HBV-infected and HBVcircle-transfected cells, and this phenomenon was reversed by cell cycle inhibitors. Incubation of HBVcircle with cytoplasmic lysates, but not nuclear lysates, resulted in its degradation. This activity required metal-ion-dependent nucleases, as it was inhibited by heat inactivation, proteinase K, EDTA, EGTA, and nuclease inhibitors. LC-MS identified nine potential nucleases, and siRNA screening pinpointed one specific CDN. CRISPR-mediated knockout of this gene rescued cccDNA levels in HBV-infected cells following cell division. The purified CDN degraded HBVcircle in a dose-dependent manner in vitro. Notably, overexpressing CDN fused with an NLS in HBV-infected cells led to significant cccDNA loss.
Conclusion: This study uncovers a novel mechanism by which cccDNA is degraded during mitosis via exposure to a cytoplasmic DNA nuclease. The findings highlight a potential therapeutic strategy to target cccDNA for HBV cure by leveraging this mechanism.

OS-026
CD4+T cells license Kupffer cells to produce IL-27 and reverse the CD8+T cell dysfunction induced by hepatocellular priming

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Background and aims: Efficient priming of $CD8^+$T cell responses against non-cytolytic pathogens like HBV is believed to rely on $CD4^+$T cell help within secondary lymphoid organs. This hypothesis is supported by an observation in experimentally infected chimpanzees, where $CD4^+$T cell depletion prior infection prevents $CD8^+$T cell priming and leads to persistent infection. However, where when and how this issue occurs has never been described or mechanistically elucidated.
Method: We took advantage of unique HBV transgenic mouse models, in which we have demonstrated that adoptive transferred HBV-specific $CD8^+$T cells that recognize hepatocellular viral antigens undergo activation and proliferation but fail to differentiate into antiviral effector cells. To understand the extent to which antigen-specific $CD4^+$T cells help intrahepatic $CD8^+$T cell differentiation, we generated HBV-specific $CD4^+$ TCR transgenic mice (Env126), where all $CD4^+$T cells recognize an I-Ab-restricted T cell epitope of the HBV envelope protein.
Results: Here, we show that the adoptive transfer of T_{H1}-like Env126 effector $CD4^+$T cells in HBV-transgenic mice counteracts the $CD8^+$T cell dysfunction induced by hepatocellular priming, boosts their proliferation and stimulates their production of IFN-γ, TNF-α, and Granzyme-B within the liver. This enhances $CD8^+$T cell-mediated liver immunopathology and suppresses viral replication. Against what the immunological dogma would dictate, our study shows that $CD4^+$T cell help to $CD8^+$T cells occurs locally within the liver, bypassing secondary lymphoid organs. Intriguingly, dendritic cells are dispensable for the observed effects and instead, Kupffer cells (KCs) show enhanced cross-presenting capacity upon Env126 effector $CD4^+$T transfer, emerging as the critical cellular platform for intrahepatic T-cell cooperation. With multiphoton intravital microscopy we indeed reveal that HBV-specific $CD4^+$ and $CD8^+$T cells simultaneously interact with KCs within the liver, and as such, the restorative process of Env126T effector $CD4^+$T cells help is impeded upon KCs depletion. Mechanistically, $CD4^+$T cells engage KCs via CD40-CD40L interactions, leading to the production of IL-12 and IL-27. IL-12 promotes $CD4^+$T cell expansion, whereas IL-27 reinvigorate the $CD8^+$T cell response. Finally, we show that exogenous administration of IL-27 reinvigorates HBV-specific $CD8^+$T cell responses in both HBV-transgenic mice and human T cells isolated from chronic HBV patients.
Conclusion: Our findings reveal a novel mechanism of $CD4^+$T cell help to $CD8^+$T cells that occurs outside secondary lymphoid organs, specifically in the liver, and involves antigen-presenting cells other than conventional dendritic cells. The described cellular and molecular mechanisms offer new insights for immunotherapeutic strategies against chronic hepatic infections and their life-threatening complications.

OS-027-YI
A human cirrhosis single-cell atlas identifies a pro-inflammatory subpopulation of scar-associated macrophages as a therapeutic target for liver fibrosis

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Background and aims: Single-cell RNA sequencing (scRNAseq) is a powerful tool for exploring the cellular mechanisms driving fibrosis in chronic liver disease (CLD). However, the use of small sample sizes in individual scRNAseq studies has hindered comprehensive cellular annotation and accurate definition of pathogenic cell types across multiple patients. To address this, we aimed to develop a human cirrhosis cellular atlas, utilising this resource to better define the specific macrophage subtypes which promote liver inflammation and fibrosis and assess how they could be targeted therapeutically.
Method: Raw human liver scRNAseq data was processed from 81 patients (42 healthy and 39 CLD). Following quality control, 843,457 high quality cells were analysed in depth. The Seurat V5 package was used for integration, clustering and marker gene detection. Iterative subclustering and manual cell type annotation was performed on each cell lineage. Differential abundance and expression analyses were conducted using Milo and MAST respectively. Ligand-receptor interactions between mononuclear phagocytes (MPs) and mesenchymal cells were assessed using CellChat. Validation of human scRNAseq data was performed by multiplex immunofluorescence (IF) and scRNAseq of mouse immune cells from the carbon tetrachloride (CCl_4) model of CLD.
Results: In total we annotated 127 cell states in the cirrhosis atlas, encompassing all major cell lineages and including rare cell types such as neurons, basophils, mast cells and haematopoietic progenitors. Focussing on MPs, analysis of 81,577 cells revealed 14 transcriptionally distinct clusters. Notably, the large cell and patient number enabled the distinction of 2 subpopulations of *TREM2+ CD9+* scar-associated macrophages (SAMacs), termed SAMac1 and SAMac2, both of which expanded significantly in patients with cirrhosis irrespective of sex or CLD aetiology. Differential expression analysis demonstrated that SAMac1 was enriched in anti-inflammatory mediators, whilst SAMac2 expressed higher levels of pro-fibrotic and pro-inflammatory cytokines such as *IL1B* and *IL18* and was predicted to interact with scar-producing myofibroblasts. IF staining confirmed the co-existence of SAMac1 and 2 in the human fibrotic niche, whilst analysis of mouse scRNAseq data demonstrated corollary pro- and anti-inflammatory SAMac subpopulations. Ongoing work aims to modulate targets specifically expressed by the pro-inflammatory SAMac2 subpopulation.
Conclusion: Our human cirrhosis cell atlas demonstrated previously undescribed liver cellular heterogeneity, including the identification of a novel subtype of SAMacs which expands in cirrhosis, has pro-inflammatory and pro-fibrotic properties and is recapitulated in mouse CLD. Specific targeting of this population may therefore inhibit liver fibrogenesis without disrupting anti-inflammatory SAMac properties.

OS-028-YI
In vivo stimulation of 4-1BB signaling enhances the efficacy of therapeutic vaccination in high-titer hepatitis B virus carrier mice

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Background and aims: Despite the availability of effective prophylactic vaccines, nearly 4% of the world population is chronically infected with the hepatitis B virus (HBV). Chronic HBV infection is characterized by a lack of neutralizing antibodies and scarce, partially dysfunctional HBV-specific T cells. Restoring virus-specific immune responses by therapeutic vaccination represents a promising treatment option. Our clinical candidate protein-prime/MVA-boost therapeutic vaccine, *TherVacB*, proved efficacious in preclinical mouse models with low-to-intermediate HBV levels; however, in high-titer mice, the vaccine failed to eliminate persistent HBV infection. This study aimed to understand the factors contributing to T-cell responsiveness by comparatively characterizing *TherVacB*-elicited liver-associated CD8 T cells in low and high-titer HBV carrier mice to eventually find potential therapeutic targets to overcome T-cell dysfunctionality in high-titer HBV carriers.
Method: We established low and high levels of persistent HBV infection in C57BL/6J mice using AAV-HBV and then applied *TherVacB*. We isolated liver-associated vaccine-elicited core-specific CD8 T cells at multiple time points and performed comparative transcriptomic and phenotypic analyses in low and high-titer HBV carrier mice.
Results: Transcriptome analysis revealed that *TherVacB* induced comparable numbers of effector CD8 T cells in low and high-titer mice; however, their functionality and long-term survival were determined by hepatic HBV levels. Following the clearance of the infection, long-lasting effector and tissue-resident memory T-cell subsets were established in low-titer mice. In high-titer mice, vaccine-induced CD8 T cells continuously expressed high levels of co-stimulatory molecule 4-1BB together with the well-known exhaustion-related co-inhibitory molecules. Thus, we wondered whether combining *TherVacB* with 4-1BB targeting monoclonal antibodies (mAb) could improve the antiviral efficacy of therapeutic vaccination in high-level HBV infection. We immunized high-titer HBV carrier mice with *TherVacB* with or without *in vivo* 4-1BB mAb treatment and compared HBV-specific immune responses and infection parameters. Co-administration of 4-1BB agonistic mAbs resulted in elevated cytokine production in vaccine-induced CD8 T cells as compared to only vaccinated mice. In addition, combinatorial treatment with 4-1BB mAbs resulted in a significant reduction of serum HBeAg and HBsAg levels accompanied by mild, transient ALT flares and efficient elimination of HBV-infected hepatocytes.
Conclusion: Combining *TherVacB* with 4-1BB stimulation improved HBV-specific CD8 T-cell functionality and enhanced the antiviral efficacy of *TherVacB*. This demonstrates that 4-1BB represents a promising therapeutic target to counteract T-cell dysfunctionality in high-titer HBV carriers.

OS-029-YI
Spatial profiling of HBV and HDV infection in human liver samples

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Background and aims: Chronic hepatitis D is the most severe form of chronic liver disease, with a rapid progression to cirrhosis and hepatocellular carcinoma. Understanding the intricate relationships between HDV, HBV, and liver cells, as well as the host immune response is essential for developing effective prevention and treatment strategies. Our study aimed to characterize the transcriptional landscape of the liver in HBV and HDV infected patients.
Method: We included 5 HBV/HDV coinfected patients (anti-HDV positive), 3 with detectable HDV-RNA (HDV+) and 2 with undetectable HDV-RNA (HDV-), and 3 HBV infected patients (as controls). We used dual chromogenic immunostaining to visualize HBsAg and HDAg in the liver (Bond RX, Leica). Spatial transcriptomics was applied to FFPE liver samples using CosMx Spatial Molecular Imaging (1000-plex RNA, Nanostring). Cell segmentation was performed using morphology visualization markers, including B2M/CD298, PanCK, CD45, CD68 and DAPI.
Results: The analysis of viral antigens revealed that in samples from HDV/HBV coinfected patients, most hepatocytes expressed high levels of HBsAg, but co-expression with HDAg was rare. Specifically, HDAg was restricted to areas with low or undetectable levels of HBsAg. By combining single-cell RNA sequencing (scRNA-seq) data with spatial transcriptomics, we identified over 30 cell types encompassing major populations of the immune system, as well as various subpopulations of hepatocytes, cholangiocytes, and Kupffer cells. Hepatocytes from HDV/HBV coinfected patients exhibited differential gene expression compared to HBV infected patients, characterized by the overexpression of more than 180 genes. Most of these genes were associated with signaling pathways related to the inflammatory response (IL6-JAK-STAT, TNF-NFκB), innate immunity (IFN response), and adaptive immunity (IL2-STAT5). These findings were also confirmed at an intra-patient analysis, where hepatocytes in areas expressing both HDAg and HBsAg showed greater activation than those expressing only HBsAg. Furthermore, in HBV infected patients, HBsAg expression was not only associated with the activation of pro-inflammatory pathways but also with pathways linked to cancer development, such as epithelial-mesenchymal transition.
Conclusion: The expression of viral antigens in the liver is associated with alterations in the host's transcriptome, highlighting the dynamic interplay between viral infection and host responses. Spatial transcriptomics provides a detailed view of the hepatic microenvironment, revealing pathway differences in HBV/HDV coinfection compared to HBV infection, at a cellular level. These findings provide a basis for identifying biomarkers and targets for hepatitis delta treatments.

FRIDAY 09 MAY

Alcohol

OS-030-YI
Discrepancies between self-reported alcohol intake and phosphatidylethanol in 2,925 individuals at risk of steatotic liver disease

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Background and aims: In the presence of hepatic steatosis and cardiometabolic risk factors, alcohol intake defines the subtypes of steatotic liver disease (SLD). However, self-reported alcohol intake is prone to recall bias and underestimation. The blood-based biomarker phosphatidylethanol (PEth) provides an objective measure of past four weeks' alcohol intake, but has primarily been used to monitor abstinence or heavy drinking in alcohol use disorder studies. We aimed to compare the correlation between PEth and self-reported alcohol intake in a screening cohort of people at risk of SLD.
Method: We conducted a single center, cross-sectional study to screen populations at risk of SLD due to current/prior harmful alcohol intake or metabolic dysfunction. PEth was measured at the time of inclusion. Participants reported their alcohol intake the past week, and average weekly intake over the past three months (hereafter: 'average'). We defined hazardous drinking as an AUDIT-C score ≥3/≥4 (f/m). We used CAP ≥ 248 dB/m to define hepatic steatosis and vibration-controlled transient elastography (VCTE) ≥ 8 kPa to define fibrosis. We divided participants into MASLD, MetALD, ALD or no SLD based on the presence of steatosis, cardiometabolic risk factors and the self-reported average alcohol intake.
Results: We included 2,925 participants distributed into MASLD/MetALD/ALD/no SLD (1,433/409/201/882). Median age was 57 years (IQR 51–64), 51% were males. Median PEth was 40.8 ng/mL (7.0–202.5) and the self-reported alcohol intake was 5 g/day (0–24) the past week, and 9 g/day (2–34) on average. AUDIT-C indicated hazardous drinking in 71% of participants overall. The correlation between PEth and past-week alcohol intake was modest (r = 0.400) and poor between PEth and average intake (r = 0.131). PEth levels increased stepwise from MASLD, to MetALD and ALD (11.2 vs. 246.1 vs. 470.3 ng/mL). In the MASLD group, 8% had a PEth indicative of heavy alcohol intake (≥200 ng/mL), while 31% had levels indicative of a significant intake (>20–199 ng/mL). However, of participants with a significant intake, the majority (22%) exhibited intermediate PEth levels (20–79 ng/mL), which could be within MASLD limits of 1–2 standard drinks per day. In participants with AUDIT-C indicative of hazardous drinking, PEth was higher as compared to those with a normal AUDIT-C (101.9 vs. 5.6 ng/mL, p < 0.001). Finally, VCTE values were independent of both PEth ≥20 ng/mL and high self-reported drinking.
Conclusion: PEth exhibit poor correlation with self-reported average alcohol intake in the population, and only modest correlation with very recent alcohol intake. PEth measurements indicate that more than one-third of MASLD participants may underestimate their alcohol intake and therefore be misclassified. This discrepancy is critical for the patient stratification in clinical trials, potentially affecting study outcomes and generalizability.

OS-031-YI
Hepatocyte-neutrophil interaction in the liver via SAA-FPR2 is key in the pathogenesis of alcohol-associated hepatitis

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Background and aims: Alcohol-associated hepatitis (AH) is the most severe form of alcohol-related liver disease (ALD). Using single-cell

RNA sequencing (scRNAseq) data from liver biopsies, we previously identified hepatocyte and neutrophil subpopulations enriched in AH. In this study, we focused on the interplay between hepatocytes and neutrophils subpopulations in AH to gain insight into the pathogenesis, with particular emphasis on the via of serum amiloid A - formyl peptide receptor 2 (SAA-FPR2).
Method: scRNAseq data from liver biopsies of patients with ALD at different stages (healthy n = 3; early ALD n = 3; AH n = 6) were analysed using CellChat to identify cellular interactions. The expression of SAA in liver biopsies was assessed by immunofluorescence (IF). SAA expression was assessed in a previously generated in vitro liver organoid model derived from liver biopsies of ALD patients treated with an AH medium containing a mixture of pro-inflammatory mediators (IL1b, TNFa, LPS, ethanol) using IF. SAA secretion in the liver organoid model was measured by ELISA. Human plasma levels of SAA were measured by ELISA in a cohort of patients with different stages of ALD (healthy n = 9; early ALD (F0/F1, F2, compensated cirrhosis) n = 34; AH n = 43) and the association with disease stage, survival (1, 3 and 12 months) and bacterial infections was analysed.
Results: scRNAseq analysis identified two hepatocyte subpopulations enriched in AH and overexpressing SAA, and a neutrophil subpopulation with high expression of IL1R1 and FPR2, the latter identified as a receptor for SAA. In silico analysis revealed a strong interaction between these subpopulations via SAA-FPR2 axis. IF of liver biopsies showed overexpression of SAA in hepatocytes and of IL1R1 and FPR2 in neutrophils from patients with AH. In liver organoids, SAA expression increased notably at the transcriptomic and protein levels in response to stimuli with AH medium. In human plasma, SAA levels increased significantly with ALD progression (healthy: 8782 ng/mL; early ALD: 19285 ng/mL; severe AH: 37710 ng/mL, p = 0.051). In patients with AH, SAA levels were higher in those who died at 1, 3 and 12 months compared to survivors (1 month: 48703 vs. 34885 ng/mL, p = 0.036; 3 months: 46034 vs. 36924 ng/mL, p = 0.038; 1 year: 53990 vs. 20361 ng/mL, p = 0.009). In addition, plasma SAA levels were increased in patients with active bacterial infections (47061 vs 33195 ng/mL, p = 0.053).
Conclusion: This study highlights the pivotal role of SAA-FPR2 in mediating interactions between hepatocytes and neutrophils, two of the most relevant cell populations in AH pathogenesis. We show how SAA increases its expression in response to inflammation, resulting in an intense interaction with neutrophils in the liver and in secretion into the general circulation, showing its utility as a biomarker of disease progression, patient survival and development bacterial infections.

OS-032

Comparative perioperative morbidity and mortality of transplantation for alcohol-related hepatitis or liver disease: data from the QuickTrans study

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Background and aims: Early liver transplantation (LT) improves term survival in patients with severe alcohol-related hepatitis (sAH) who do not respond to medical management, but few perioperative data are available. The aim of this study was to compare the perioperative morbidity outcomes and mortality of patients transplanted for sAH or decompensated alcohol-related cirrhosis.
Method: In the prospective multicenter QuickTrans study (19 centers), perioperative data (up to 90 days post-LT) of patients transplanted for sAH or decompensated alcohol-related cirrhosis were collected retrospectively. Pre-LT, perioperative, postoperative data and survival at 90 days and 2 years were compared between the 2 groups.
Results: Between 2012 and 2016, 68 patients with sAH were transplanted (group A) and 93 patients underwent standard LT for decompensated alcohol-related cirrhosis (group B). The Charlson index (with a median of 4, p = 0.3) and the median age of the donor (61 years in group A *vs.* 59.5 in group B, p = 0.46) were similar. Median cold ischemia time was also similar: 467 (A) *vs.* 465 minutes (B), p = 0.95. Patients transplanted for sAH tended to receive more transfusions during LT (median of 6 vs. 4 packed red blood cells, p = 0.08). During LT, patients with sAH had more often hemodynamic instability or bleeding (39.7 *vs.* 24.7%, p = 0.04). Patients transplanted for sAH had a trend toward being still intubated after 24 hours (79.4 *vs.* 65.9%, p = 0.07) and being on vasopressive support (32.1 vs. 20.2%, p = 0.12). After LT, 31.3% of patients with sAH needed renal replacement therapy *vs.* 19.1% in group B, p = 0.08. The length of stay in ICU after LT was two times longer in group A (10 vs. 5 days, p = 0.0002) and the total length of stay after LT was longer in group A (32 *vs.* 22.5 days, p = 0.0006). In univariate analysis, being transplanted for sAH and the MELD score at LT were associated with the risk of being still hospitalized 30 days after LT. In multivariate analysis, only sAH was independently associated with this risk (p = 0.04), whereas the MELD score was not (p = 0.22). After LT, 80.9% of patients (group A) *vs.* 76.3% (group B) had complications (p = 0.5), with infections or surgical complications being the most frequent, with no difference between the two groups (respectively 35.3 *vs.* 31.2%, p = 0.58 and 36.8 *vs.* 32.3, p = 0.55). Survival in the 2 groups was identical at 90 days (94.1 ± 2.9 *vs.* 94.6 ± 2.4%, p = 0.9) and 2 years after LT (89.6 ± 3.7 *vs.* 88 ± 3.4%, p = 0.77).
Conclusion: While patients transplanted for sAH have similar survival and complication rate after LT as patients transplanted for cirrhosis, their ICU and hospital stays are longer. These patients also have a more frequent need for renal replacement therapy and a trend toward postoperative delayed extubation and discontinuation of vasopressors. These results underline the need for adapting perioperative management of patients transplanted for alcohol-related hepatitis.

OS-033

Liver injury induced by CDK4/6 inhibitors for metastatic breast cancer: characterization and management. Data from a multicenter study

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Background and aims: The cyclin-dependent kinase 4/6 inhibitors (CDKi) are the first line therapy for HER2-metastatic breast cancer. Rate of grade 3/4 CDKi-induced liver injury (CDKi-ILI) in the registry studies was 5–9%. However, real-world data on CDKi-ILI characteristics and, specifically management, is scarce.
Method: Multicenter retrospective study that included all patients who started CDKi between 2018 and 2022 and developed CDKi-ILI ≥2 (CTCAE: AST/ALT >3xULN).
Results: A total of 1716 women were identified (861 palbociclib, 504 ribociclib, 351 abemaciclib) and 85 (4.9%) developed CDKi-ILI: 27 (31.8%) grade-2, 46 (54.1%) grade-3, 12(14.1%) grade-4. Rate of CDKi-ILI was higher ($p < 0.001$) among those treated with ribociclib (8.5%) or abemaciclib (8.0%) than palbociclib (1.6%). No differences were observed in severity (CTCAE: grade≥3: 76.7% ribociclib, 57.1% palbociclib, 60.7% abemaciclib, $p = 0.227$; DILI-IEWG ≥ moderate: 14.0% ribociclib, 7.1% palbociclib, 14.3% abemaciclib, $p = 0.778$). DILI-IEWG ≥ moderate was more frequent in those with increased ALT at baseline ($p = 0.089$), or progressive disease at the time of DILI ($p = 0.015$). Pattern of DILI differed according to the CDKi ($p < 0.001$), with hepatocellular as the most common in patients receiving ribocicib (65.1%) and palbociclib (61.5%), and mixed for abemaciclib (59.3%). Five out of 25 (20%) tested for ANAs presented titers ≥1/80. Half of CDKi-ILI cases presented within the first 3 months of therapy (52.9%), with no difference according to the type of CDKi ($p = 0.521$) or severity ($p = 0.516$). Regarding management, 16 (18.8%) were treated with corticosteroids (CS), especially among those with grade-4 CTCAE ($p < 0.001$) or moderate DILI-IEWG ($p = 0.005$). A tendency to higher rate of CS was observed for those on ribociclib ($p = 0.092$). Median duration of CS was 43 days (IQR 26–57). Liver biopsy was performed in 10 (11.8%) patients, more frequent in patients with grade-4 CTCAE ($p = 0.002$), but similar according to the CDKi ($p = 0.794$). The most frequent findings were presence of eosinophils (90%), bridging necrosis (40%), cholestasis (40%), interphase hepatitis (30%), lymphocytic/lymphoplasmacytic infiltrate (50%). After a median of 36 days (IQR, 16–80), 70 (82.4%) patients were rechallenged, rate lower in case of prior DILI-IEWG ≥moderate ($p = 0.022$), but similar regardless of the initial CDKi ($p = 0.287$) or CTCAE ($p = 0.507$). Change on the CDKi was more common among those previously treated with ribociclib ($p = 0.031$), presenting with hepatocellular pattern ($p = 0.039$) and grade 3/4 CTCAE ($p < 0.001$). Recurrence of CDKi-ILI was observed in 19/70 (27.1%) patients, all of them mild.
Conclusion: CDKi-ILI is common, especially within the first months of therapy with ribociclib or abemaciclib. Management of CDKi-ILI is heterogeneous and its standardization a necessity in view of the recent approval of ribociclib and abemaciclib as adjuvant therapy.

OS-034

Corticosteroids are ineffective in individuals with severe alcohol-associated hepatitis and early spontaneous improvement: a multicenter randomized controlled trial

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Background and aims: Severe alcohol-associated hepatitis (AH) is a life-threatening disease for which corticosteroid therapy is recommended in the absence of contraindication. A significant proportion of patients with severe AH have a spontaneous serum bilirubin decrease early after admission. Our aim was to determine whether corticosteroid therapy is more effective than placebo in individuals with severe AH and early spontaneous improvement.
Method: In this multicenter, randomized, controlled trial conducted between February 2018 and May 2024 in 10 Belgian hospitals, patients aged 18 or older, who were heavy drinkers, with recent onset of jaundice, with a biopsy-proven severe AH (mDF ≥ 32 at admission), and with a spontaneous early improvement (i.e. serum bilirubin level decrease > 10% at day 5–10 after admission) were randomized to either corticosteroids (CS) (methylprednisolone 32 mg/d) or placebo (P) for 28 days. Primary endpoint was to compare 3-month mortality rate between both groups of treatment. Secondary endpoints were to compare 1-month mortality rate and infection rate during study period between both groups.
Results: A total of 69 patients were randomized, 38 in the corticosteroid group and 31 in the placebo group. Baseline characteristics were not significantly different between the two groups (CS vs P) for age (52 ± 8 vs. 51 ± 10), male gender (76% vs. 63%), total bilirubin (7.4[5.1–10.8] vs. 9.3[6.0–17.6] mg/dL), INR (1.64 [1.48–1.80] vs 1.70 [1.48–1.98]), mDF at admission (44[37–57] vs. 45[40–58]) and MELD score (21[19–23] vs 21[19–24]). Decrease in bilirubin level between admission and screening was not different between both groups (31 ± 15% vs 27 ± 11%). Lille score at day 7 of treatment was 0.18 [0.07–0.30] and 0.18 [0.07–0.40] in CS and P group, respectively ($p > 0.9$). At 3 months, the probability of survival was not different between both groups (83[72–96] vs 82[69–98] % in CS and P groups respectively, $p = 0.88$). There was no difference in the probability of 1-month survival between CS and P groups (95[88–100] vs 94[85–100] %, $p = 0.85$). Probability of infection during the study period was 48% in the CS group and 36% in the P group ($p = 0.41$). Age and Lille score were significantly associated with 3-month survival. The study was prematurely interrupted due to a low recruitment rate.
Conclusion: The present study failed to identify any benefit from corticosteroid therapy in patients with severe AH and early decrease in bilirubin level after admission. Even if the number of included patients initially planned was not reached, it is unlikely that corticosteroids provide a survival benefit when bilirubin level spontaneously decreases by at least 10%. Waiting five days after admission before deciding to start steroids seems to be a reasonable strategy.

Cirrhosis 1

OS-035-YI

Gut colonization guided versus routine empiric antimicrobial therapy to manage infections in patients with cirrhosis: a pragmatic randomized trial

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Background and aims: Infections in cirrhosis are a major cause of death, and early, effective empirical antimicrobial treatment is critical. However, in high-burden settings like India, where multi-drug-resistant (MDR) infections are prevalent, empirical therapy often fails. Recognizing the strong correlation between rectal colonization and MDR infections, we evaluated whether rapid polymerase chain reaction (PCR) for carbapenemase genes (Xpert Carba-R) and microbial culture of rectal swabs could guide antimicrobial choices and improve outcomes in cirrhosis patients with infections.
Method: This pragmatic, parallel-group, open-label randomized trial [CTRI/2023/02/049479] was conducted at a tertiary-care center from 2023 to 2024. Adult cirrhosis patients hospitalized with bacterial infections (per EASL criteria) were included, excluding those with severe comorbidities, active malignancy, immunosuppression, or recent exposure to polymyxins or ceftazidime/avibactam. Patients were randomized to either an intervention group (rectal swab testing with Xpert Carba-R and microbial culture, followed by antimicrobial adjustments based on detected carbapenemase genes or colonizing bacteria) or a control group (standard empirical treatment per guidelines). Both groups received standard of care. The primary outcome was 28-day overall survival. Secondary outcomes included infection resolution, changes in severity scores, organ failure rates, hospital length of stay, adverse events, and patient costs.
Results: A total of 101 patients (median age 42 years; 90% male; median MELD score 30.1) with predominantly healthcare-associated infections (81.2%), such as pneumonia (46.5%) and spontaneous bacterial peritonitis (35.6%), were randomized (intervention: 51; control: 50). Baseline characteristics were similar between groups. Of 43 carbapenemase-positive patients, 40 in the intervention group received ceftazidime-avibactam plus aztreonam or polymyxin-based therapy. The intervention significantly improved 28-day survival (51% vs. 26%, $p = 0.014$; HR: 0.53, 95% CI: 0.32–0.88; NNT = 4) and led to better resolution of index infections (94.2% vs. 74.1%, $p = 0.011$). MELD and CLIF-C OF scores also improved over time (group time interaction $p = 0.009$ and <0.001). There was no increase in secondary or fungal infections or length of stay ($p > 0.05$). The intervention was cost-effective, with an incremental cost of INR 3,602 (40.5 Euros) per death averted.
Conclusion: This is the first randomized trial to show that Xpert Carba-R and rectal colonization-guided antimicrobials improve survival, infection resolution, and organ function in cirrhosis patients with infections. These findings support integrating gut colonization assessments into the routine care of cirrhosis patients.

OS-036

A multicentre randomised double-blind placebo-controlled phase 1b clinical trial evaluating the safety and mechanism of action of EBX-102, an oral pooled intestinal microbiota product, in liver cirrhosis: the IMPuLCE trial

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Background and aims: Changes in the intestinal microbiome, its function, and impaired gut barrier integrity contribute to the establishment and progression of cirrhosis. The IMPuLCE (Intestinal Microbiota Product in Liver Cirrhosis and Encephalopathy) study was the first in human study of EBX-102, a novel oral full-spectrum microbiome drug in patients with cirrhosis. The objectives were to evaluate the safety, tolerability and dose of EBX-102 and to assess its effects on the gut microbiota taxonomy. Exploratory objectives assessed the impact of changes to the gut microbiota on clinical assessments and translational biomarkers.
Method: Patients with stable cirrhosis (no previous encephalopathy, not on lactulose or rifaximin and MELD <12) were recruited and randomised 2:1 active to placebo in two cohorts to receive a single dose of either 2 (Cohort 1) or 10 capsules (Cohort 2) of EBX-102 or matching placebo. Safety from Cohort 1 was reviewed before dosing Cohort 2. Follow-up was 12 weeks. Serial stool and blood were collected at Baseline/Day 1, Day 3, Weeks 1, 4, 8 and 12 for next generation sequencing, metabolomics, and lipopolysaccharide binding protein (LBP).
Results: Twenty-four participants were randomised and 96% (23/24) completed follow-up. Seventeen (17/24, 71%) reported 53 adverse events. There were no treatment emergent serious adverse events (TEAEs) reported during the study. The commonest AEs were gastrointestinal, 53% (10/19) in Cohort 1, 32% (6/19) in Cohort 2 and 16% (3/19) in Combined Placebo. They were mainly mild or moderate and self-limiting. The microbiota of Cohort 2 became more similar to the composition of EBX-102 after dosing measured by Aitchison distance (Week 1 $p = 0.022$, Week 4 $p = 0.007$, Week 12 $p = 0.016$), while Cohort 1 did not ($p > 0.05$ at all time points post-dosing). Functional changes with reduced concentrations of total short chain fatty acids, reduced primary to secondary bile acid ratio, and increased faecal ammonia concentrations were observed in the stool of active treatment groups. A decrease in plasma LBP was observed in Cohort 2 at Weeks 1, 4, and 8, however this did not reach statistical significance when compared to LBP at Baseline/Day 1. Scores on the Hospital Anxiety and Depression Scale (HADS) reduced in subjects who received active treatment. The total anxiety score changed −0.2 at Week 12 compared to Baseline in Cohort 1, −1.5 in Cohort 2, and +0.7 in Placebo.
Conclusion: EBX-102 treatment was well tolerated with an acceptable safety profile in stable cirrhosis subjects. There was a significant shift in the microbiota composition in patients who received the higher dose of EBX-102. Changes to the microbiota and their functional outputs appeared to be dose-dependent and were linked to potential clinical benefits. These data support a further study in a larger population of patients with more advanced cirrhosis to measure efficacy and determine the mechanism of action.

OS-037

Prognostic scores and clinical outcomes after covered TIPS placement: analysis of 987 cirrhotic patients from the multicenter international EASL-endorsed EuroTIPS registry

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Background and aims: Covered transjugular intrahepatic portosystemic shunt (TIPS) effectively treats portal hypertension (PH)-related complications such as variceal bleeding and refractory ascites. However, the variability in indication and technical practices across centres may significantly influence outcomes. The EASL-endorsed EuroTIPS registry, established in 2020, collects prospective detailed data from 19 European reference centres. This study aimed to assess the value of various prognostic scores: MELD, Child-Pugh, CLIF-C AD, FIPS, and a composite of bilirubin <3 mg/dL with platelets >75 G/L on ascites resolution, rebleeding rates, overt hepatic encephalopathy (OHE) and survival.

Method: Prospective clinical and technical data of all consecutive TIPS placed since 2020. Patients were followed for 1 year.

Results: Of 1,881 patients enrolled since January 2020, 987 cirrhotic patients had one-year follow-up. Mean age was 56.6 ± 11.3 years, with 71.3% male. The primary aetiologies were ALD (67.3%), MASLD (20.2%) and HCV (8.9%). Baseline MELD was 14.1 ± 5.9, Child-Pugh score 8.1 ± 1.9, CLIF-C AD 48.9 ± 10.9 and FIPS – 1.3 ± 1.1. TIPS was implanted for PH-related bleeding in 465 cases (47%) (pre-emptive: 145; rescue: 159; secondary prophylaxis: 130; ectopic varices: 31), recurrent/refractory ascites in 356 (36%); portal vein thrombosis (n = 55, 5.5%), pre-surgery, (n = 54, 5.5%) and other (n = 57, 5.7%). During follow-up, post-TIPS PH-related bleeding (first episode or rebleeding) occurred in only 61 patients of the full cohort of 987 (6%). 433/987 patients (45%) experienced at least one episode of OHE during follow-up. 185 patients died and 88 were transplanted, yielding a one-year transplant-free survival of 72%. In the 356 patients receiving TIPS for recurrent/refractory ascites, TIPS completely controlled ascites in 244 (69%). All the evaluated scores were independently associated with post-TIPS survival and OHE development, while Child Pugh and MELD also predicted post-TIPS bleeding and ascites control. However, none of them had a strong predictive capacity of neither survival nor clinical outcomes, with all C-index estimates being modest <0.7, both when analysed globally or by TIPS indication.

Conclusion: Current scores have limited accuracy to reliably predict clinically relevant outcomes such as survival, OHE development or post-TIPS ascites control. Future analyses within the EuroTIPS cohort will focus on improving predictive models to address this unmet clinical need.

OS-038-YI

Urinary neutrophil gelatinase-associated lipocalin (NGAL) as a diagnostic and prognostic biomarker of acute kidney injury in patients with decompensated cirrhosis: an individual patient data meta-analysis

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Background and aims: Urinary NGAL (uNGAL) has been proposed as a biomarker for classifying acute kidney injury (AKI) phenotypes in patients with decompensated cirrhosis, primarily to differentiate acute tubular necrosis (ATN) from hepatorenal syndrome (HRS). Several studies have shown favorable results, but despite of this its clinical application remains limited. Moreover, it is unknown whether factors such as etiology of cirrhosis or gender affect its accuracy. This study aims to perform an individual patient data meta-analysis to evaluate the diagnostic and prognostic accuracy of uNGAL in patients with decompensated cirrhosis and AKI.
Method: A systematic literature review was conducted to identify studies evaluating uNGAL as a biomarker to identify AKI phenotype in patients with decompensated cirrhosis. Data were obtained from the primary or corresponding authors. An individual patient data meta-analysis was conducted to identify the optimal cut-off point, as well as sensitivity studies to assess confounding factors in the diagnostic and prognostic accuracy of uNGAL.
Results: Data from 7 cohorts from 3 different continents comprising 824 patients were included. No differences were found in the diagnostic accuracy of uNGAL for ATN based on the timing of measurement (at AKI diagnosis or 48–72 hours later) ($p > 0.05$). The uNGAL cut-off for ATN diagnosis was calculated by replicating 20,000 samples using bootstrapping techniques, identifying 232 (163–302) ng/mL as the optimal value, with higher values being indicative of ATN. The pooled area under receiving operating curve (SAUROC) of urinary NGAL for identifying ATN was 0.84 (0.81–0.87), with a sensitivity of 0.73 (0.63–0.81) and a specificity of 0.81 (0.75–0.86). Sensitivity analysis in subgroups (MASLD etiology of cirrhosis and women) ruled out changes in the diagnostic accuracy of uNGAL. The analysis also evaluated the predictive ability of uNGAL for the resolution (total or partial) of AKI, showing uNGAL to be an independent factor of improvement of renal function, regardless of creatinine levels or AKI phenotype. Additionally, uNGAL was predictive of three-month survival, independent of MELD score, sex, or etiology. No evidence of publication bias was identified, and no study was classified as low quality based on the QUADAS-2 assessment.
Conclusion: Urinary NGAL is an excellent biomarker for diagnosis and prognosis in AKI in patients with decompensated cirrhosis. The value of 232 ng/mL correctly classifies up to 80% of patients with decompensated cirrhosis and AKI, maintaining diagnostic accuracy regardless of the timing of its determination, the cause of liver disease, or patient gender. It also predicts the likelihood of AKI resolution and survival status at 3-month follow-up. These results reinforce the idea that determination of uNGAL should be implemented in hospitals managing a high volume of patients with decompensated cirrhosis. *Project PI23/00798", funded by Instituto de Salud Carlos III and co-funded by the European Union.*

OS-039-YI
Effect of albumin treatment duration on response rates and outcomes in patients with cirrhosis and acute kidney injury
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Background and aims: Current guidelines recommend volume expansion with albumin for 48 hours in patients with cirrhosis and acute kidney injury (AKI) to address hypovolemia and rule out prerenal AKI. Recent updates in the Acute Disease Quality Initiative (ADQI)-International Club of Ascites consensus guidelines suggest shortening this duration to 24 hours, primarily based on expert opinions. This study aimed to evaluate the response rates to albumin treatment at 24 and 48 hours, to compare and assess the prognostic significance of three different definitions of response to albumin therapy and to identify cut-offs.
Method: Data from 214 prospectively recruited patients with cirrhosis and AKI from two German centers were analyzed. After applying inclusion and exclusion criteria (e.g., no ascites, inadequate/no albumin treatment at AKI diagnosis), 127 patients were available for analysis. We examined three response definitions after 24 and 48 hours: (1) serum creatinine (SCr) decrease > 0.3 mg/dl, (2) SCr decrease >25%, and (3) SCr decrease in at least one AKI stage. Follow-up was prolonged until transjugular intrahepatic portosystemic shunt (TIPS) initiation, liver transplantation (LTX), death or hemodialysis (HD).
Results: The median age of the cohort was 60 years, and the median MELD was 22 (Child-Pugh A/B/C: 6%/44%/50%). The stages of AKI at the time of diagnosis were classified as follows: AKI 1A 4%, AKI 1B 37%, AKI 2 34%, AKI 3 25%. Overall, 54.3%, 30.7%, and 46.5% of the patients responded to albumin treatment after 48 hours depending on the applied definition (1–3). Notably, irrespective of the definition, 27.6%, 22.0%, and 18.1% of patients responding after 48 hours did not show a response within the first 24 hours of treatment according to definitions 1, 2, and 3, respectively. 28%, 22%, and 18% of the cohort responded to albumin therapy during the second 24 hours of the treatment. Response according to definition 3 was associated with a better HD- and LTX-free survival in multivariate Cox regression analysis (HR 3.2, 95%CI 1.8, 5.6, $p < 0.001$), while response according to the other two definitions was not. For this definition, at a cut-off of 16% SCr increase at 24 hours, sensitivity was 100% and the negative predictive value was 100%. Subsequently terlipressin treatment could have been initiated in 12% of the patient cohort.
Conclusion: Response to albumin treatment is frequent in the second 24 hours of therapy. Shortening volume expansion therapy may lead to overtreatment with terlipressin. Treatment with albumin should aim for a SCr decrease in at least one AKI stage as this definition is associated with a better prognosis. Finally, one can identify at 24 hours those patients in whom further administration of high dose albumin is futile using a cut-off of 16% SCr increase, so that treatment with terlipressin can be initiated early on.

Cirrhosis 2

OS-040
Acute-on-chronic kidney disease in cirrhosis- a global study
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Background and aims: The presence of chronic kidney disease (CKD) predisposes a patient to the development of acute kidney injury (AKI). While AKI and CKD are well understood in cirrhosis, the entity of acute-on-chronic kidney disease (AoCKD) in cirrhosis is not well defined. To define AoCKD in a global cohort of inpatients with cirrhosis, and its impact on patient outcomes.
Method: AoCKD is defined by AKI superimposed on CKD (GFR<60 ml/min /1.73m^2 for >3months), either as 0.3 mg/dL increase in <48 hours, or a 50% rise from an elevated serum creatinine (sCr) in ≤7 days. The CLEARED consortium enrolled in-patients with cirrhosis worldwide from 127 countries & collected data on demographics, cirrhosis complications, co-morbid conditions, and patient outcomes. The incidence and features of AKI superimposed on CKD (CKD+) were compared to those without (CKD-), and its impact on patient outcomes assessed.
Results: 38% (n = 2733 of 7040) CKD+ patients had a median [interquartile range or IQR] baseline sCr of 1.2 [0.92, 1.70]mg/dL, significantly higher than that in CKD- patients (0.71 [0.60, 0.86]mg/dL, p < 0.001). 63.5% of CKD+ patients developed AKI, with 42%, 28% and 30% being stage 1, 2 and 3 AKI respectively. In contrast, only 12.4% of CKD- patients developed AKI (p < 0.001), who mostly had stage 1 (54%) with less having stage 2 (22%) and stage 3 (24%) AKI (p < 0.001

vs. CKD+ patients). The median [IQR} peak sCr in CKD+ patients were 2.40 [1.76, 3.59] mg/dL, significantly higher than that of 1.52 [1.20, 2.27]mg/dL in CKD- patients ($p < 0.001$). More CKD+ patients (85%) received albumin for their AKI, vs. 72% in CKD- patients ($p < 0.001$). Similar proportions of patients received either norepinephrine or terlipressin as treatment for their AKI ($p > 0.05$), but significantly more CKD+ patients received midodrine (11.9% vs.7.0 in CKD- patients, $p = 0.0018$). 48.3% of CKD- patients recovered from their AKI vs. 41.5% of CKD+ patients, who mostly had a partial resolution of their AKI (30.1% vs. 19.6% in CKD- patients) ($p < 0.001$). The median [IQR] discharge sCr in the CKD+ patients was 1.49 [1.02, 2.40]mg/dL, which was significantly higher than that in CKD- patients (1.10 [0.80, 1.65]mg/dL, $p < 0.001$). Hence more CKD+ patients (15.2%) went onto dialysis compared to CKD- patients (7.3%) ($p = 0.02$). The factors associated with the development of AoCKD were prior AKI/HRS (Odds Ratio or OR: 3.22), infection at admission (OR:1.73) and admission MELD-Na (OR: 1.11), Factors associated with AKI resolution amongst CKD+ patients were a lower peak sCr (OR: 0.70), norepinephrine use (OR: 0.51), living in a high-income country (OR:0.65).

Conclusion: AoCKD is common amongst inpatients with cirrhosis, particularly in those with prior AKI, often associated with lower chance for resolution, especially if admitted with infection. Therefore, it is imperative that prompt treatment, especially in well-resourced countries be provided to improve patient outcomes.

OS-041

Nutritional therapy prevents overt hepatic encephalopathy (OHE) in patients with cirrhosis after transjugular intrahepatic portosystemic shunt (TIPS): a randomized controlled trial

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Background and aims: Hepatic encephalopathy (HE) is the most common complication following TIPS in patients with cirrhosis. Nutritional status, including sarcopenia, is an important predictor of post-TIPS HE. Efficacy of nutritional therapy in improving minimal HE (MHE) in patients with cirrhosis is well studied. However, its efficacy in preventing the first episode of OHE in patients with cirrhosis after TIPS has not been established. Therefore, we aim to determine whether different nutritional therapies prevent OHE after TIPS.

Method: Patients were randomized into three groups receiving various nutritional therapies (**Gp1**: 35 kcal/kg/d, with the protein intake started at 20 g for the first 3 days, increased by 10 g every 2 days until reaching 1.2–1.5 g/kg/d, then maintained for 24 week; **Gp2**: 35 kcal/kg/d, with the protein intake that started at 20 g for the first 3 days, increased protein by 10 g every 8 days until reaching 1.2–1.5 g/kg/day, then maintained for 24 weeks; **Gp3**: continued their usual dietary habits for 24 weeks without additional nutritional intervention). Prophylactic use of rifaximin or lactulose was not allowed during the 24 weeks. The primary outcome was the incidence of OHE (grades II or higher based on the West Haven criteria) within 24 weeks after TIPS. The secondary outcomes were MHE [defined by number connection test-A (NCT-A) and line-tracing test (LTT)] and sarcopenia [defined by changes in skeletal muscle index (SMI) measured by computed tomography scan at 3rd lumbar spine level (L3-SMI)] at 24 weeks.

Results: 78 participants were randomized into Gp1 (n = 27), Gp2 (n = 26) or Gp3 (n = 25). Baseline characteristics were comparable between three groups. In three groups, HBV infection was the most common etiology of cirrhosis (62.0%). The main indication for TIPS was variceal rebleeding (80.5%) and more than half of patients combined with sarcopenia (59.7%). Our preliminary results indicated that cumulative incidence of OHE at 24 weeks after TIPS was significantly lower in Gp1 patients (18.5% vs 48.0%, log-rank p = 0.034) compared to Gp3 patients. There was no significant difference between Gp2 and Gp3 patients (34.6% vs 48.0%, log-rank p = 0.296). NCT-A and LTT significantly decreased at 24 weeks compared to baseline in Gp1 (NCT-A: 67.01 ± 43.50 vs 40.00 ± 35.87, p = 0.03; LTT: 68.26 ± 23.76 vs 50.13 ± 25.79, p = 0.04). No significant differences were observed in Gp2 or Gp3. L3-SMI increased similarly in three groups ($\Delta 4.6 \pm 2.8$ vs $\Delta 6.7 \pm 1.8$ vs $\Delta 4.4 \pm 1.2$ cm^2/m^2, p = 0.946). There were no significant difference in other cirrhosis-related complications in three groups.

Conclusion: Nutritional therapy can prevent OHE and improve cognitive function in patients with cirrhosis after TIPS. Patients with cirrhosis should restore their daily dietary intake to the target state (35 kcal/kg/d, with 1.2–1.5 g/kg protein intake) as soon as possible after TIPS.

OS-042

Benchmarking spleen stiffness in assessing response to beta-blocker therapy for secondary prophylaxis of acute variceal bleed-BE-RESPONSE study (NCT05166317)

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Background and aims: Response to non-selective beta-blockers (NSBB) is assessed by measuring hepatic vein pressure gradient (HVPG). Non-invasive tests (NITs) are promising in reflecting response to NSBB for primary prophylaxis. Acute variceal bleed (AVB) poses challenges for NITs due to associated inflammation and splanchnic congestion. We evaluated - efficacy of liver and spleen stiffness measurement (LSM, SSM) post-AVB using transient elastography, as non-invasive correlates of HVPG for NSBB response and rebleed.

Method: This study prospectively assessed 220 cirrhosis patients with g AVB using HVPG, LSM, and SSM within 5 days of bleed, followed by carvedilol therapy. NITs were measured at 0, 3, and 6 weeks, and HVPG at 0 and 6 weeks, with rebleeding followed-up for 90 days. Repeated measures analysis, Cox regression, and Intention-to-Treat (ITT) analysis was used. The primary objective was to determine NIT accuracy in predicting NSBB response at 6 weeks, while secondary goals included correlating NITs with HVPG, rebleeding, and liver related events.

Results: Cirrhosis with AVB [age 49.56 ± 10.34 years, 91.4% male, predominantly ethanol (45%) related cirrhosis] with a mean MELD score of 15.13 ± 2.75, baseline HVPG of 18.66 ± 2.2 mmHg, mean LSM of 59.24 ± 15.44 kPa and SSM of 84.06 ± 15.74 Kpa were included. At 6 weeks, there were 86 (39%) HVPG responders, mean dose of carvedilol used was 11.91 ± 2.03 mg/d. Baseline HVPG, LSM, SSM were comparable between responders and non-responders. NSBB responders compared to non-responders, showed greater reductions in HVPG (24% vs. 8%; $p < 0.05$), LSM (7.4% vs. +1%; $p < 0.05$), and SSM (15.5% vs. 1.6%; $p < 0.05$) at 6 weeks. The predictive accuracy of change in SS (delta SS) for HVPG response at 6 weeks was higher (AUROC 0.85) than change in LS (delta LS; AUROC 0.74). Rebleeding occurred in 31 (14.36%) patients, dominantly in HVPG non-responders (18.6% vs 7.1%; p = 0.027). Importantly, no change in SSM from baseline to week 3, and an increase in SS by 4.18% (3.5 Kpa) from baseline at 6 weeks predicted rebleeding. None of the patients with HVPG ≤12 mmHg at 6weeks rebled within follow-up of 90days.

Conclusion: Lack of reduction in spleen stiffness at week 3is a strong non-invasive predictor of rebleeding risk and non-response to NSBB therapy in patients with AVB. SSM offers a practical alternative to invasive HVPG, allowing timely intervention in high-risk patients with AVB.

OS-043-YI

Clinical impact of non selective beta-blockers in patients with cirrhosis and acute kidney injury: a post hoc analysis of the international club of ascites GLOBAL-AKI study

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Background and aims: Non-selective beta-blockers (NSBBs) are extensively used for preventing decompensation in patients with cirrhosis. International guidelines recommend NSBBs discontinuation in patients with cirrhosis and acute kidney injury (AKI). However, this recommendation is based on experts' opinion and, few studies have evaluated the effects of NSBBs on AKI outcomes.
Method: Post hoc analysis of ICA GLOBAL-AKI study, a multicenter intercontinental study that prospectively enrolled patients hospitalized for acute decompensation (AD) of cirrhosis from July 2022 to May 2023. AKI outcomes were compared between patients on NSBBs at AKI diagnosis and those who were not. A subgroup analysis further examined outcomes between patients in whom NSBBs were continued during hospitalization and those in whom were tapered/withdrawn within 48–72 hours from AKI diagnosis. Propensity score-matching (PSM, 1:1 ratio) was used to balance age, sex, MELD-Na, mean arterial pressure (MAP), presence of ascites, hepatic encephalopathy, AKI stage, acute on chronic liver failure (ACLF) grade at AKI diagnosis and whether patients were from low or middle-income countries. Main outcome were 28-day mortality and AKI non-resolution.
Results: 503 out of 1,238 patients with AKI were on NSBBs treatment at AKI diagnosis (propranolol 55%; carvedilol 45%). Most of patients were receiving less than 80 mg of propranolol and ≤12,5 mg of carvedilol (89%). Before PSM, patients on NSBBs were older and had significantly lower MAP, MELD-Na score and significantly lower prevalence of grade 2 and 3 ACLF. After PSM, all covariates were balanced between the two groups (standardized mean difference [SMD] <0.1). Patients on treatment with NSBBs had lower white blood cells count than those without (9.2 vs 7.4×10^9/l; $p < 0.001$). In PSM analysis, patients on NSSBs had lower risk of AKI non-resolution (OR = 0.65, p = 0.001) and lower risk of 28-day mortality (sHR = 0.68; p = 0.005). During the first 48/72 hours of hospitalization, NSBBs were continued in 123 patients (26%) and tapered/withdrawn in 350 (76%). Data about NSBBs management were missing in the remaining 37 patients. After PSM, all covariates were balanced between the two groups ([SMD<0.1). Continuation of NSBBs was neither associated with AKI non-resolution (OR = 1.00; p = 0.999) nor with 28-day mortality (sHR = 0.56; p = 0.190). Subgroup analyses in patients with MAP<70 mmHg, serum Na<130 mmol/l and ACLF confirmed the findings.
Conclusion: NSBBs treatment at AKI diagnosis is associated with higher resolution of AKI and lower 28-day mortality in patients with cirrhosis and AKI. Continuation of treatment with NSBBs in patients with cirrhosis and AKI does not seem to be harmful in these patients.

OS-044

Liver sinusoidal endothelial cell BRD4 drives inflammatory angiocrine signaling in liver fibrosis

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Background and aims: Chronic liver injury results in inflammation and extracellular matrix deposition, ultimately leading to liver fibrosis. Liver sinusoidal endothelial cells (LSECs) have been shown to initiate liver inflammation through an angiocrine-dependent mechanism in response to injury. The roles of bromodomain-containing protein 4 (BRD4), an epigenetic reader that binds to the super-enhancer (SEs) of active genes, in liver fibrosis are poorly understood. Here, we aimed to investigate the epigenetic regulation of LSECs mediated by SEs in angiocrine signaling during liver fibrosis.
Method: Liver fibrosis was induced in mice with LSEC-specific *Brd4* knockout (*Brd4*$^{fl/fl}$/*Cdh5*^{Cre}) mice and littermate controls (*Brd4*$^{fl/fl}$) by carbon tetrachloride (CCl_4) administration. Following a 6-week treatment, histological and molecular analyses were conducted to assess liver inflammation and fibrosis, and single-cell RNA sequencing (scRNA-seq) was performed to explore communications between LSECs and other cell types. Primary human LSECs were treated with TNFα and BRD4 inhibitor iBET151, with these samples subsequently utilized for ChIP-seq analysis.
Results: In CCl_4 mouse model, collagen I deposition was significantly decreased in *Brd4*$^{fl/fl}$/*Cdh5*^{Cre} mice compared to littermate *Brd4*$^{fl/fl}$ control mice (n = 8/group, $p < 0.001$). Additionally, hepatic stellate cell (HSC) activation marker aSMA and macrophage marker F4/80 were also decreased in *Brd4*$^{fl/fl}$/*Cdh5*^{Cre} mice (n = 8/group, $p < 0.001$). scRNA-seq analysis identified nine different clusters including endothelial cells (ECs), bone marrow-derived macrophages (BMDMs), HSCs and other immune cells (n = 3/group). Subgroup analysis of ECs revealed eight clusters based on marker genes. Pseudotrajectory analysis illustrated a transition from normal to inflammatory gene expression among liver EC subsets, highlighting EC7 as a key player in EC inflammation. Notably, this inflammatory transition was normalized in *Brd4*$^{fl/fl}$/*Cdh5*^{Cre} mice. Ligand-receptor pair analysis showed a strong interaction between *Timp1* in EC7 and *Cd63* in BMDMs. Furthermore, RNA-FISH assays confirmed that TIMP1$^+$ ECs recruit CD63$^+$ BMDMs during liver fibrosis, whereas this interaction was absent in *Brd4*$^{fl/fl}$/*Cdh5*^{Cre} mice. In human LSECs, BRD4 ChIP-seq analysis revealed that SE activity of *TIMP1* was blocked by iBET151, and qPCR analysis confirmed that iBET151 reduced TNFα-induced TIMP1 expression (n = 3, $p < 0.05$).
Conclusion: LSEC-derived TIMP1 facilitates the recruitment of CD63$^+$ BMDMs, thereby promoting liver inflammation. SE-induced TIMP1 expression is dependent on BRD4. Inhibition of the SE activity of TIMP1 by LSEC-BRD4 deletion alleviates liver inflammation and fibrosis.

Fibrosis, Hepatocyte and Liver regeneration

OS-045

Defective autophagy in CD4 T cells drives liver fibrosis via type 3 inflammation

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Background and aims: Sustained inflammation is a driving force of chronic liver disease progression to fibrosis and end-stage cirrhosis. A major source of inflammatory and fibrogenic mediators originates from conventional CD4 T cells, in particular the Th17 cell subset. Dysregulation of autophagy in immune cells is associated with an uncontrolled inflammatory response during various inflammatory diseases. Here, we combined studies in human samples and mice models, to evaluate the role of T cell autophagy in liver fibrosis progression.
Method: Autophagy was evaluated in the liver and blood T cells isolated from patients with extended fibrosis or controls by single-cell RNA sequencing (Sc-RNAseq), flow cytometry, immunofluorescence and western blot. Liver fibrosis was induced in mice specifically lacking the autophagy proteins (ATG5)$^{Tlymph-/-}$ or rubicon (RUBCN)$^{Tlymph-/-}$ in T cells, by repeated carbon tetrachloride (CCl_4) injections or by bile duct ligation (BDL). Comparison of genes differentially regulated in CD4 T cells from ATG5$^{Tlymph-/-}$ CCl_4-mice compared to control group was performed by RNA sequencing.
Results: Sc-RNAseq and functional studies indicated that intrahepatic and circulating CD4 T cells from patients with extended fibrosis show defects in the autophagy machinery. Fibrotic (CCl_4 or BDL) mice deficient for autophagy in T cells (ATG5$^{Tlymph-/-}$) displayed reduced CD4 T cell frequency associated with a shift toward an activated glycolytic Th17 phenotype, and with enhanced type 3 cytokine release. These mice exhibited enhanced hepatic inflammation and were more susceptible to liver fibrosis. Co-culture experiments showed that ATG5-deficient CD4 T cells shift hepatic myofibroblasts, hepatocytes and macrophages toward a pro-inflammatory phenotype. As a proof of concept, pharmacological autophagy activation decreased the release of type 3 cytokines in CD4 T cells from patients with extended fibrosis, and mice with specific T cell deletion of the autophagy inhibitory protein Rubicon developed limited fibrosis.
Conclusion: Our findings unravel autophagy in CD4 T cells as a key therapeutic target to control inflammation-driven fibrosis during chronic liver injury.

OS-046

Endothelial Heg1 promotes liver sinusoidal endothelial cells capillarization to aggravate liver fibrosis

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Background and aims: Liver fibrosis represents a global health burden, given the paucity of approved antifibrotic therapies. Liver sinusoidal endothelial cells (LSECs) play a major gatekeeping role in hepatic homeostasis and liver disease pathophysiology. The transmembrane protein heart of glass1 (HEG1) has been proved highly expressed in LSECs and regulates liver vascular/biliary Network patterning and metabolic zonation; however, its function in liver fibrosis in LSECs remains unclear. Here, we investigated the role of LSEC-expressed Heg1 in liver fibrosis.
Method: Hepatic endothelial Heg1 expression was characterized in patients with cirrhosis and chronic carbon tetrachloride (CCl_4) exposure and methionine–choline-deficient (MCD) diet induced liver fibrosis mouse models. Single-cell RNA sequencing (scRNA-seq) and double-immunohistochemistry were employed to explore Heg1 expression patterns in fibrotic livers. The effects of LSECs-specific Heg1 deletion on liver fibrosis were evaluated. Heg1 knockout LSECs were isolated to assess the role of Heg1 in capillarization, fenestration of LSECs were observed via applying two high-resolution microscopy modalities: structured illumination microscopy (SIM) and scanning electron microscopy (SEM). Molecular mechanisms underlying Heg1 function were investigated, while chemical and genetic investigations were performed to assess its potential as a therapeutic target.
Results: Heg1 expression was significantly elevated in LSECs in both patients with cirrhosis and mice. LSECs specific deletion of Heg1 improved liver injury, inhibited LSECs capillarization and attenuated collagen deposition in fibrosis. Furthermore, deletion of Heg1 prevented spontaneous capillarization of isolated LSECs and downregulated capillarization-associated genes, suggesting that Heg1 has critical impact on LSECs capillarization regulating. Mechanistically, Heg1 overexpression promoted phosphorylation of myosin light chain (MLC) via changing intracellular distribution and promoting kinase activity of p21-activated kinase 4 (PAK4) to regulate fenestration. Inhibition of PAK4 by PF-3758309 reversed LSEC capillarization triggered by Heg1 overexpression. Consistently, administration of PF-3758309 alleviated liver fibrosis in mouse model induced by CCl_4 exposure. Finally, a novel nanoparticle carried Heg1 siRNA targeting LSECs was shown to be effective in protecting against liver fibrosis pathology in mice.
Conclusion: In conclusion, our results demonstrate that Heg1 promotes liver fibrosis by inducing LSECs capillarization, underscoring Heg1 as a promising druggable target for liver fibrosis treatment.

OS-047-YI

Unveiling the link between neddylation and hepatic zonation: key insights into liver metabolism and diseases

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Background and aims: The liver exhibits metabolic zonation, with gene expression and metabolic functions distributed across specific zones along the lobule radial axis. Disruption of zonation is linked to the initiation and progression of liver pathologies. Neddylation, a post-translational modification essential for metabolism, influences zonal metabolic processes and is associated with liver pathogenesis. However, its relationship with liver zonation remains understudied. This study aims to investigate the connection between neddylation and liver zonation, evaluating its metabolic implications and role in liver diseases.
Method: Spatial transcriptomics was used to assess the localization of neddylation machinery gene expression in mice. Biotinylated Ubiquitin (bioUb) and Biotinylated NEDD8 (bioNEDD8) mice were employed to evaluate post-translational modifications in known zonated proteins. We also utilized different transgenic mouse models to study: 1) the impact of zonation loss on neddylation, using Li-TSC1KO RagAGTP mutants, which exhibit zonation disruption without hepatic disease at early stages, and 2) the role of neddylation modulation on zonation, using models that silence or overexpress NEDD8, overexpress NAE1 (key NEDD8 activator), or silence NEDP1 (a major de-neddylation protease).
Results: Neddylation genes were more highly expressed in pericentral hepatocytes than periportal ones. Proteomic data from bioNEDD8 and bioUb mice revealed neddylation and ubiquitination enrichment on periportal zonation markers (e.g., ALB, ASS, ASL, CYP2F2). In Li-TSC1KO RagAGTP mutant mice, zonation loss altered neddylation mediators' expression. Immunofluorescence showed a decentralized pattern of NEDD8 in the mutants, compared to its periportal localization in controls. Overexpressing NAE1 or silencing NEDP1 disrupted periportal marker gene expression, while NEDD8 modulation also affected central zone markers mRNA levels. Mutant models showed altered expression of genes involved in zonated metabolic processes, with pronounced effects when NEDD8 or NAE1 were manipulated.
Conclusion: Our results demonstrate a significant association between neddylation and liver zonation, suggesting a zonal expression pattern of the neddylation machinery. Genetic manipulation of neddylation mediators influenced zonal markers and altered the expression of genes involved in zonated metabolic processes, reinforcing the link between neddylation and liver zonation. Future research will explore zonal neddylation modulation to elucidate its role in liver metabolism and pathology.

OS-048

Mucosal-associated invariant T cells promote liver regeneration

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Background and aims: Mucosal-Associated Invariant T (MAIT) cells, which are non-conventional T cells that are restricted by the non-classical MHC class I-related protein MR1, display altered functions during chronic liver diseases. We have previously demonstrated the profibrogenic properties of MAIT cells in the liver and their negative impact in fibrosis regression (1,2). Moreover, recent data demonstrated that MAIT cells have a tissue-repair gene signature and regenerative functions in skin (3) and colon (4). We thus wondered whether MAIT cells might also play a role in liver regeneration.
Method: We analyzed MAIT cell signature from published scRNA-seq data of liver biopsies from patients undergoing portal vein embolization, which induce liver regeneration prior to large hepatectomy (5). Hepatocyte proliferation was measured by Ki-67 immunostaining in human precision cut liver slices (PCLS) that were obtained from liver explants of patients with extended fibrosis. These human PCLS were exposed for 48 hours to the synthetic MAIT cell inhibitor acetyl-6-formylpterin (Ac-6-FP) or its vehicle. We also studied liver regeneration in control B6 mice submitted or not to Ac-6-FP injections, in MAIT cells enriched mice (B6-MAIT^{CAST}) and in mice without MAIT cells (MR1$^{-/-}$ B6-MAIT^{CAST}). Mouse liver regeneration was induced either by 2/3 partial hepatectomy (PHx) or by an acute or chronic intraperitoneal injection of carbon tetrachloride (CCl_4). Hepatocyte proliferation was measured by BrdU incorporation, PHH3 immunostaining and liver cyclin expression at different time points after regeneration stimulus. Finally, co-culture between primary mouse hepatocytes and non-activated or activated MAIT cells (anti-CD3/anti-CD28 antibodies) allowed to determine whether MAIT cells have a direct impact on hepatocyte DNA synthesis.
Results: In humans, (i) MAIT cells from regenerating liver biopsies highly express tissue-repair gene signature compared to healthy liver biopsies; (ii) MAIT cell inhibition by Ac-6-FP blunts hepatocyte proliferation in PCLS from patients with liver extended fibrosis (n = 8). (iii) In mouse models, pharmacological MAIT cell inhibition by Ac-6-FP, or lack of MAIT cells (MR1$^{-/-}$ mice) delays liver regeneration following an acute stimulus (single CCl_4 injection or 2/3 PHx) or a chronic insult (repeated CCl_4 administration) compared to control mice; (iv) in vitro, activated MAIT cells induce hepatocyte proliferation in co-culture experiments.
Conclusion: Using human samples and mouse models, we show that MAIT cells promote liver regeneration. Our in vitro co-culture experiments suggest that this effect could be due, at least partially, to a direct impact of activated MAIT cells on hepatocyte proliferation.

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OS-049

PPAR-alpha agonist GW7647 targeted to macrophages using dendrimer–graphite nanoparticles reduces liver fibrosis

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Background and aims: Macrophages play an essential role in the progression of chronic liver diseases (CLD) by regulating the balance between hepatic fibrogenesis and fibrosis resolution. It is known that systemic therapy with PPAR-alpha agonists inhibits TGF-beta transcription in smooth muscle cells and reduces the production of pro-inflammatory cytokines in macrophages. However, the specific contribution of this pathway on macrophage regulation in liver fibrosis has not been fully elucidated yet. In this study, we evaluate the therapeutic effects of PPAR-alpha activation on macrophages in liver inflammation and fibrosis using macrophage-selective dendrimer-graphite nanoparticles (DGNPs) that deliver the PPAR-alpha agonist GW7647.
Method: DGNPs bound to the GW7647 PPAR-alpha agonist (DGNPs-GW) or to mannitol (DGNPs-Man) as a control were synthesized and characterized. For *in vivo* studies, fibrosis was induced in twelve Balb/c mice with i.p. CCl_4 (1:8 v/v in corn oil) twice a week for 10 weeks. Dispersions of DGNPs-Man or DGNPs-GW were i.v. injected (50 μg/Kg DGNPs and 50 μg/Kg GW7647 or mannitol) to fibrotic mice every 3 days for 10 days. The therapeutic utility of DGNPs-GW on fibrosis, liver function and inflammation was studied via real-time PCR and histological techniques.
Results: Physicochemical characterization of DGNPs-GW and DGNPs-Man revealed a mean nanoparticle size of 270.1 nm and 300.5 nm, respectively, and a negative surface charge of −19 mV and −18 mV, highlighting their suitability for *in vivo* administration. The treatment with DGNPs-GW in fibrotic mice increased the hepatic synthesis and expression of anti-inflammatory markers (MRC: 1.0 ± 0.1 vs. 1.4 ± 0.1 fc, $p < 0.01$ and ARG1: 1.0 ± 0.1 vs. 1.3 ± 0.1 fc, $p < 0.05$) compared to mice receiving DGNS-Man, while no changes were observed in the synthesis and expression of pro-inflammatory markers (NOS2 and COX2). Reduced inflammation was accompanied with a decrease in liver fibrosis (8.3 ± 0.3 vs. 6.8 ± 0.1% fibrosis area, $p < 0.001$) and a lower hepatic stellate cell activation, denoted by a decrease in the hepatic expression of collagen-I (1.0 ± 0.1 vs. 0.7 ± 0.1 fc, $p < 0.05$), TIMP-1 (1.0 ± 0.1 vs. 0.6 ± 0.1 fc, $p < 0.05$) and TIMP-2 (1.0 ± 0.0 vs. 0.9 ± 0.0 fc, $p < 0.05$). These effects were attributed to a reduction in the hepatic expression of macrophage profibrogenic factors TGF-beta (1.0 ± 0.0 vs. 0.8 ± 0.0 fc, $p < 0.01$), PDGFB (1.0 ± 0.0 vs. 0.8 ± 0.0 fc, $p < 0.01$) and OSM (1.0 ± 0.0 vs. 0.8 ± 0.0 fc, $p < 0.05$). The treatment with DGNPs-GW did not affect serum parameters of liver injury, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and total protein.
Conclusion: The selective activation of PPAR-alpha in liver macrophages using GW7647 delivered by DGNPs reduces liver fibrosis and stimulates an anti-inflammatory response highlighting the potential of this nanoscale therapy for chronic liver diseases.

Gut microbiota

OS-050-YI

Unravelling the therapeutic potential of novel peptides derived from the human gut microbiome in mouse models of MASLD and acute liver injury

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Background and aims: The interplay between the liver and human gut microbiome is increasingly recognized as a pivotal factor in liver development, health, and disease. While metabolites from the bacterial secretome, such as secondary bile acids and vitamins, have long been acknowledged for their vital role in liver maturation and function, the impact of peptides derived from microbiome proteins processed by intestinal enzymes remains largely unexplored. Preliminary work showed that four peptides promoted cell survival, enhanced functionality and differentiation of hepatocytes by increasing the expression of liver-specific metabolic genes and albumin secretion. These findings highlight the untapped potential of microbiome-derived peptides in maintaining liver homeostasis, as well as their role in modulating inflammatory and metabolic pathways beneficial for liver disease treatment.
Method: Several synthetic peptides were generated via an *in-silico* digestion of the entire human gut microbiota secretome when exposed to all known intestinal enzymes. Four peptides (B2, B3, B4, and B20) were selected based on their predicted anti-inflammatory properties and ability to ability to enhance hepatocyte function. To assess therapeutic potential, peptides were evaluated in two mouse models of drug-induced acute liver injury (DILI) induced by carbon tetrachloride and acetaminophen. Following the promising outcomes, the peptides were tested in both a disease-established and a preventive protocol in mice with MASLD induced by a choline-deficient, high-fat diet (HF-CDAA).
Results: First, the anti-inflammatory effect of the peptides was demonstrated by reducing TNFa and IL-6 levels in LPS-induced human monocytes. In DILI models, peptide B4 significantly improved inflammation-induced hepatomegaly and liver morphology and reduced serum levels of transaminases and lactate dehydrogenase (LDH), showing comparable or better effects than the standard treatment with N-acetylcysteine. Additionally, B4-treated mice showed significant protection against apoptosis and increased proliferation 48 hours post-injury after histological, immunofluorescence and RT-qPCR analysis. In MASLD-established mice treated daily with peptides for 2 weeks, a significant reduction in liver fibrosis of 30% was observed in mice treated with peptide B2. In a preventive protocol, with mice treated daily during HF-CDAA diet administration, B2-treated mice showed a 66% reduction in fibrosis by histological and RT-qPCR analysis, as well as a reduction in serum levels of transaminases and LDH.
Conclusion: Overall, these findings underscore the therapeutic promise of microbiome-derived peptides in treating liver diseases. Moreover, this is the first study to describe the role of gut microbiota peptides in liver cell proliferation, survival, and function, positioning microbial secretome peptides as a novel and promising therapeutic avenue for the management of liver diseases.

OS-051-YI

Cathepsin B-mediated occludin degradation increases gut permeability and progression of alcohol-associated liver disease

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Background and aims: Disruption of the gut barrier permits the translocation of microbial products to the liver, driving the progression of liver disease in patients with alcohol-associated hepatitis (AH). We aimed to study the contribution of the faecal proteome to disease progression in patients with AH.
Method: We used high-quantitative fidelity Tandem Mass Tag faecal proteomics analysis with LC/MS in a multicenter cohort of patients with AH (n = 80) or alcohol use disorder (AUD) (n = 21), and controls (n = 19) (InTeam), and a cathepsin B (CTSB) activity assay in a second independent multicenter cohort of patients with AH (n = 67) or AUD (n = 20), and controls (n = 18) (AlcHepNet). Mice lacking *Ctsb* in myeloid cells (LysM-Cre) or Kupffer cells (Clec4f-Cre), and transgenic mice overexpressing occludin in intestinal epithelial cells (occludin-IEC-Tg) were subjected to the chronic-plus-binge ethanol feeding model (NIAAA).
Results: Faecal CTSB levels and activity progressively increased in patients with AUD and AH compared with controls, and were associated with higher 90-day and 180-day mortality in patients with AH in the exploratory and validation cohort. Immunofluorescence analysis in patients with AUD and ethanol-fed mice revealed that CTSB is upregulated and predominantly expressed in macrophages in the intestine. Secretion and release of CTSB into the intestinal lumen are induced by ethanol intake, evidenced by increased CTSB activity in intestinal luminal contents and isolated intestinal cell fractions. Ethanol alone suffices to induce secretion of CTSB in cultured macrophages. Cell-specific deletion of *Ctsb* in myeloid cells, but not in Kupffer cells, stabilized the gut barrier by restoring levels of the intestinal tight junction protein occludin and lowering systemic LPS levels, and reduced ethanol-induced steatohepatitis in mice. Oral administration of the gut-restricted and specific CTSB inhibitor CA074 (5 mg/kg/day) in wildtype mice stabilized occludin levels, restored gut barrier function by reducing systemic LPS levels, and attenuated ethanol-induced steatohepatitis. In contrast, CA074 did not change these parameters in occludin-IEC-Tg mice, indicating that CA074 requires the stabilization of occludin to exert its beneficial actions. Moreover, occludin-IEC-Tg mice were protected against ethanol-induced steatohepatitis. *In vitro*, faecal supernatant from

patients with AH, or conditioned media from macrophages exposed to ethanol, or recombinant CTSB induced barrier disruption independent of cell death and degradation of occludin in Caco2 cell monolayers, mouse and human enteroids; these effects were blocked with CA074. Finally, enzymatic analysis revealed that CTSB directly cleaves occludin.
Conclusion: Intestinal macrophage-derived CTSB promotes intestinal barrier disruption through degradation of occludin, and its inhibition exerts promising beneficial effects in ethanol-induced steatohepatitis.

OS-052
Chronic exposure to microplastics and nanoplastics exacerbates western diet-induced metabolic dysfunction-associated steatohepatitis: the role of gut microbiota
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Background and aims: Microplastics (MPs) and nanoplastics (NPs) are ubiquitous pollutants that disturb lipid metabolism and liver function. However, the roles of MPs and NPs in metabolic dysfunction-associated steatohepatitis (MASH) remain unclear. Our study aims to evaluate the role and mechanism of long-term exposure to MPs and NPs in the progression of MASH, and reveal the potential mechanism from the prospective of gut microbiota in this process.
Method: 7-week-old male C57BL/6J mice were fed either a normal chow diet (NCD) or a Western diet (WD) for 18 weeks, with exposure to 5-micrometer MPs or 100-nanometer NPs via drinking water. The liver phenotype was analyzed with regard to steatosis (Oil Red O staining; hepatic TC, TG), inflammation (H&E staining; IL-6, TNF-alpha, IL-1beta) and fibrosis (Sirius red staining; Col1a1, alpha-SMA, expression). Liver transcriptomics and 16S rRNA sequencing were used to evaluate the effects of MPs and NPs on liver gene expression and gut microbiota in MASH mice. Feces were collected from mice exposed to MPs or NPs and transplanted to WD-induced MASH mice after one-week antibiotics administration.
Results: Exposure to MPs and NPs both significantly exacerbated WD-induced MASH and its associated liver fibrosis. MPs mainly promoted MASH-related obesity, hepatic steatosis, and liver injury, whereas NPs exacerbated liver inflammation in mice with MASH. The liver transcriptome suggests that MPs mainly affect gene expression in metabolic pathways, whereas NPs predominantly regulate inflammatory and cancer-related pathways. 16S rRNA sequencing indicated that MPs and NPs had different effects on gut microbiota. MPs upregulated the relative abundance of *Coriobacteriaceae* and *Dubosiella* and downregulated *Ruminococcus* and *Oscillospiraceae*, and NPs increased the relative abundance of potentially pathogenic bacteria such as Staphylococcus and *Muribaculum*. The fecal microbiota transplantation experiment indicated that the gut microbiota of MPs-exposed mice could replicate the aggravating effect of MPs on MASH. However, the gut microbiota of mice exposed to NPs exacerbated liver fibrosis, not inflammation.
Conclusion: MPs and NPs promote the progression of Western diet-induced MASH, with gut microbiota involved and partially driving this process. Our findings provide new evidence for the role of MPs and NPs in MASH and offer new insights into the interactions among environmental pollutants, gut microbiota, and liver diseases.

OS-053-YI
Periodontitis drives steatotic liver disease progression via a microbiome-dependent oral-gut-liver circuit
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Background and aims: The global obesity pandemic is paralleled by a surge in metabolic dysfunction-associated steatotic liver disease (MASLD). Intestinal dysbiosis exacerbates hepatic inflammation in MASLD. However, the interplay of environmental and host-derived factors underlying gut-liver crosstalk and its connection to MASLD remains incompletely understood. Here, we aimed to elucidate a molecular link between MASLD and periodontitis, a disease that affects up to 40% of the population.
Method: In a translational approach, we combined population-based data from 500,000 UK Biobank participants, a prospective liver transplant (LTx) cohort, and a mechanistic mouse model. Clinical investigations included pre- and post-LTx assessments of liver and dental health, blood testing, and periodontal examinations. In mice, periodontitis was induced via silk ligatures, coupled with a Western-style diet (WSD) to induce MASLD. Using transcriptomics, protein, and imaging data, we assessed oral and gut microbiome, hepatic inflammation, and liver fibrosis. Finally, mice were treated with proton pump inhibitors (PPI) or underwent microbiome modulation using broad-spectrum antibiotics (ABx) and cohousing experiments.
Results: Patients with periodontitis exhibited elevated liver transaminase levels and a higher prevalence of liver fibrosis compared to controls. In mice, periodontitis caused significant dental bone loss in µCT, hepatic steatosis, fibrosis, and inflammation. This was linked to intestinal dysbiosis and gut microbiome alterations. PPI-mediated disruption of the gastric acidic barrier further aggravated these phenotypes, promoting severe liver fibrosis and gut microbiome shifts. Mechanistically, flow cytometry and immunofluorescence revealed pronounced infiltration of $IL17A^+$ lymphocytes in periodontitis mice. Similarly, serum proteomics in patients with periodontitis demonstrated elevated IL17, IL6, and M-CSF levels and overall enrichment of pathways associated with T-cell activation. This

phenotype was microbiome-dependent in mice, transmissible via cohousing, and reversible with ABx.
Conclusion: Our study highlights periodontitis as a significant risk factor for liver disease progression in MASLD via a microbiome-dependent oral-gut-liver circuit that fuels IL17-mediated hepatic inflammation. Screening and proper management of periodontal disease should be prioritized in MASLD patients to mitigate liver disease progression and improve outcomes.

OS-054
CD8+ tissue-resident memory T cells promotes liver fibrosis resolution and are regulated by intestinal microbiota
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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a major cause of chronic liver disease that can progress to liver fibrosis. Recent clinical advances suggest that liver fibrosis can be reversed, but the cellular and molecular mechanisms behind MASH resolution are not well understood. This study uses a murine diet-induced MASH model to investigate the role of CD8+ tissue-resident memory T cells (CD8+ Trm) and the mechanisms regulating these cells in resolving liver fibrosis.
Method: To study the resolution process in liver fibrosis, we used a murine model where mice were fed a high-fat and high-cholesterol (HFHC) diet for 24 weeks, then switched to a normal diet (RES mice). We examined changes in intrahepatic immune cells during MASH development and resolution using flow cytometry. Additionally, we performed metagenomic analysis and antibiotics treatment to remove intestinal microbiota to examine the effects on immune responses in the liver.
Results: We found that the number of intrahepatic CD8+ T cells remained significantly high in RES mice compared to normal diet-fed (ND) mice, while other cell subsets returned to normal levels with fibrosis regression 8 weeks after the diet switch. Single-cell transcriptome analysis showed that most intrahepatic CD8+ T cells had Cd44+Sell-S1pr1- tissue-resident memory T cell (Trm) phenotypes during MASH resolution. Bulk RNA-seq analysis of isolated CD8+ T cell subsets revealed that both Trm subsets from HFHC and RES mice expressed core Trm signature genes. Depleting CD8+ T cells with a killing antibody during the resolution phase prevented recovery from liver inflammation and fibrosis. During resolution, CD8+ Trm attracted hepatic stellate cells (HSCs) in a CCR5-dependent manner and induced FasL-Fas-mediated apoptosis in activated HSCs. Antibiotic administration during the fibrosis recovery phase further increased CD8+ Trm and promoted fibrosis recovery, indicating that intestinal microflora regulates CD8+ Trm and is involved in fibrosis recovery. Metagenomic analysis suggested that certain bifidobacteria are upregulated during fibrosis recovery and may influence CD8+ Trm differentiation and proliferation.
Conclusion: This study provides new insights into the liver-protective function of CD8+ Trm during the MASH resolution phase. Regulating CD8+ Trm through microbiota manipulation may offer a potential therapeutic option for MASH in the future.

Immune-mediated & Cholestatic Diseases

OS-055
Novel dual-acting ABCB4/MDR3 and ABCB11/BSEP positive functional modulator demonstrates anti-cholestatic and anti-cholangitis activity in two orthogonal models of hepatobiliary disease
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Background and aims: ATP binding cassette subfamily B members 4 (ABCB4/MDR3) and 11 (ABCB11/BSEP) facilitate the translocation of phosphatidylcholine (PL) and the efflux of bile acids (BA) from hepatocytes to the canalicular space, respectively. Mutations in these transporters cause monogenic cholestatic diseases (PFIC2 [BSEP deficiency] /PFIC3 [MDR3 deficiency]) and are associated with the hepatobiliary diseases intrahepatic cholestasis of pregnancy (ICP) and low phospholipid-associated cholelithiasis (LPAC), highlighting their critical role in maintaining hepatobiliary health. We have discovered RTY-694, a novel, potent, dual-acting ABCB4/BSEP positive functional modulator (PFM) and characterized it in *in vitro* pharmacology studies.[1] Here we present *in vivo* pharmacology data that RTY-694 demonstrates anti-cholestatic and anti-cholangitis efficacy in animal models of PFIC2 and cholangiopathy.
Method: RTY-694 was evaluated with twice daily oral dosing in; 1) a 2-week model of PFIC2 harboring the pathogenic E297G variant in *Bsep*, and 2) a 6-week model of *Abcb4* heterozygous animals fed a lithogenic diet[2]. Liver function, and biliary endpoints were measured in both models. In addition, gene expression, chemokines, and histology for ductular reaction, cholangitis, and fibrosis were assessed in the *Abcb4* model.
Results: In the PFIC2 model oral RTY-694 led to increased biliary levels of BA, demonstrating Bsep target engagement. Additionally, RTY-694 decreased serum levels of BA, alkaline phosphatase (ALP), alanine transaminase (ALT), liver taurocholic acid (TCA) and liver weight. In the *Abcb4* heterozygous model, oral RTY-694 increased biliary PL levels, demonstrating Abcb4 target engagement. Serum markers of cholestasis and inflammation were reduced by RTY-694, and histology demonstrated a reduction in markers of ductular reaction, cholangitis, and fibrosis.
Conclusion: RTY-694, a first-in-class, orally active dual PFM for ABCB4/BSEP, was characterized in a genetic and a mixed genetic/diet model of hepatobiliary diseases. By enhancing the function of Abcb4 and Bsep, RTY-694 provided a beneficial impact on relevant markers of cholestasis and biliary health. These data demonstrate the promise of our dual BSEP/ABCB4 PFM to provide a benefit for multiple hepatobiliary diseases such as Primary sclerosing cholangitis (PSC) and PFIC2.
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OS-056

Integrative spatial proteomics and transcriptomics of patient liver tissues unravel Claudin-1 as a mediator and therapeutic target for primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a progressive fibrosing cholangiopathy with no effective therapeutic options. We have previously discovered Claudin-1 (CLDN1) as a therapeutic target for liver and biliary fibrosis in PSC. Here, we aimed to investigate the functional role of CLDN1 in PSC as a therapeutic target using patient liver tissues, monoclonal antibodies (mAbs) and patient-derived mouse models.

Method: CLDN1 expression was investigated in liver tissues from three well characterized PSC cohorts from European tertiary care centers combining integrative scRNA-seq, spatial transcriptomics and proteomics analyses. For proof-of-concept and perturbation studies CLDN1-specific mAbs were applied to bile duct ligation, DDC and MDR2-/- mouse models including human liver chimeric FRG-NOD mice engrafted with human hepatocytes.

Results: CLDN1 expression is significantly upregulated in liver tissues of PSC compared to healthy controls and correlates with serum alkaline phosphatase levels and disease stage. Multi-omics molecular profiling of CLDN1+ cells in PSC liver tissues unraveled high CLDN1 expression in a subset of PSC-cholangiocytes characterized by ductular proliferation, cell plasticity and pro-fibrogenic and pro-carcinogenic signaling. CLDN1+ cholangiocytes and hepatocytes line fibrotic scar lesions, co-expressing TNF-alpha and osteopontin, thus playing a central role in disease progression. Treatment with CLDN1-specific mAbs resulted in a marked reduction of fibrosis and cholestasis across mouse models by inhibition of NFkB, SRC, NOTCH and AKT signaling in cholangiocytes and de-differentiated hepatocytes. In a human liver chimeric mouse model, CLDN1 mAb treatment modulated the cell plasticity of human liver epithelial cells.

Conclusion: CLDN1 expression is a candidate biomarker of PSC progression. Co-expression data in patient cohorts combined with mechanism of action and proof-of-concept studies identify CLDN1 as therapeutic target and open the perspective for the clinical development of CLDN1-specific mAbs to treat PSC.

OS-057-YI

Evaluating the 2023 EASL guidelines for intrahepatic cholestasis of pregnancy: risk stratification and outcomes in 4,000+ U.S. patients

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Background and aims: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy, varying in incidence based on population and associated with adverse fetal outcomes. We assessed the prevalence and outcomes of ICP categories defined by the 2023 European Association for the Study of the Liver (EASL) guidelines in a diverse U.S. population.

Method: We conducted a retrospective cohort study (January 2009-April 2024) using data from our large, ethnically diverse health system. Suspected ICP patients were identified by pregnancy records with total serum bile acids (TSBA) ordered and categorized based on EASL guidelines: Group A (normal TSBA, ALT/AST), B (elevated ALT/AST, normal TSBA), or C (TSBA > 19, normal or elevated ALT/AST). Analyses included first pregnancies, with 76% having obstetric outcome data. Post-pregnancy diagnoses were defined as occurring 6 months after peak TSBA. Multinomial and binary logistic analyses, adjusted for potential confounders, were performed to identify predictors and outcomes of each group.

Results: Among 178,889 pregnancies, we identified 4,764 (2.7%) cases of suspected ICP, involving 4,240 unique patients. Of these, 875 (21%) had TSBA ≥ 10 and 83 (2%) had levels ≥ 100. The cohort (36% White, 23% Hispanic, 12% Asian, 10% Black) was classified as Group A (64%), B (25%), or C (11%). Ursodiol was prescribed to 10% of A, 25% of B, and 67% of C. Mean age (32.5 years) and BMI (29) were similar across groups. Hispanic ethnicity was associated with Group C, compared to A (RRR 1.72, 95% CI: 1.31–2.24) and B (RRR 1.50, 95% CI: 1.12–2.01). Compared to A, pre-existing liver disease was associated with a higher likelihood of being classified in Groups C (RRR 5.12, 95% CI: 3.17–8.26) and B (RRR 1.94, 95% CI: 1.44–2.61). Odds of post-pregnancy liver disease were highest in B (OR 3.24, 95% CI:1.97–5.34) compared to A. Group B showed independent associations with gestational hypertension (OR 2.25, 95% CI: 1.55–3.26), preeclampsia (OR 3.78, 95% CI: 2.46–5.81), and fetal respiratory distress syndrome (OR 2.32, 95% CI: 1.61–3.33), compared to A. Group C had higher odds of preterm birth compared to A (OR 10.93, 95% CI: 8.20–14.56) and B (OR 4.06, 95% CI: 2.99–5.50). Within C, preterm birth rates increased with rising TSBA: 44% with TSBA < 40, 50% with TSBA ≥ 40 and <100, and 69% with TSBA ≥100 (p = 0.003).

Conclusion: This study evaluates the applicability of the 2023 EASL guidelines for suspected ICP, demonstrating how group characteristics can guide risk stratification. Our findings suggest that both elevated TSBA (Group C) and elevated ALT/AST alone (Group B) warrant surveillance. Identifying elevated ALT/AST alone as a potential surveillance indicator has global relevance, offering an accessible screening tool when TSBA may be unavailable. The association of ICP with Hispanic ethnicity and pre-existing liver disease highlights the importance of targeted screening, while post-pregnancy liver disease risk underscores the value of long-term follow-up.

OS-058

Screening for biliary dysplasia using brush cytology in PSC: Accuracy, risk factors and outcomes

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Background and aims: PSC is a chronic inflammatory condition resulting in strictures in bile ducts, leading to cholestasis and cirrhosis. Chronic inflammation significantly increases the risk of biliary dysplasia (BD) and cholangiocarcinoma (CCA), with a relative risk up to 973-fold. The cumulative risk of developing CCA after 10, 20, and 30 years of PSC is 6%, 14%, and 20%, respectively. CCA has a poor prognosis, with a 5-year survival <10%. The optimal screening strategy for CCA remains controversial, but EASL and AASLD guidelines recommend annual surveillance using US and/or MRI/MRCP. Brush cytology (BC) allows for the early detection of BD, potentially identifying malignant transformation before CCA develops. In our unit, BD detected ≥3 times during screening is an indication for transplantation (LTx) evaluation. This study aimed to evaluate the sensitivity and specificity of BC in detecting CCA and assess risk factors for BD in a prospective cohort of patients with PSC undergoing ERCP. Patient outcomes were also analyzed.
Method: We included 989 patients from a prospective registry who underwent ERCP and BC for dysplasia surveillance. Exclusions (n = 102) were age <18 or >65 years, CCA ≤1 year of diagnosis (n = 35), serious concomitant disease or malignancy (n = 1), or LTx (n = 2). We analyzed demographic, laboratory, and imaging data, including liver function tests, ERCP scores, and biliary biomarkers (IL-8 and calprotectin), comparing patients who developed BD≥3 times or CCA (composite endpoint) to those who did not. We calculated optimal cutoff values, time-weighted AUCs, and sensitivity/specificity for potential predictors of the composite endpoint.
Results: Among the cohort, 10% had BD detected once or more, and 43 patients (4.3%) reached the composite endpoint. Median follow-up was 10.6 years (IQR: 5.6–16.6) for patients without BD/CCA and 6.7 y (IQR: 2.4–10.9) for those with dysplasia/CCA. Factors associated with the composite endpoint included intra- and extrahepatic disease, high ERCP scores, elevated AST, bil, IgG4, CA19–9, IL-8, and calpro levels. However, the ERCP score (≥7) was the only significant predictor (AUC 0.87) for composite end point. Only 10 (1,2%) patients with negative BC (n = 884) developed CCA during 25 years f/u. For BD detected ≥1x, sensitivity was 0.61 (95% CI: 0.42–0.78) and specificity 0.92 (95% CI: 0.90–0.93). The negative predictive value was 0.99 (95% CI: 0.98–1.00), and accuracy 0.91 (95% CI: 0.89–0.92). Among 24 patients who underwent LTx for suspected malignancy based on BD in BC≥3 times, explant analysis confirmed dysplasia in all cases: LGD (n = 10), HGD (n = 10), ca in situ (n = 1), and CCA (n = 3).
Conclusion: Brush cytology demonstrates an excellent negative predictive value, effectively excluding CCA development over a 25-year follow-up. Repeated BD is a highly sensitive marker for biliary neoplasia in explant. The ERCP score emerged as the sole significant predictive marker for biliary neoplasia or CCA, underscoring its critical role in PSC surveillance.

OS-059

Volixibat for the treatment of cholestatic pruritus in primary biliary cholangitis: an adaptive, randomized, placebo-controlled phase 2b trial (VANTAGE): 28-week interim results

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Background and aims: Cholestatic pruritus (CP) is a debilitating symptom of primary biliary cholangitis (PBC) which greatly impacts overall quality of life. Elevated serum bile acids (sBAs) have been implicated to play a role in CP. Volixibat (VLX) is an ileal bile acid transporter inhibitor (IBATi) which blocks the enterohepatic recirculation of bile acids, leading to reductions in sBA. Here we present the

interim analysis (IA) for VANTAGE which evaluated two doses of VLX for efficacy and safety in PBC.
Method: VANTAGE is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in adults with PBC and CP. The study has an adaptive design with a dose selection period with an IA (1:1:1 randomization, VLX 20 mg, 80 mg or PBO BID) and a pivotal period (1:1 randomization, selected dose or PBO BID), where efficacy and safety of the selected dose will be confirmed. The primary efficacy endpoint is the mean change in Adult ItchRO score (0–10 pruritus scale) from Baseline through Week 28 in participants with moderate-to-severe pruritus. The PBC-40 assessment scale was a key secondary endpoint. The IA was conducted when approximately 12 participants per treatment arm completed Week 16 or prematurely discontinued study drug. Previously, results were reported through Week 16. Here, we report on data out to 28 weeks of treatment.
Results: A total of 31 participants with moderate-to-severe pruritus were randomized (20 mg VLX = 10; 80 mg VLX = 10; PBO = 11). Mean Baseline ItchRO scores were balanced between groups. Volixibat treatment led to rapid reductions in ItchRO with the VLX combined dose group achieving a statistically significant −3.78-point reduction from Baseline ($p < 0.0001$) and a placebo-adjusted response of −2.51 ($p = 0.0004$). Each VLX dose achieved statistically significant and similar responses. Overall, 70% of participants who received VLX achieved ≥50% reduction in sBA. Improvements in some domains of the PBC-40 were observed with VLX. No new safety signals were observed, with a similar incidence of adverse events between VLX treatment groups. The most common adverse event in the VLX groups was diarrhea; all were mild in severity; 1 patient discontinued therapy due to mild diarrhea.
Conclusion: Volixibat led to early and significant reductions in PBC-associated cholestatic pruritus and fatigue, with no new safety signals observed through 28 weeks of treatment. Given similar results between VLX doses, the 20 mg BID dose was selected for Part 2 of VANTAGE, constituting a new promising therapy to address important symptoms in PBC..

Liver tumours: Clinical aspects except therapy

OS-060-YI
Phase III trials in hepatocellular carcinoma: IMbrave 050 and strategies to address non-proportional hazards
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Background and aims: Immunotherapy has revolutionized the management of hepatocellular carcinoma (HCC), although it has resulted in issues with non-proportional hazards (NPH) in phase III randomized trials (RCTs). Notably, the IMbrave050 study showed a positive interim analysis (IA) followed by a subsequent negative outcome. Our study aims to analyze the presence and impact of NPH in the most relevant RCTs in HCC and to propose strategies to ensure a robust interpretation of both interim and final analyses (FA).
Method: Key phase III RCTs in HCC reported from 2008–2024 were selected. Kaplan-Meier survival curves were reconstructed, and the proportional hazards assumption was evaluated using the Grambsch-Therneau test. For NPH, we proposed optimal timing for IA defined by a minimum follow-up of twice the estimated median of the primary endpoint for the control group or by reaching ≥60% of estimated events. In these RCTs, we assessed efficacy by MaxCombo test and effect size by the ratio of restricted mean survival time (rRMST) and piecewise HR (pHR).
Results: Out of 17 phase III RCTs included, 4 exhibited NPH, all of them assessing immunotherapies. We identified different patterns of NPH: 1) diminishing effects (IMbrave050, recurrence-free survival; and LEAP-012, progression-free survival), 2) delayed effects (HIMALAYA, overall survival) and 3) crossing of curves (CheckMate 9DW, overall survival). All NPH trials showed concordance between the log-rank and MaxCombo tests. In IMbrave050, IA showed a MaxCombo p-value: 0.028, whereas FA showed a p-value: 0.326. Correspondingly, the magnitude of benefit showed rRMST ratios at 12, and 36 months of 0.89 ($p < 0.001$) and 0.93 ($p = 0.08$) and the pHR prior/after 12 months was 0.59 (0.43–0.73) and 1.12 (0.88–1.37). In the LEAP-012 trial, the rRMST were significant at both 12 and 24 months, with 0.83 ($p < 0.001$) and 0.79 ($p < 0.001$) respectively. HIMALAYA displayed a pattern of delayed effects [rRMST at 12 and 36 months: 0.96 ($p = 0.134$) and 0.87 ($p = 0.004$)], whereas CheckMate 9DW displayed one of crossing of curves [rRMST at 12 and 36 months: 1.05 ($p = 0.074$) and 0.93 ($p = 0.003$)]. The pHR in LEAP-012 was 0.55 (0.38–0.69) and 0.83 (0.52–1.13) prior/after 12 months, respectively. In HIMALAYA, the pHR at 12 months was 0.87 (0.69–1.06) and 0.72 (0.57–0.86) thereafter, while in CheckMate 9DW was 1.09 (0.80–1.36) and 0.66 (0.50–0.83).
Conclusion: The inconsistency between interim and subsequent efficacy analysis of IMbrave050 was related to NPH. In cases of NPH at IA, analysis of the significance and magnitude of benefit requires a minimum follow-up duration or number of events prior prematurely stopping an RCT. We propose implementing these criteria in the IA of phase III RCTs in HCC, particularly in the setting of immunotherapy.

OS-061
A holistic approach of systematic tumor and non-tumor biopsy during percutaneous radiofrequency ablation for hepatocellular carcinoma: diagnostic, prognostic and therapeutic impact
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Background and aims: We prospectively assess the feasibility, safety, and diagnostic/prognostic value of systematic tumor and non-tumor liver biopsies collected during radiofrequency ablation (RFA) for a first diagnosis of hepatocellular carcinoma (HCC).

Method: We included patients diagnosed with a first diagnosis of HCC between 2015 and 2021, treated with percutaneous RFA and with both tumor and non-tumor biopsies in a tertiary center. We analyzed the percentage of diagnostic tumor biopsies and correlated results of histological findings with prior diagnoses and oncological outcomes. Non-tumor liver biopsy results were compared with multidisciplinary tumor board (MTB) diagnosis of cirrhosis.
Results: 248 patients (86% male, median age 68) with 302 tumors treated by RFA were included. HCC was single in 78%, bifocal in 21%, with a median size of 24 mm. 87% of the patients had cirrhosis (based on the results of the non-tumor liver biopsy done per-procedure). Bleeding occurred in 6 cases (1.9%), requiring intervention in 2, with no death. Nor low platelets-count (<100000/mm^3) nor anticoagulation nor antiplatelet agent were associated with bleeding. Biopsies were diagnostic in 66% with positivity linked to nodule size ($P < 0.0001$), location ($P = 0.04$), and ultrasound visibility ($P = 0.004$). Among the 302 biopsies, 34% were not diagnosis, 61% diagnosed HCC, 3% cholangiocarcinoma (n = 3)/hepatocholangiocarcinoma (n = 6), and 2% dysplastic nodules (n = 7). Discrepancies between MTB and histological diagnosis occurred in 5% of cases. To note, all the cholangiocarcinoma or hepatocholangiocarcinoma diagnosed with the per-ablation biopsy were classified as LIRADS 5 by imagery reviewing. Survival was significantly shorter in patients with cholangiocarcinoma/hepatocholangiocarcinoma ($P < 0.001$). Pathological subtypes of HCC were not otherwise specified HCC in 55%, steatohepatitic-HCC in 19%, macrotrebacular massive-HCC (MTM-HCC) in 15%, scirrhous-HCC in 6.3%, clear cell-HCC in 2.8%, and lympho-epithelioma like-HCC in 2.3%, MTM-HCC was associated with higher rate of tumor recurrence ($P = 0.037$). Presence of more than 30% of tumor cells at formalin-fixed paraffin-embedded samples was associated with expression of cancer-related genes at transcriptomic of the corresponding frozen samples assuring their usefulness for molecular analysis. Among non-tumor biopsies, cirrhosis was histologically confirmed in 82% of cases with a 15% discrepancy between diagnosis of cirrhosis at MTB and biopsy, 10.9% (n = 27) were considered cirrhotic by MTB and identified as non-cirrhotic on the non-tumor biopsy.
Conclusion: Systematic tumor and non-tumor biopsy during RFA for a first diagnosis of HCC is feasible, safe, and has diagnostic, therapeutic, and prognostic value.

OS-062
Liver transplantation after downstaging of intermediate and advanced HCC with atezolizumab-bevacizumab: a prospective study (ImmunoXXL)

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Background and aims: Tumor downstaging (DS) is an accepted strategy to increase liver transplantation (LT) eligibility in patients with hepatocellular carcinoma (HCC). Given the results of the atezolizumab-bevacizumab (A + B) therapy in advanced HCC, its use within DS protocols should be investigated.
Method: The ImmunoXXL study (NCT05879328) is a phase 2 study investigating LT after successful DS with A + B. Primary endpoint is safety of LT after A + B while secondary endpoint is whether LT can increase progression-free survival (PFS) compared to that reported by the IMbrave150 RCT for patients with advanced HCC in response to A + B. Adverse events (AE) graded ≥3 were recorded throughout and assessed if immune-related (irAE). Spectral quantitative pathology imaging and deconvolution of immune RNA signatures were part of explant pathology analysis.
Results: 16 patients with HCC beyond expanded transplant criteria at presentation obtained a successful DS to within transplant criteria after a minimum of 3 months of A + B (30% PR, 70% CR according to mRECIST). HCC at presentation had median size: 6.5 cm (IQR: 3 - 8), median AFP 283 (IQR: 6 - 1080) portal vein thrombosis (PVT) and multifocality in 50% of cases. 15 (94%) patients had received previous loco-regional therapies (Y^{90} in 9 pts). Median A + B treatment duration was 4.7 months (IQR: 2.4 - 7.6) for 7.5 cycles (IQR: 4 - 9). Interval from last A + B dose to LT (washout period) was 46.5 days. Median follow-up from LT listing was 16 months. Pretransplant irAE occurred in 3 (19%) pts (1 liver decompensation, 2 hypertension) while posttransplant irAE (25%) were 4 acute rejections (RAI > 4) requiring biopsy and steroids boluses. Patients with acute rejection had a significantly larger pre-LT naive T cell pool (null antigen-specificity) with respect to non-rejecting patients. Overall, 90 days morbidity (with 2 reLT) and mortality (1 death) after LT were 62.5% and 6.3% respectively, with12mo. graft survival of 87.5%. Explant pathology revealed 10 complete and 6 partial responses with a concordance between preLT radiology and postLT pathology of 62.5% (Pearson's rho: 0.04 p: 0.883). Tumor microenvironment (TME) of A + B down staged tumor specimens, revealed a composite milieu enriched in tertiary lymphoid structures, trained myeloid effectors and antigen experienced CD8+ T cells. TME changes could be correlated to the duration of pretransplant A + B washout period. As there was 1 HCC recurrence in the lung, the recurrence free survival and overall survival after transplant is 94% and 90% at 2 yrs, respectively.
Conclusion: LT after consistent downstaging with atezolizumab-bevacizumab alone or in combination with loco-regional treatments is safe, effective and competitive strategy for improving outcomes of patients carrying HCC beyond current transplant indications. LT in this contest has implications on HCC control and surveillance.

OS-063
Digital risk stratification management platform improves the early diagnosis and surveillance of liver cancer in china: a real-world study in Zhuhai people's hospital

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Background and aims: Liver cancer imposes a substantial burden on China, with hepatocellular carcinoma (HCC) accounting for 85%-90%. The prognosis for HCC patients remains poor, primarily due to late-stage diagnoses, especially among patients with chronic hepatitis B (CHB). Various diagnostic methodologies demonstrate potential in enhancing early-stage HCC detection rates, including serum

biomarkers such as alpha-fetoprotein (AFP) and PIVKA II, and algorithmic scores such as GAAD, which has been recommended by the latest China Anti-Cancer Association guideline. Zhuhai People's Hospital developed a digital risk stratification platform aimed at facilitating the early screening and diagnosis of HCC, particularly utilizing the GAAD score. This study evaluates the clinical performance of this platform in a real-world setting.

Method: This study included CHB patients without prior diagnoses of HCC who visited the Department of Hepatology and Infectious Disease at Zhuhai Hospital since March 2023. Each patient followed a standardized clinical pathway encompassing screening, diagnosis, treatment, and follow-up management based on individual HCC stages and risk stratification result. The digital platform integrated various HCC risk assessment results, including the GAAD score. Patients were categorized into four distinct risk groups: low, medium, high, and very high risk, with corresponding surveillance intervals of 12, 12, 6, and 3 months, respectively. Total follow-up rate and the rate of early-stage HCC diagnoses (defined as CNLC stage Ia and Ib) were recorded and compared with reported national average value. Receiver-operating characteristic (ROC) curves were plotted to evaluate HCC diagnostic performance, and the area under the ROC curve (AUC) and corresponding sensitivity and specificity of AFP, PIVKA-II, and GAAD were calculated and compared.

Results: From March 2023 to October 2024, a total of 3,958 CHB patients were enrolled, with 3,952 successfully completing the risk assessment. Among these, 32 patients (0.8%) were diagnosed with HCC, predominantly males (81.3%). 30 patients were identified at the early stage of HCC, with a higher early diagnosis rate compared to the national average (93% vs. 30%). Additionally, 2,519 patients attended at least one screening visit, resulting in an enhanced follow-up rate (63.6% vs. 30%). In the subgroup of 1,803 patients with available GAAD scores, 16 HCC cases were detected, with 15 of them identified at an early stage (94%). The ROC curve analysis indicated that the GAAD score exhibited superior performance in detecting HCC compared to AFP and PIVKA II alone (AUC: 0.8426 vs. 0.6558 vs. 0.6674), with a high specificity of 99.22%.

Conclusion: This digital risk stratification platform for standardizing HCC screening and management has improved early diagnosis and follow-up rates relative to national averages. The GAAD score stands out as a reliable tool for early-stage HCC screening, showcasing high diagnostic accuracy performance and specificity.

OS-064

Integrating gut microbiota composition and machine learning to predict therapeutic response in hepatocellular carcinoma treated with Atezolizumab and Bevacizumab: exploratory analysis from the phase 3b AMETHISTA study

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Background and aims: This exploratory analysis aimed to assess gut microbiota (GM) composition as a potential predictive biomarker of treatment response in patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab (AtezoBev) in the multicenter, phase IIIB, single-arm AMETHISTA study.

Method: Fecal specimens were collected from 114 HCC patients at baseline, immediately before starting AtezoBev. We analyzed GM profiles at baseline, and at 3 and 6 weeks (corresponding to immediately before the second and third infusions, respectively). Radiological responses were classified at 6 weeks as progressive disease (PD, n = 18, 15.8%), stable disease (SD, n = 84, 73.7%), or objective response (R, n = 12, 10.5%, none with complete response). Two types of patient grouping were carried out: a) patients were divided into Objective Responders (R) and Non-Responders (NR) to test the prediction of objective response; b) patients with primary PD were separated from those with Disease Control (DC). Predictive models were developed using machine learning (ML) techniques, with class balancing performed by Synthetic Minority Over-sampling Technique (SMOTE). A group of 437 healthy controls from a previous study was used as a comparator at baseline.

Results: At baseline, HCC patients exhibited reduced GM diversity and increased pro-inflammatory taxa compared to healthy controls. Within the HCC group, R patients showed lower levels of inflammatory genera (*Senegalimassilia*, *Eggerthella*, *Turicibacter*) and higher levels of anti-inflammatory taxa (*Dialister*) at baseline compared to NR patients. ML models demonstrated high accuracy in predicting response (Neural Network AUC: 0.998; Random Forest AUC: 1.0). At 3 weeks, NR patients retained higher abundances of pro-inflammatory genera (*Tyzzerella*, *Eggerthella*, *[Ruminococcus] torques*), while R patients showed enrichment in lactic acid bacteria linked to immune support (*Lactobacillus*, *Dialister*). Primary PD patients were enriched in inflammatory taxa (*Senegalimassilia*, *[Eubacterium] hallii*), while DC patients had higher *Bifidobacteriu*m.

Conclusion: Our findings suggest that GM configuration at baseline may serve as a biomarker to predict group-level response to AtezoBev in HCC. Distinct inflammatory taxa associated with NR and PD underscore the role of GM in modulating therapeutic efficacy. These results warrant further studies about GM and microbiome-targeted interventions to enhance treatment outcomes.

Viral Hepatitis B/D Current clinical practice

OS-065

The multi-center study of functional cure for inactive hepatitis B surface antigen carriers in China: interim analysis of E-cure study

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Background and aims: Approximately 30% to 60% of inactive hepatitis B surface antigen carriers (IHCs) exhibit significant liver inflammation (G ≥ 2) or fibrosis (F ≥ 2) on liver biopsy, underscoring the need for therapeutic intervention. This study aimed to investigate the efficacy of different peginterferon alpha (PegIFNα)-based treatment strategies and factors influencing HBsAg clearance for IHCs.
Method: A multi-center real world study (E-cure) started in January 2022. The study enrolled IHCs consistent with the definition of inactive CHB in the guideline of AASLD 2018. The patients received one of the following treatments: Nucleos(t)ide analogues (NAs) monotherapy, PegIFNα monotherapy, Initial combination therapy (PegIFNα-2b with NAs for 12–24w followed by PegIFNα-2b monotherapy), Whole process combination therapy (combination of PegIFNα-2b and NAs for the entire period) and Sequential combination therapy (NAs for 12–24w followed by PegIFNα-2b add-on).
Results: As of November 4, 2024, 7899 individuals were screened and 5328 eligible IHCs were included. Of these, 1038 completed 48 weeks of treatment, with 691 in the PegIFNα monotherapy group, 94 in the Initial combination therapy group, 212 in the Whole process combination therapy group, and 41 in the s Sequential combination therapy group. The median (IQR) age of all patients was 41.0 (34.0–48.0) years, 62.1% were male, 38.2% had a baseline HBsAg < 100 IU/mL, 35.0% had levels between 100 and 1000 IU/mL, 26.8% had levels ≥ 1000 IU/mL, and 90.8% had a baseline HBV DNA < 1000 IU/mL. The HBsAg clearance and seroconversion rates in patients treated with PegIFNα-2b increased as the duration of treatment progressed. By week 48, the cumulative HBsAg clearance rates for the PegIFNα monotherapy, Initial combination therapy, Whole process combination therapy and Sequential combination therapy groups reached 53.3%, 34%, 58% and 65.8%, respectively (P < 0.001), and the cumulative HBsAg seroconversion rates reached 36.8%, 17.6%, 30.1% and 53.3%, respectively (P < 0.001). The cumulative HBsAg clearance rates at 48 weeks for the baseline HBsAg <100 IU/ml, 100–1000 IU/ml, and >1000 IU/ml groups were 72.56%, 42.62%, and 8.89%, respectively. HBV DNA was undetectable in more than 90% of patients in the above 4 groups (92.8%, 95.7%, 97.9% and 95%). Multivariate logistic regression analysis indicated that a lower baseline HBsAg level (OR = 0.220, 95%CI 0.169–0.280, p < 0.001), a higher HBsAg reduction at 24 weeks (OR = 5.168, 95%CI 3.909–7.031, p < 0.001), and the Whole process combination therapy group (OR = 3.064, 95%CI 1.589–6.106, p = 0.001) had a higher likelihood of achieving HBsAg clearance at 48 weeks.
Conclusion: PegIFNα-2b based therapy proved effective for IHCs to pursue functional cure. The efficacy for HBsAg clearance is associated with baseline HBsAg level, HBsAg reduction at 24 weeks, and the treatment regimen.

OS-066

Predictors of undetectable hepatitis delta virus RNA at 48 weeks after end of treatment with bulevirtide monotherapy in the MYR 301 study

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Background and aims: Bulevirtide (BLV) is approved in Europe for the treatment of compensated chronic hepatitis delta (CHD). In MYR301, a Phase 3 study evaluating BLV monotherapy for 2–3 years, a subset of patients who achieved undetectable HDV RNA by end of treatment (EOT) maintained undetectable viraemia at 48 weeks (W) after EOT (FU48). Here, we present predictors of sustained HDV RNA undetectability through FU48 after 96W or 144W of BLV treatment.
Method: Data were analysed from 149 patients with CHD in MYR301 who were randomised to immediate treatment with BLV 2 or 10 mg/d for 144W, or to 48W of no treatment followed by BLV 10 mg/d for 96W (DT → 10 mg). All patients were to be followed through FU48. Logistic regression modelling (adjusted for treatment group) was performed to examine potential predictors of sustained HDV RNA undetectability (defined as less than the lower limit of quantitation [LLOQ; target not detected at follow-up in patients with available data]) through FU48 in those with undetectable viraemia at EOT.
Results: Baseline (BL) characteristics were similar between all treatment arms. Across all arms, 65/149 (44%) patients achieved HDV RNA undetectability at EOT, of whom 23/64 (36%) with available follow-up HDV RNA data had sustained undetectability through FU48. Rates of sustained undetectability were higher in the immediate treatment arms (2 mg: 7/14, 50%; 10 mg: 10/25, 40%) vs the delayed treatment arm (DT → 10 mg: 6/26, 23%). Undetectability rates at EOT were higher in patients who received BLV 10 mg, but the relapse rate was lower in the few patients with HDV RNA

undetectable in the BLV 2 mg group. BL predictors of sustained undetectability posttreatment included BL HDV RNA less than a median of 4.5 log_{10} IU/mL (odds ratio [OR]: 6.2; 95% CI [1.9, 20.8]; p = .003) and lower BL hepatitis B surface antigen (HBsAg) level (OR: 0.3 per log_{10} IU/mL; 95% CI [0.1, 0.8]; p = .019). On-treatment predictors included greater duration of continuous undetectability at EOT (OR per additional week: 1.0; 95% CI [1.0, 1.1]; p < .0001), HBsAg loss or decrease by ≥ 1 log_{10} IU/mL (OR: 7.2; 95% CI [1.2, 42.3]; p = .030), and W144 antidrug antibody (ADA) incidence (OR: 10.2; 95% CI [1.9, 55.7]; p = .008). The proportion of patients with sustained posttreatment undetectability was 9/10 (90%) in those with ≥ 96W of undetectability at EOT, 11/22 (50%) in those with ≥ 48 to < 96W, and 3/32 (9%) in those with < 48W. Of patients with ADA incidence by W144, 8/10 (80%) had sustained undetectability vs 15/54 (28%) of those without. BL cirrhosis was not a predictor of sustained posttreatment undetectability; 13/32 (41%) with cirrhosis had sustained undetectability vs 10/32 (31%) without cirrhosis.
Conclusion: In patients with CHD treated with BLV monotherapy for 96W or 144W, early and sustained HDV RNA undetectability predicted sustained undetectability during follow-up. Note: PL and HW contributed equally.

OS-067-YI

Long term outcomes after nucleos(t)ide analogue cessation – an extended follow up study from the RETRACT-B cohort

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Background and aims: Stopping nucleos(t)ide analogues (NA) in a selected group of patients with chronic hepatitis B (CHB) can result in increased rates of HBsAg loss. However, long-term follow up (FU) data after NA cessation is lacking. This study aimed to assess the long-term outcomes after NA withdrawal in a large global cohort.
Method: Extended FU data were collected from patients previously enrolled in the RETRACT-B cohort. New patients were added if they met the inclusion criteria, i.e. virally suppressed, HBeAg negative and HBsAg positive at end of therapy (EOT). Patients with a history of HCC, co-infection at EOT, Peg-IFN therapy <1 year prior to EOT or ALT≥5xULN at EOT, were excluded. Retreatment criteria were study specific or according to local guidelines.The primary outcome was the 10-year off-treatment (off-Rx) HBsAg loss rate. Secondary outcomes were retreatment- and ALT-flare (≥5xULN) rates. Time to event was defined until HBsAg loss or loss to follow up, censoring if therapy was re-stopped. Cumulative incidences were derived using Aalen-Johansen (AJ) estimators considering retreatment as competing event. Gray's test was used to test equality of these incidences between different groups.
Results: In total, 2029 patients were included. At EOT, mean age was 52 (±11) years, 1647 (81%) were Asian, 299 (15%) Caucasian, and 83 (4%) Black/other. 1464 (72%) were male and 801 (40%) received TDF/TAF and 1094 (54%) ETV. 211 (10%) patients had a history of cirrhosis, 283 (14%) were HBeAg positive at start of therapy and median treatment duration was 3 [IQR 3–5] years. Mean HBsAg at EOT was 2.7 (±0.8) log10 IU/mL (<100/100–1000/>1000: 16/45/38%) and median ALT was 23 [18–32] U/L. Median total and off-Rx FU time after EOT were 65 [36–99] and 28 [10–66] months, respectively. The 10-year cumulative incidence for off-Rx HBsAg loss was 17% (<100/100–1000/>1000: 53/13/6%, p < 0.001) and 4% for HBsAg loss after retreatment. When applying the RETRACT-B stopping criteria, 8-year off-Rx HBsAg loss was 56% for Caucasian <1000 IU/mL vs. 43% for Asian <100 IU/mL, compared to 5% and 5% when not meeting these criteria (p < 0.001). Results were consistent in newly included patients. The 10-year retreatment rate was 59% (<100/100–1000/>1000 IU/mL: 27/62/71%). The 5- and 10-year cumulative incidence for ALT-flares were 29 and 30%, respectively. 55 (3%) patients developed hepatic decompensation, of whom 19 (35%) had clinical symptoms (i.e. jaundice, ascites, hepatic encephalopathy or variceal bleeding). 41 (2%) patients died of whom 16 due to liver related events (e.g. HCC).
Conclusion: The 10-year cumulative off-treatment HBsAg loss rate was 17%, with more than half of the patients being retreated. Patients with HBsAg levels <100 IU/mL seem to benefit the most from NA cessation (HBsAg loss rate 53%), whereas NA withdrawal in patients >1000 IU/mL should be discouraged when aiming for functional cure (HBsAg loss rate 6%).

OS-068

Course and clinical outcomes of chronic hepatitis delta: a longitudinal analysis of 565 patients from the D-Solve consortium and HDV1000 database

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Background and aims: Chronic hepatitis Delta (CHD) is considered the most severe viral hepatitis. The predictors of liver disease progression are ill-defined and some studies challenged this accelerated course. Aim of the study was to examine the clinical course and outcomes of CHD patients in a large real-life cohort.
Method: CHD patients with at least 3 years follow-up from the multicenter retrospective D-SOLVE consortium and HDV1000 database (6 European centers) were enrolled. Longitudinal changes in biochemical and laboratory markers were assessed. Time to event analysis was performed and predictors of liver-related events (LREs) were assessed in univariable and multivariable Cox regression analysis.
Results: Among a total of 1004 patients, 565 (56%) with ≥3 years follow-up were included: median (IQR) age was 44 (45–56) years, 55% males, 60% of European origin. 192 patients (34%) had cirrhosis and 55 (10%) history of previous LRE. At study start, median ALT were 57 (36–98) U/L, GGT 35 (23–66) U/L, platelets 170 (115–218) × 10^9/L, liver stiffness measurement (LSM) 8.2 (5.9–13.6) kPa, HBV genotype was D in 62%, HDV genotype 1 in 83%, 86% HBeAg negative, HBsAg 3.7 (3.0–4.1) Log_{10}IU/mL, HDV RNA detectable in 72%; 56% received interferon (IFN), 18% Bulevirtide, 83% were under NUC therapy. During a median follow-up of 55 (46–62) months, patients with normal ALT increased from 31% to 47%, median AST and GGT levels improved. In 264 patients with ≥2 LSM, LSM remained stable in 151 (57%), improved in 75 (28%) and increased in 38 (14%). De-novo cirrhosis was diagnosed in 48 patients; cumulative 1-, 3- and 5-year incidence rates of cirrhosis were 1.3%, 5.1% and 13.1%, respectively. 46 (8%) patients developed a de-novo LRE (HCC n = 21, ascites n = 17, variceal bleeding n = 5, hepatic encephalopathy n = 3). The overall 1-, 3-, and 5-year cumulative rates of LREs were 0.8%, 2.4% and 9.6%, respectively. The corresponding figures were 0.2%, 0.9%, 5.2% for HCC and 0.6%, 1.3% and 4.0% for decompensation, respectively. 14 (2%) patients died and 11 (2%) underwent liver transplantation (LT). The overall LT or death-free survival rates at 1-, 3- and 5-years were 98.9%, 98.6% and 95.3%, respectively. At Cox regression univariate analysis, ALT>ULN and detectable HDV RNA at study start were associated with cirrhosis onset; at multivariate analysis, only ALT>ULN (HR 2.75; 95% CI 1.04–7.28, p = 0.04) remained significant. Age, HBV duration, HDV duration, NUC treatment, ALT>ULN, and detectable HDV RNA at study start predicted LREs at univariate analysis, while at multivariable analysis only age (HR 1.05; 95% CI 1.03–1.07, p < 0.0001) and detectable HDV RNA (HR 5.72, 95% CI 2.25–14.52, p = 0.0002) remained significant.
Conclusion: In a large real-life cohort of CHD patients, cumulative rates of cirrhosis and LREs were lower than expected. ALT, age and detectable HDV RNA were the main determinants of liver-related outcomes.

OS-069

A Randomised trial of nucleos(t)ide withdrawal vs nucleos(t)ide withdrawal with adjuvant pegylated-interferon in HBeAg-negative hepatitis B virus infection to promote HBsAg clearance (NUC-B)

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Background and aims: Finite therapy resulting in a functional cure (sustained hepatitis B surface antigen (HBsAg) loss) for patients with chronic HBV infection (CHB) is an important therapeutic goal. In patients with HBeAg-negative infection, nucleos(t)ide analogue (NA) withdrawal may achieve HBsAg loss in 5–20% of patients 3 years after cessation of NA therapy depending on duration of NA therapy, HBsAg level, HBV genotype and patient age. Pegylated interferon (pIFN) is a recognized treatment for CHB but is currently under-utilised and simultaneous treatment with pIFN and NA does not enhance rates of HBsAg loss. We hypothesized that sequential NA withdrawal followed by a short course of pIFN might enhance HBsAg clearance.
Method: NUC-B was a randomized, open-label multi-centre UK trial in NA-treated non-cirrhotic HBeAg negative patients with CHB. Patients were allocated to either NA withdrawal alone or NA withdrawal followed by a 16 week course of pIFN 180ug weekly commencing 4 weeks after NA cessation. Randomisation was stratified according to HBsAg quantification. The primary endpoint was HBsAg loss at 3 years. Exaggerated flares were defined according to the following criteria: 1. Bilirubin >35 uMol/l, 2. INR >1.3, 3. ALT > 20 × upper limit of normal, 4. HBV DNA and/or ALT remain persistently elevated for more than 6 months.
Results: 156 patients (82 to NA withdrawal, 74 to NA withdrawal + pIFN) were recruited between 2017 and 2021; median age 45 years, 24% of patients were female, 13.5% were Caucasian, 42% were African and 37% Asian, HBV Genotypes were A 14%, B 4%, C 4%, D 20%, E 15%, other 1%, unknown 42%. HBsAg titre at baseline was 5717 IU/ml in the NA withdrawal group and 4132 IU/ml in the NA withdrawal + pIFN group. HBsAg was < 2000 in 52% of patients in the NA withdrawal group and 51% in the NA withdrawal + pIFN group. In this globally representative group, at 3 years 3% of patients in the NA withdrawal arm and 14% of patients in the NA withdrawal + pIFN arm lost HBsAg (odds ratio 5.39, P = 0.037). In the NA withdrawal arm 34.9% of patients returned to NA therapy compared to 28.4% in the NA withdrawal + Peg-IFN arm. Exaggerated flares occurred in 27.9% of patients in the NA withdrawal arm compared with 13.4% in the NA withdrawal + pIFN arm. Serious adverse events did not differ between the groups.
Conclusion: The use of adjuvant pIFN therapy after withdrawal of NA therapy increases the rate of functional cure of chronic HBV whilst simultaneously reducing the number of exaggerated hepatitis flares thereby improving safety.

Viral Hepatitis B/D – Therapy

OS-070

Achieving undetectable hepatitis delta virus RNA at end of therapy with bulevirtide 10 mg/day with or without with pegylated interferon alpha is strongly associated with post-treatment virologic response in chronic hepatitis delta

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Background and aims: Bulevirtide (BLV) 2 mg is approved for the treatment of chronic hepatitis delta (CHD) in Europe. In an integrated analysis of BLV 10 mg monotherapy or combined with pegylated interferon alpha (PegIFN), we aim to explore whether hepatitis delta virus (HDV) RNA levels undetectable (target not detected; TND) vs below the lower limit of quantification (<LLOQ; target detected [TD]) at end of treatment (EOT) affect post-treatment virologic response.

Method: A pooled analysis of data from patients who completed 2 or 3 years of BLV 10 mg/d with or without PegIFN in the Phase 2 study MYR204 (NCT03852433) and the Phase 3 study MYR301 (NCT03852719) was performed. Patients received (A) BLV 10 mg + PegIFN for 48 weeks (W) followed by 48W of monotherapy with BLV 10 mg (n = 50), (B) BLV 10 mg for 96W (n = 100), or (C) BLV 10 mg for 144W (n = 50). Patients were followed for up to 48W after EOT (FU-48). HDV RNA levels were determined by reverse transcription–quantitative polymerase chain reaction using RoboGene 2.0 (LLOQ 50 IU/mL, limit of detection 6 IU/mL). Virologic response rates at FU-48 were compared between patients with undetectable HDV RNA and those with HDV RNA < LLOQ, TD at EOT.

Results: Demographics were generally similar across groups: male (65%), White (85%), and mean (SD) age 41 (8.2) years. Overall, 41% had compensated cirrhosis, and 53% had prior interferon experience. Mean (SD) HDV RNA, alanine aminotransferase, and liver stiffness were 5.1 (1.38) $\log_{10}$ IU/mL, 109 (88.2) U/L, and 14.0 (9.11) kPa, respectively. At EOT, 48.5% (97/200) overall achieved undetectable HDV RNA: (A) 70% (35/50), (B) 37% (37/100), and (C) 50% (25/50). Additionally, 24% (48/200) had < LLOQ, TD: (A) 16% (8/50), (B) 30% (30/100), and (C) 20% (10/50). At FU-48 in the whole population, undetectable HDV RNA was observed in 24.5% (49/200): 23/50 (46%) of those receiving combination therapy, 14% (14/100) of patients who received BLV monotherapy for 2 years, and 24% (12/50) of those who received 3 years of BLV monotherapy. Of the patients with undetectable HDV RNA at EOT, 46% (45/97) maintained undetectable HDV RNA at FU-48: (A) 60% (21/35), (B) 35% (13/37), and (C) 44% (11/25); 6% (6/97) had < LLOQ, TD at FU-48: (A) 6% (2/35), (B) 9% (3/37), and (C) 4% (1/25). Of those who had < LLOQ, TD at EOT, only 6% (3/48) had undetectable HDV RNA (1 in each group) and 4% (2/48) remained < LLOQ, TD at FU-48, while 71% (34/48) had HDV RNA > LLOQ: (A) 62.5% (5/8), (B) 80% (24/30), and (C) 50% (5/10); during the follow-up period, 9 discontinued the study early.

Conclusion: In patients with compensated CHD, achieving undetectable HDV RNA with TND at EOT is strongly associated with a virologic suppression at 48W post-treatment. Combination therapy with BLV 10 mg/d and PegIFN and longer treatment with BLV monotherapy were associated with higher rates of undetectable HDV RNA at EOT and FU-48. Patients with HDV RNA < LLOQ, TD at EOT are likely to have HDV RNA rebound off therapy.

OS-071

Mitigation of immune dysfunction in patients with sustained suppression of hepatitis B surface antigen after siRNA treatment

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Background and aims: Chronic hepatitis B (CHB) infection is characterized by host immune dysfunction, related to high viral antigen load. Restoration of immune function is critical for achieving and maintaining HBV cure. Novel drugs aiming for finite treatment through achieving functional or partial cure, are in development.[1] We explored the immunological profile of CHB patients who received small interfering RNA (siRNA). (Reference 1: Marc G Ghany et al. Hepatology 2023; 78: 1654–1673.).

Method: CHB patients in our center who received siRNA in clinical trials[2,3] at a median duration of 5.8 years (range 5.0–8.3) from last dose were recruited. We identified 10 patients with sustained HBsAg <100 IU/mL (low HBsAg; median 1.77 log) during long-term follow-up (LTFU), and matched (baseline age and HBeAg) 10 patients with HBsAg ≥100 IU/mL (high HBsAg; median 2.98 log) at LTFU. Peripheral blood mononuclear cells (PBMCs) were evaluated by multicolor flow cytometry characterizing CD4+, CD8+, regulatory (Treg; CD25+CD127^{lo}FoxP3+), T cell subsets, B cells, and markers of exhaustion (PD-1, CTLA-4, TIM-3, LAG-3). Synthetic HBV peptides were co-cultured with PBMCs to assess HBV T cell effector functions including activation (CD38, HLA-DR), proliferation (Ki-67), cytokine production (IFNγ, IL-2) and cytotoxicity (Granzyme B). (References 2–3: Yuen MF et al. J Hepatol 2022; 77:1287–98; Yuen MF et al. Hepatology 2020; 72:19–31).

Results: In the low HBsAg group, the frequency of Treg among CD4+ was significantly lower compared to the high HBsAg group (6.474% vs. 8.646%, p = 0.0006). Expression of LAG-3 and TIM-3 was significantly reduced in CD4+, CD8+, Treg and B cells in the former group (all p < 0.05) along with reduced PD-1 and co-expression of PD-1+CTLA4+ on CD8+ T cells (all p < 0.05). There was a trend for enrichment of central memory (CD45RA-CCR7+CD27+CD28+) among CD4+ T cells (36.6% vs 30.22%, p = 0.056) in the low HBsAg group. Upon HBsAg stimulation, IFNγ production in CD4+ and IL-2 production in CD8+ T cells were markedly increased in the low HBsAg group. No significant differences were observed for the degree of activation, proliferation and cytotoxicity. HBsAg at LTFU, but not at baseline, positively correlated with frequency of Tregs (r = 0.531, p = 0.016), TIM-3 and LAG-3 expression on B and T cells, and negatively correlated with Ki-67 (r = –0.501, p = 0.025) and IFNγ (r = –0.516, p = 0.020) expression on CD4+ T cells.

Conclusion: In patients who received siRNA and achieved sustained low HBsAg <100 IU/mL at >5 years from last dose, the degree of

immune dysfunction in peripheral blood lymphocytes was diminished. Effective siRNA treatment calibrates a new equilibrium between host immunity and the virus.

OS-072-YI

HBV integration can sustain HDV persistence especially in the setting of an absent HBV reservoir and can be a biomarker of response to bulevirtide

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Background and aims: To elucidate the contribution of HBsAg production from HBV-DNA integration in sustaining HDV replicative activity and the potential role of intrahepatic viral markers and transcriptome profiles in modulating response to bulevirtide (BLV).
Method: 70 liver biopsies from eAg-negative patients (pts) (74% NUC-treated) were included: 35 with CHB and 35 with CHD, 6 of them completed 24 weeks of BLV. Combined response to BLV was defined as >2log HDV-RNA decay plus ALT normalization. Droplet-digital PCR was used to quantify intrahepatic levels of cccDNA, pgRNA, HDV-RNA and HBs transcripts from cccDNA and from integrated HBV-DNA (Grudda, 2022). HBs isoforms were quantified by ELISAs. RNA-Seq by Illumina was applied for transcriptome analysis.
Results: CHD and CHB pts had comparable age and NUC-treatment duration. CHD was characterized by lower cccDNA and pgRNA than CHB (median [IQR]: 1 (0.02–12) vs 24 (8–93) copies (cps)/1000 cells and 8 [1–147] vs 518 [57–3,894] cps/1000 cells, $P < 0.0001$ for both). Despite this, in both CHD and CHB, a comparable production of HBs transcripts was observed with >99% of them from integrated HBV-DNA (median [IQR]: 6,041 [323–29,446] and 12,776 [4,570–55,977] cps/1000 cells). In CHD, cccDNA positively correlated with all HBV intrahepatic markers (Rho from 0.55 to 0.58, $P < 0.01$). Conversely, no correlation was observed between cccDNA and intrahepatic HDV-RNA (Rho = 0.1, $P = 0.6$). Notably, 8 pts, despite having undetectable cccDNA, cccDNA-derived HBs transcripts and serum HBV-DNA, had considerable levels of intrahepatic and serum HDV-RNA (median [IQR]: 5,495 [976–14,946] cps/1000 cells and 6.0 [4.8–6.9] logIU/ml), as well as of integration-derived HBs transcripts (median [IQR]: 3 [1–497] cps/1000 cells) and of all three HBs isoforms (median [IQR] ng/ml: 1,116 [123–3,987] for S-HBs, 368 [8–1,894] for M-HBs and 1.4 [0.2–5.6] ng/ml for L-HBs). Focusing on 6 CHD pts undergoing BLV therapy, 3 achieved combined response at week 12 and 3 at week 24. At baseline, the levels of intrahepatic HDV-RNA and integration-derived HBs transcripts tended to be lower in pts achieving combined response at week 12 (median [IQR]: 2,262 [1,777–2,913] vs 8,760 [4,656–9,046] for HDV-RNA and 12,770 [6,730–22,421] vs 55,417 [30,729–56,982] cps/1000cells for integration-derived HBs transcripts). Notably, in pts achieving an earlier combined BLV response, an upregulation of genes specifically involved in immune responses was observed (CHI3L1, CXCL2, C4B2, FYB2 [log2 fold-change: 1.79, 1.5, 1.25, 1.19, respectively; adjusted $P < 0.02$ for all comparisons]).
Conclusion: HDV persistence is independent from the intrahepatic HBV reservoir and is sustained by HBsAg production from integrated HBV-DNA. Moreover, a reduced intrahepatic HDV reservoir and limited HBV integration may correlate with a rapid control of HDV replication under BLV. The role of the immune system in modulating BLV response deserves further evaluation.

OS-073

Entry inhibitor Hepalatide combined with pegylated interferon-alpha 2a therapy resulted in cccDNA clearance in CHB patients: a phase II randomised, double-blind, placebo-controlled trial

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Background and aims: Hepalatide (HLT) is a peptide designed to block the HBV entry receptor sodium-bile acid cotransporter (NTCP). This study aimed to evaluate the efficacy and safety of HLT in combination with pegylated interferon-alpha 2a (PEG-IFN) in patients with chronic hepatitis B (CHB).
Method: This Phase II multicentre, randomised, double-blind, placebo-controlled trial enrolled 96 patients aged 18–60 years with HBV DNA ≥ 20,000 IU/mL (HBeAg-positive) or ≥ 2,000 IU/mL (HBeAg-negative), no cirrhosis, and naïve to interferon treatment (NCT 04426968). Participants were randomly assigned to receive 2.1 mg, 4.2 mg, 6.3 mg of HLT treatment, or placebo for 24 weeks in a 1:1:1:1 ratio. All subjects received PEG-IFN (180 μg/week) foundational treatment for 48 weeks. The primary endpoint was safety and HBV DNA loss (cut-off: 20 IU/mL) at 24 weeks of treatment. HBsAg, Pg RNA, cccDNA and histological response in liver biopsy were also assessed at the end of the 24-week treatment.
Results: A total of 96 subjects (77 HBeAg-positive and 19 HBeAg-negative) were included in the trial, with 24 patients in each group. Two patients withdrew due to interferon-related AEs. A total of 1281 AEs ranging from grade 1 to 3 were recorded, and mainly interferon-related. Only 26 AEs were related to HLT, and all AEs were graded 1 or 2. The proportion of patients with virological response (HBV DNA < 20 IU/mL or a decrease from baseline ≥ 2 $\log_{10}$) at the end of the 24-week HLT treatment in the 2.1 mg, 4.2 mg, or 6.3 mg and placebo group were 78.3%, 87.5%, 70.8% and 58.3%, respectively. The virological response rate in the 4.2 mg group was significantly higher than that in placebo group ($p = 0.0248$). At baseline and the end of 24-week HLT treatment, 21 and 14 liver biopsies were obtained, respectively. All four groups had positive baseline biopsies cccDNA of 3.463 ± 1.03, 2.383 ± 0.97, 3.850 ± 1.08, and 3.018 ± 0.76 $\log_{10}$ copies/μL, respectively. Surprisingly, cccDNA became undetectable (<5 copies/μL by verified PCR assay) in 33.3% (1/3) and 40.0% (2/5) of samples from the 4.2 mg and 6.3 mg groups at the end of the 24-week HLT treatment, while all samples from 2.1 mg and placebo groups remained cccDNA positive. The three subjects with cccDNA clearance remained HBsAg-positive at the end of HLT treatment. Pg RNA levels and HBsAg levels were progressively reduced in all groups during the treatment. The fact that all indicates that this HBsAg may be expressed from integrated HBV DNA.
Conclusion: The combination therapy in the present trial may alter the balance of the HBV reservoir by blocking cccDNA replenishment

through inhibiting HBV entry via HLT and accelerating cccDNA decay via PEG-IFN. This strategy provides great potential to achieve a sterilising cure for patients with CHB.

OS-074

Recombinant polyclonal antibody GIGA-2339 potently neutralizes hepatitis B and hepatitis D virus

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Background and aims: While current treatments effectively control viral replication in chronic hepatitis B virus (HBV) infection, hepatitis B surface antigens (HBsAg) are produced at high levels and induce hepatitis B-specific immune tolerance. HBsAg clearance is required to support immune control of viral replication. GIGA-2339 is a first in class recombinant polyclonal antibody therapeutic designed to target the conserved HBsAg to block infection and clear circulating HBsAg in infected individuals.
Method: Memory B cells from HBV vaccinated donors were captured by GigaGen's single cell antibody capture technology to isolate natively paired antibody sequences, which were displayed as single chain variable fragments on yeast to enrich for HBsAg-specific sequences. These antibody sequences were cloned into human IgG1 expression vectors and full-length antibody sequences were transfected *en masse* by single-site integration into a Chinese hamster ovary (CHO) cell line. Recombinant polyclonal antibodies were produced and purified using monoclonal antibody (mAb) production and purification techniques. GIGA-2339 was tested for potency by ELISA, *in vitro* and *in vivo* neutralization, antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) immune activation capacity, and cross-mutant binding compared to HBIG and an HBsAg-specific mAb.
Results: GIGA-2339 contains more than 1000 antibodies targeting HBsAg epitopes. Using HBV laboratory strain AD38 genotype D to infect primary hepatocytes, GIGA-2339 demonstrated neutralizing potency greater than 2000x higher than a plasma-derived HBV-specific polyclonal hyperimmune HBIG and 2.5x lower than HBsAg-mAb. Furthermore, GIGA-2339 exhibited neutralization of live HDV-1 expressing each globally circulating HBV genotype (A-H). ADCC (Fc gamma receptor IIIA engagement) and ADCP (Fc gamma receptor IIA engagement) signal activity showed that GIGA-2339 had 10-fold greater potency than HBIG and 2.5x lower potency than HBsAg-mAb; however, GIGA-2339 had the greatest efficacy in signal induction for both ADCC and ADCP. While GIGA-2339 and HBsAg-mAb bound to wild-type HBsAg, GIGA-2339 had enhanced binding to P142L and G145R mutants. In a C57BL/6 mouse model of AAV-HBV infection, treatment with 10 mg/kg or 100 mg/kg of GIGA-2339 induced a dose dependent reduction of serum HBsAg on average by 1.2 and 2.8 log and of HBV DNA on average by 1.5 and 2.2 log, respectively.
Conclusion: GIGA-2339 is a novel antibody therapeutic that captures the HBsAg-specific antibody repertoire and is manufactured using the same production and purification techniques as a mAb. It demonstrated robust activation of cell-mediated immune responses, retained binding to HBsAg mutants commonly found during chronic HBV infection, and exhibited clearance of HBsAg in an animal model. GIGA-2339 is in Phase I clinical studies and adds an important new therapeutic modality to the treatment landscape to achieve HBV functional cure.

SATURDAY 10 MAY

Acute (on Chronic) Liver failure

OS-075

Dual plasma molecular adsorption system therapy in patients with acute-on-chronic liver failure: a non-randomized cluster-controlled study (PADSTONE)

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Background and aims: Acute-on-chronic liver failure (ACLF) is a life-threaten syndrome and cause high short-term mortality. Double plasma molecular adsorption system (DPMAS) is one of the available artificial liver support systems which combines plasma filtration and two-specific adsorption membranes. In this study, we aimed to evaluate the real-world use and outcomes of DPMAS for the treatment of ACLF.
Method: A prospective, multicentre and non-randomized cluster-controlled study was conducted (NCT05129904) and 57 tertiary hospitals were recruited and allocated to the DPMAS treatment clusters (n = 28) and standard medical treatment (SMT) clusters (n = 29). Outcomes included disease progression rate, survival, death and liver transplantation and safety of DPMAS therapy. Twelve-months is required for each participant to complete post-discharge follow-up.
Results: In total, 644 patients were enrolled in DPMAS group and 626 patients in SMT group. MELD score was comparable between these two groups (24 ± 5 vs. 24 ± 6, p = 0.128). Totally, 1615 treatment sessions in DPMAS group within 4 weeks and 31.7% patients had 2 DPMAS treatment sessions and 77.1% of the initial DPMAS treatment was with subsequent plasma exchange. Unfractionated heparin was the most common anticoagulants used in DPMAS treatment. The total bilirubin, ALT and CRP levels were all significantly improved after the initial DPAMS therapy. The 4-week and 12-week transplant-free mortality was both lower in DPAMS group than SMT group (4-week: 15.8% vs. 23.1%, p = 0.001; 12-week: 29.5% vs. 38.0%, p = 0.002). For the non-ACLF patients at baseline, no significantly difference was observed in the progression to ACLF within 4 weeks between those two groups (25.2% vs. 29.0%, p = 0.226). Plasma allergy (2.3%) and dialyzer coagulation (3.1%) as well as the arterial hypotension (2.7%) were the common adverse events during DPMAS treatment.
Conclusion: DPMAS treatment for ACLF patients can significantly improve the short-term mortality as well as the liver function markers. DPMAS therapy was associated with few adverse events and its safety is confirmed.

OS-076-YI

Patients with acute decompensation of cirrhosis present a unique methylation signature associated with their outcome

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Background and aims: Acute decompensation (AD) of cirrhosis and its progression to acute-on-chronic liver failure (ACLF) are associated with high short-term mortality. There are no therapies due to an incomplete understanding of the pathophysiology and patient heterogeneity. The previous decompensating events are crucial in disease progression and ACLF development. These events may induce changes in DNA methylation, providing insights into the cirrhosis pathophysiology and prognosis.
Method: Prospective clinical and epigenomic data from two well-characterized AD cohorts - the European PREDICT (N = 623) and the Latin American ACLARA (N = 460) - were analyzed to investigate DNA methylation alterations. This study represents a novel epigenetic analysis to characterize AD as part of the H2020-funded DECISION project. A multi-state survival analysis was conducted with four transitions (baseline to ACLF, death, and liver transplant, and ACLF to death), using bootstrapping and permutation test to estimate confidence intervals and permuted p-values. Two complementary analyses were performed per CpG site: (1) without and (2) with clinical covariates associated with each transition (including age and sex).
Results: We observed a significant difference in median global methylation levels between individuals with and without adverse events, suggesting DNA methylation may provide prognostic value in AD. Therefore, we focused on characterizing the predictive value of the CpG sites. Using a multi-state survival model, we identified CpG sites not associated with cell type proportions that showed (1) predictive power (without clinical variables) and (2) added predictive power (including clinical variables). Notable, most significant CpG sites were transition-specific, with some overlap between models for the same transitions. Besides, enrichment in CpG islands and promoter regions suggests functional significance in gene regulation. Validation using the independent ACLARA cohort revealed a global methylation pattern similar to that of the PREDICT cohort. Furthermore, in the ACLAR Caucasian subset, we validated 13 and 14 CpG sites with potential predictive power and added predictive power, respectively.
Conclusion: Our study identified novel blood methylation alterations associated with AD, providing insights into its pathophysiology. Notably, several identified CpG sites are located near genes involved in inflammation, immune response, metabolic regulation, and liver function pathways, including those linked to complications such as septic shock and hepatic steatosis. These findings highlight potential mechanisms underlying disease progression through DNA methylation patterns. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847949. This reflects only the author's view and the Commission is not responsible for any use that may be made of the information it contains.

OS-077

Single-cell RNA sequencing of peripheral blood mononuclear cells in patients with acutely decompensated cirrhosis reveals a specific monocyte subset associated with an increased risk of progression to ACLF

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Background and aims: Patients with acute decompensation of cirrhosis (ADC) are at high risk of developing acute-on-chronic liver failure (ACLF), a syndrome characterized by multiple organ failure and high short-term mortality. This study aimed to prospectively analyse alterations in peripheral blood mononuclear cells (PBMCs) in patients with ADC using single-cell technologies and to explore their implications for pathophysiology and prognosis.

Method: 64 patients admitted due to ADC and 15 healthy controls were enrolled in 5 European centres. Blood samples were obtained at hospital admission. Patients were followed up for up to 90 days after study inclusion, and hospital readmission due to ADC or ACLF development was monitored. Cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) was applied to PBMCs from 16 out of the 64 patients representing different clinical trajectories and 4 healthy controls, to quantify gene expression and targeted surface protein at single-cell resolution. Whole blood for the same 16 patients was assessed by bulk RNA-seq and whole blood transcriptional profiles from two independent prospective multicentre cohorts of patients with ADC (PREDICT (n = 689) and ACLARA (n = 521)) were included as validation cohorts.
Results: Cell proportion analysis revealed a significant increase of classical monocytes in patients with subsequent ACLF development. Notably, classical monocytes represented the cell type with the highest transcriptional alterations. Within the classical monocyte population, a specific subcluster, termed "C2," was identified and found to increase during progression towards ACLF. In addition to reduced expression of *HLA-DR* and upregulation of *MERTK,* this monocytic subpopulation was primarily characterized by decreased expression of genes encoding enzymes relevant to cellular energy supply, such as oxidative phosphorylation and ATP production. Pathway analysis confirmed a marked impairment of energy metabolism pathways as well as a tendency towards reduced inflammatory and bacterial response within the C2 subcluster. Using two independent prospective multicentre cohorts of patients with ADC, we found that a gene signature derived from that monocytic subpopulation was significantly upregulated especially in patients with bacterial infection, ACLF development and non-survivors.
Conclusion: Patients with acute decompensation of cirrhosis who subsequently develop ACLF are characterized by the presence of a subpopulation of classical monocytes with features of impaired energy metabolism pathways.

OS-078-YI

Elevated plasma chenodeoxycholic acid as a prognostic marker and therapeutic target in acute liver failure: role of bacteroides intestinalis AM1 intervention in bile acid modulation and mitigation of liver injury

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Background and aims: Acute liver failure (ALF) is a life-threatening condition with altered metabolic and microbial profiles contributing to liver disease severity. We studied circulating metabolites, bile acids and microbial signatures to differentiate ALF non-survivors and explored the potential of *Bacteroides intestinalis* AM1 in bile acid modulation and mitigation of liver injury.
Method: Plasma metabolomics and meta-proteomics were conducted in 40 ALF patients and 5 healthy controls (training cohort), with validation in 160 ALF patients (test cohort) using High resolution mass spectrometry (HRMS) and machine learning (ML). A non-survival indicator panel identified chenodeoxycholic acid (CDCA) as a key inflammatory driver (logFC > 10; $p < 0.05$; AUC > 0.95), particularly in non-survivors. Increase in CDCA levels prompted us to explore Bacteroides intestinalis AM1 (10^9 CFU/ml), which successfully reduces CDCA (PMID: 19243441). A therapeutic dose was administered to an APAP-induced mouse model (250 & 500 mg/kg, i.p.), and liver injury and hepatocyte death were analyzed through histological, proteomic, and metabolomic changes in the liver.
Results: ALF non-survivors had distinct metabolomic profile showing increase in CDCA, tryptophan, tyrosine, pathways related to inflammation, cell death and stress response ($p < 0.01$, FDR<0.01, FC>1.5). Plasma of non-survivors showed higher alpha/beta diversity ($p < 0.05$) with increase in Proteobacteria, Firmicutes, Actinobacteria ($p < 0.05$), functionally associated to energy, amino acid and xenobiotic metabolism ($p < 0.05$). In the non-survivors, the increase in bacterial-taxa and functionality correlated with specific increases in CDCA (cell death and inflammation), 4-(2-Amino phenyl)-2,4-dioxobutanoate, L-Tyrosine, other metabolites, clinical parameters and outcome (R^2>0.85, $p < 0.05$). Probability of detection (POD) of non-survival based on these metabolites was >99% with a diagnostic accuracy of 98% (AUC = 0.98(0.92–1.0). Elevated levels of CDCA (logFC>10) correlated with disease severity and mortality in ALF patients and mice model. Using an ALF mouse model, we colonized the mice with *Bacteroides intestinalis AM1* to examine its therapeutic effects on CDCA breakdown. B. intestinalis AM1 colonies reduced CDCA levels, suppressed inflammation, and prevented acute liver injury by reversing necroapoptosis and modulating glutathione (oxidative repair), tryptophan (inflammation), histidine (tissue repair) metabolism.
Conclusion: The plasma microbiome and metabolome of ALF non-survivors exhibits distinct characteristics. Elevated baseline CDCA levels are linked to a higher risk of early mortality. Intervention with *"B intestinalis AM1"* shows promise in lowering CDCA levels, reducing necrosis, and mitigating inflammation in ALF. A clinical trial is needed to validate these findings.

OS-079-YI

Hemodynamic and non-hemodynamic effects of non-selective beta-blockers in experimental and human acute-on-chronic liver failure

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Background and aims: The effects of non-selective beta-blocker (NSBB) treatment on hemodynamics (HDs) and systemic inflammation (SI) in acute-on-chronic liver failure (ACLF) remains understudied. This study investigated the impact of NSBBs in experimental and human ACLF.
Method: Cirrhosis was induced in Sprague-Dawley rats by carbon-tetrachloride (CCl4; 12 weeks). In the last induction week, carvedilol (CAR, 5 mg/kg), propranolol (PRO, 15 mg/kg), or vehicle (VEH) was gavaged (2x/day). ACLF was induced by a single i.p. injection of lipopolysaccharide (LPS; 1 mg/kg) 3 hours prior to hemodynamic characterization (portal pressure PP, heart rate HR, mean arterial pressure MAP). Resulting groups were: ACLF+VEH (n = 6), ACLF+CAR (n = 9), ACLF+PRO (n = 8). IL-1β, IL-6, TNF-α, MCP1 and IL-10 were quantified in plasma (ELISA) and liver tissue (RT-qPCR). Patients with ACLF (graded G1-G3 by EASL-CLIF criteria) admitted to the Vienna General Hospital (2003–2022) were characterized for PH severity by

hepatic venous pressure gradient (HVPG), platelet count (PLT) and varices (EV). NSBB intake, liver injury (AST/ALT), SI biomarkers (WBC, CRP, IL-6) were recorded at pre-ACLF, ACLF diagnosis (D0) and ACLF day 7 (D7). Survival was recorded at D28, D90 and D365.
Results: In the animal study, ACLF+CAR and ACLF+PRO had significantly lower HR compared to the ACLF+VEH group (331 ± 15 and 326 ± 10 vs. 410 ± 21 bpm; p = .002), lower MAP (42.4 ± 8.4 and 47.9 ± 5.4 vs. 52.9 ± 7.4 mmHg; p = .437) and similar PP (p = .759). ACLF+CAR group had a trend towards lower AST (797 ± 141 vs. 1341 ± 491 U/L; p = .058) and ALT (491 ± 77 vs. 894 ± 176 U/L; p = .169), and no amelioration of ACLF-induced inflammation as reflected by hepatic inflammatory gene expression and circulating cytokine levels (all p > .05). The clinical study included 189 patients with ACLF (G1: 91 [48.1%], G2: 61 [32.2%], G3: 37 [19.6%]) and 116 [61.4%] patients received NSBB prior to D0 [NSBB(+)]. Before ACLF, NSBB(+) patients showed higher HVPG (p = .006), more EV (p = .019), lower PLT (p = .036), lower WBC (p = .034) but similar SI and MELD (all p > .05) than NSBB(-) patients. At D0, ACLF grade was similar between NSBB groups (p = .831). Significantly lower WBC (7.7 [6.4] vs. 9.1 [6.6], p = .013) but similar CRP (p = .631) and liver injury markers (AST p = .722; ALT p = .969) were noted in NSBB(+) vs. NSBB(-) patients at D0. D90 mortality was similar between groups: 56.6% in NSBB(+) vs. 61.5% in NSBB(-) patients (ACLF grade-adjusted p = .680).
Conclusion: Patients on NSBB prior to ACLF presented more pronounced PH - consistent with NSBB indication. Interestingly, the NSBB+ group had similar short-term ACLF mortality compared to NSBB-naïve patients. In the LPS-induced ACLF rat model, NSBB precipitated the hemodynamic state, while not improving hepatic or systemic inflammation. These results indicate that NSBB treatment may be continued in ACLF patients with PH and HD stability, while non-HD benefits in infection-induced ACLF seem negligible.

Basic Science – MASLD

OS-080-YI
Multimodal single-nuclei atlas of MASLD progression uncovers a link to type 2 diabetes
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Background and aims: The course of metabolic dysfunction-associated steatotic liver disease (MASLD) is highly heterogeneous. MASLD and type 2 diabetes (T2DM) are closely intertwined, and hepatic insulin resistance has been associated with hepatocyte steatosis and inflammation. The cellular and genetic underpinnings for disease heterogeneity are poorly characterised. We hypothesised that joined profiling of gene expression and chromatin accessibility at single cell resolution in patients with MASLD and increasing fibrosis would elucidate the distinct cell populations and processes associated with disease progression.
Method: We therefore generated a large multi-modal single-nuclei atlas of gene regulation with paired snATAC-Seq and snRNA-Seq (10X Multiome) in percutaneous or transjugular liver biopsies. Our analyses included over 300.000 cells from 10 healthy controls and 48 patients with MASLD and F0 to F4 fibrosis (F0 n = 9, F1 n = 10, F2 n = 10, F3 n = 9, and F4 n = 10). Based on the analyses, we evaluated disease progression in terms of changes in cell type abundance, transcription and chromatin landscape. The multimodal RNA expression and chromatin accessibility data allowed us to map the activity and interactions of promoters and enhancers in the individual cell types. Integration of genome-wide association studies (GWASs) of MASLD and T2DM related traits allowed us to identify cell types causally implicated for the different traits.
Results: Our analyses revealed that hepatocytes were most affected by MASLD progression and identified a disease progression gradient perpendicular to the porto-central zonation gradient. In particular, we identified a MASLD-associated subpopulation of hepatocytes that were not present in the healthy controls. These MASLD-associated hepatocytes form a bridge between hepatocytes and cholangiocytes and are enriched for tissue regeneration associated transcription factor motifs and pathways. In comparison to the other hepatocyte populations, the MASLD-associated hepatocytes have distinct signalling and metabolic phenotype. Furthermore, genetic enrichment analysis revealed that the genetic risk of T2DM is enriched in the accessible chromatin of the MASLD-associated hepatocyte subpopulation.
Conclusion: Taken together, our atlas provides a unique resource to study cellular and genetic underpinnings of MASLD progression and highlights the changes in hepatocyte composition underlying heterogeneity among MASLD patients.

OS-081
Induction of liver injury in metabolic dysfunction-associated steatotic liver disease by microbial metabolite 3-4-Hydroxyphenyllactate through hepatic cellular senescence
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Background and aims: Cellular senescence, a stress-induced stable cell-cycle arrest, is a growing focus in metabolic dysfunction-associated steatotic liver disease (MASLD) research. While the gut microbiome is implicated in MASLD development, the role of microbial metabolites in liver senescence and progression to steatohepatitis remains unclear. This study examines liver senescence and the causal impact of gut microbial metabolites on senescence-driven liver disease.
Method: We analysed liver RNA transcriptomics and fasting and post-prandial plasma metabolomics from 300 individuals with severe obesity (median age 48, 76.4% women; median BMI 38 kg/m², 23.9% diabetes, and 60.5% MASLD). Senescent cells were identified through liver transcriptomics (using two senescence signature sets: Sennet and Senmayo and the canonical marker p21), immunohistochemistry, and Western blotting. The cohort was stratified into tertiles based on senescence marker expression (low, medium, high) to calculate odds ratios for MASH and diabetes. Correlations between senescence markers and plasma metabolites were assessed, and candidate metabolites were validated in a Finnish cohort of 10,187 men using Cox regression for liver-related mortality. To explore causality, wild-type mice on a chow diet were administered the candidate metabolite daily, with or without senolytics

(dasatinib and quercetin, D+Q). After 14 days, liver enzymes, liver triglycerides, and senescence markers were measured.
Results: Liver senescence, independent of age, was strongly associated with MASH, with an odds ratio (OR) of 4.75 (95% CI: 2.44–9.51, p < 0.001) in individuals in the highest tertile of senescence. Similarly, the OR for diabetes was 3.95 (95% CI: 1.85–8.92, p < 0.001) for individuals in this tertile. A significant association was observed between senescence markers and the microbial metabolite 3-(4-hydroxyphenyl)lactate (HPLA) in both fasting (R = 0.27, p-FDR < 0.001) and post-prandial conditions (R = 0.39, p-FDR <0.001). In the validation cohort, Cox regression showed that elevated HPLA levels were associated with increased liver-related mortality (HR = 2.14, 95% CI: 1.74–2.62, p < 0.005). In mice, intraperitoneal HPLA administration led to dose-dependent increases in serum ALT, hepatic triglycerides, and senescence marker expression. Senolytic treatment alleviated liver steatosis and reduced serum ALT levels in HPLA-treated mice.
Conclusion: Liver senescence is linked to more severe disease in individuals with obesity. The microbial metabolite HPLA correlates with senescence markers and is associated with liver disease severity and increased liver-related mortality risk. In mice, HPLA induces hepatic injury and steatosis, effects that are mitigated by senolytic treatment. These findings suggest that HPLA drives liver injury through hepatic cellular senescence.

OS-082
Metabolic molecular subtyping identifies actionable targets in MASLD and hepatocellular carcinoma: an integrative multi-omics and machine learning strategy for precise treatment
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Background and aims: In addition to histological evaluation and pathological classification, a comprehensive analysis of the metabolic landscape and metabolism-related molecular subtyping is urgently needed to categorize Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) patients into distinct subgroups with diverse risks for precise treatment.
Method: A total of 806 MASLD and 267 normal liver samples from 10 public datasets were collected, and alterations in 114 metabolic pathways in MASLD were comprehensively analyzed. Two distinct metabolic clusters exhibiting diverse biological characteristics and fibrotic phenotypes were identified in nonalcoholic steatohepatitis (NASH). Single-cell RNA-sequencing (scRNA-seq) data was analyzed to decipher the metabolic characteristics involved in the microenvironment of MASLD-derived liver cirrhosis. Gaussian Mixture Model (GMM) and logistic regression (LR) analysis were combined to develop a refined fibrotic-prediction model. The multi-omics data and potential therapeutic drugs were comprehensively analyzed in hepatocellular carcinoma (HCC) samples with different metabolic dysfunction scores (MBDS). A total of 78 combinations derived from 9 survival-related machine learning algorithms were applied to MBDS-related genes to select an optimal prognostic model for patients with HCC.
Results: Two distinct metabolic clusters (MBCs) were identified in NASH. The two MBCs exhibited distinct metabolic patterns and immune microenvironment. ScRNA-seq analysis revealed heterogeneous metabolic activities across various cell types and subpopulations in MASLD-derived cirrhosis. The GMM-LR model exhibited its superior capacity in fibrosis discrimination in multiple independent cohorts, including public databases and our in-house cohort. Distinct genomic alterations, immune landscapes, and potential therapeutic drugs were observed in HCC samples with different MBDS levels. Furthermore, MBDS was significantly correlated with EMT in pan-cancer samples, especially in hepatobiliary tumors. Finally, a survival-SVM prognostic model was constructed based on MBDS-related genes and exhibited the best performance across multiple HCC cohorts.
Conclusion: We provide evidence for the necessity of metabolic molecular subtyping and its potential clinical applicability in risk stratification, aiming to facilitate personalized management and treatment strategies for MASLD and HCC individuals.

OS-083
Inhibition of the CCR9-CCL25 axis improves the visceral fat environment and ameliorates liver steatosis
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Background and aims: Obesity, frequently complicated with metabolic-associated steatohepatitis (MASH), is a chronic inflammatory condition involving inter-organ correlations, though many mechanisms remain unclear. We previously reported that CCR9-CCL25 axis inhibition improves the condition of diabetes, but its role in obesity and MASH is unknown. This study aims to investigate the role of CCR9-CCL25 axis in obesity using samples from severely obese patients before and after bariatric surgery and from diet-induced obesity (DIO) mouse.
Method: Serum samples from 32 cases of severely obese (SO) patients who underwent bariatric surgery were subjected to a comprehensive analysis of cytokines and chemokines using a multiplex assay. To investigate the involvement of CCL25, one of the key factors identified from serum analysis, in obesity, wild-type and Ccr9 knockout (Ccr9KO) mice were fed a high-fat diet (HFD) for 12 weeks to induce obesity. Immune cells in white adipose tissues (epididymal: eWAT, inguinal subcutaneous: iWAT, mesenteric: mWAT), small and large intestine, and liver were analyzed longitudinally.
Results: In SO patients, serum CCL25 was significantly higher than in healthy controls and correlated with visceral fat area, while it decreased significantly after surgery. Consistently, increased *Ccl25* expression in small intestinal epithelium was observed in WT-DIO mice. Immunological analysis of the small intestine in WT mice identified type 2 innate lymphoid cells (ILC2s) as CCR9-expressing immune cells whose numbers increased during obesity. The increase in ILC2s during obesity was specific to the small intestine (SI-ILC2), whereas a significant decrease in ILC2s was observed in eWAT and iWAT (WAT-ILC2). RNA-seq analysis of SI-ILC2 showed decreased expression of *Gata3* and *Il5* and increased expression of *Tbx21* and *Ifng* in the obese state compared to that in the steady state. Of note, Ccr9KO mice showed similar weight gain to WT mice on HFD feeding, but showed significantly improved glucose tolerance. Interestingly, Ccr9 deficiency partially cancelled the obesity-induced increase in SI-ILC2 and decrease in WAT-ILC2 demonstrated in WT mice. Histological analysis revealed that intestinal leaky gut, adipose inflammation/fibrosis, and hepatic steatosis/inflammation were significantly improved in Ccr9KO mice compared to WT mice.
Conclusion: In obesity, increased serum CCL25 levels were associated with visceral fat accumulation. Obesity-induced SI-ILC2s exhibited an ILC1-like phenotype, suggesting a pro-inflammatory role that might promote intestinal inflammation and leaky gut. Inhibition of the CCR9-CCL25 axis shifted the inter-organ distribution of ILC2s toward WAT and contributed to the improvement of pathology. These findings highlight the potential for targeting the CCR9-CCL25 axis as a therapeutic approach for obesity and MASH.

OS-084-YI

HSD17B13 loss-of-function protects against steatosis-induced hepatic phosphatidylcholine depletion by promoting polyunsaturated fatty acid retention in humans in vivo and in experimental models

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Background and aims: Phosphatidylcholines (PCs) are a major hepatic reservoir of polyunsaturated fatty acids (PUFAs). In murine models of metabolic dysfunction-associated steatotic liver disease (MASLD), liver injury is induced by PUFA-PC depletion. The lipid droplet enzyme HSD17B13 metabolizes PUFA derivatives, and its loss-of-function variant rs72613567:TA protects against steatohepatitis (MASH) and fibrosis, although the mechanism underlying this protection remains unknown. We investigated whether hepatic PUFA-PC metabolism is influenced by MASLD or the protective *HSD17B13* variant.

Method: Obese patients with a liver biopsy (n = 135) underwent genotyping for *HSD17B13* rs72613567:TA and analysis of the hepatic lipidome by UPLC-MS. A state-of-the-art deep learning image analysis method (Aiforia Technologies) quantified steatosis via the hepatic parenchymal fat fraction. Using a recruit-by-genotype approach, we studied homozygous rs72613567:TA carriers (n = 13) and non-carriers (n = 13) to determine whether the variant affects incorporation of ^{13}C-labeled PUFAs linoleic acid (LA) and alpha-linolenic acid (ALA) into triglycerides (TGs) and phospholipids (PLs) secreted by the liver in very-low-density lipoprotein (VLDL). We tested whether targeting HSD17B13 with a small molecule inhibitor, INI-822, affects PC metabolism using two models: *in vitro*, a primary human liver-on-a-chip system challenged with high-fat media for 20 days; and *in vivo*, Zucker obese rats fed either an atherogenic diet or a choline-deficient, L-amino acid-defined high-fat diet for 21 days.

Results: Human MASLD livers were characterized by a marked depletion of hepatic PUFA-PCs containing 5–8 double bonds. Steatosis had a particularly accentuated effect to lower PUFA-PCs in individuals without the *HSD17B13* rs72613567:TA variant. However, this effect was abolished in variant carriers due to markedly increased concentrations of hepatic PUFA-PCs compared to non-carriers. Homozygous carriers had significantly decreased incorporation of [U-^{13}C]LA into VLDL-TG ($P < 0.001$) and of [U-^{13}C]LA and [U-^{13}C]ALA into VLDL-PL ($P = 0.01$ and 0.05), consistent with retention of these PUFAs in the liver. *In vitro*, inhibition of HSD17B13 by INI-822 in the human liver-on-a-chip system lowered fibrotic markers while stabilizing choline utilization and increasing PC concentrations. *In vivo*, inhibition of HSD17B13 in Zucker obese rats fed MASH-inducing diets reduced liver enzymes and dose-dependently increased hepatic PC concentrations.

Conclusion: In humans, *HSD17B13* rs72613567:TA prevents MASLD-induced hepatic PUFA-PC depletion by retaining PUFAs within the liver. Pharmacological inhibition of HSD17B13 recapitulates the human phenotype *in vitro* and *in vivo*. These findings suggest that hepatic PC enrichment is central to the protective effects associated with HSD17B13 loss-of-function.

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OS-085-YI

Clinical prediction model with good discriminative capacity for mortality risk in autoimmune hepatitis

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Background and aims: Autoimmune hepatitis (AIH) is a complex condition with various prognostic factors linked to increased mortality risk. To date, only one prediction model for survival in AIH has been developed, which incorporates age, cirrhosis at diagnosis, and non-Caucasian ethnicity. However, this model is based on a relatively small dataset, limited to AIH type 1 without variant syndromes and does not include significant predictors such as achievement of complete biochemical response (CBR). Therefore, our study aims to develop and internally validate a prediction model for transplant-free survival in AIH that incorporates the achievement of CBR at 12 months.

Method: We included all patients with available follow-up data from the International AIH Group Retrospective Registry. The endpoint of the study was overall mortality or liver transplantation. The prediction model was developed using backward selection. We calculated the C-index and plotted the calibration curve. The model was updated after internal validation was performed with 250 bootstrap samples. The coefficients of the model were updated with the slope from internal validation.

Results: With a median follow-up of 8 years, our study encompasses 1139 patients with AIH, of whom 159 died or received a liver transplantation. Among included patients 42.4% did not achieve CBR within 12 months. The prognostic model includes age and cirrhosis at diagnosis, non-Caucasian ethnicity, variant syndrome with PSC, and absence of CBR within 12 months. The model demonstrates C-index of 0.885 with a linear calibration curve. Internal validation yielded a C-index of 0.879 with a slope shrinkage factor of 0.932. This resulted in the following formula: Prognostic index = (0.034 × Age) + (0.960 × Ethnicity) + (1.430 × Cirrhosis) + (1.343 × PSC) + (1.601 × CBR).
Age: age in years at diagnosis of AIH.
Ethnicity: non-Caucasian = 1; Caucasian = 0.
Cirrhosis: cirrhosis at diagnosis = 1; no cirrhosis at diagnosis = 0.
PSC: PSC at diagnosis = 1; no PSC at diagnosis = 0.
CBR: No CBR within 12 months = 1; CBR within 12 months = 0.

Survival(10y) = 1 – exp(–(0.049147616 × exp(PI))).
Conclusion: Our study establishes a predictive model for survival in AIH that incorporates age, cirrhosis at diagnosis, non-Caucasian ethnicity, variant syndrome with PSC, and absence of CBR within 12 months. The model demonstrates robust predictive performance in bootstrap samples and shows promising utility for clinical application.

OS-086

Evaluation of the response criteria following second-line treatment with bezafibrate in patients with primary biliary cholangitis

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Background and aims: Multiple criteria exist to assess the response to ursodeoxycholic acid in primary biliary cholangitis (PBC); however, their efficacy in evaluating the response to second-line (2L) therapy remains undetermined. We aimed to analyze the capacity of response criteria at one year of treatment with bezafibrate (BZF) as 2L to predict event-free survival (EFS) and develop a predictive score for response to BZF.
Method: We conducted a retrospective analysis of 400 patients with PBC with at least one year of treatment with BZF as 2L from 37 centers of the Spanish ColHai registry. EFS was defined as the absence of decompensation, hepatocellular carcinoma (HCC), liver transplantation (LT) or liver-related death (LRD).
Results: Most patients were female (89%), with a median age of 56 years (IQR: 49–64), 45 (11%) had cirrhosis (LC) and in 15.5% obeticholic acid was added as a third line. Median BZF treatment duration was 3.8 (IQR: 1.7–6) years. During follow-up, 51 (14%) patients developed LC, 29 (7%) decompensation, 5 (1%) HCC, 9 (2%)

LRD, and 14 (3.5%) required LT. Of the patients, 11% discontinued BZF due to adverse events or patient´s decision after a median of 25 (3–42) months. According to the Paris II and Poise criteria, 51% and 68% of patients, had a response, respectively, and 53% had ALP < 1xUNL. In LC patients, the response rates were 31% and 61%. To detect SLE, Paris II had an AUC 0.74 with a sensitivity (Se) 91% and specificity (Sp) 56% and an AUC 0.74 (Se 88%, Sp 61%) for developing LC. Poise had lower accuracy for both SLE (AUC 0.68; Se 64%, Sp 71%) and developing LC (AUC 0.66; Se 58%, Sp 74%). Response according to Paris II was associated with improved EFS (HR 9.5; 95%CI 2.2–40.5) and a risk of events of only 1.5%. In non-responders, the Globe-score with a cut-point of 0.35 allowed discrimination of EFS (AUC 0.75; Se 79%, Sp 71%). Thus, only 6% of non-responders according to Paris II and a Globe score ≤ 0.35 presented events vs. 37% with Globe-score >0.35, p < 0.001. ALP normalization vs ALP 1–1.5 xUNL did not improve EFS (HR 1.0; 95%CI 0.3–3.7), However, total bilirubin (TBi) <0.6 mg/dl improved EFS vs TBi 0.6–1.2 (HR 4.4; 95%CI 1.2–15.6) and TBi >1.2 (HR 18.2; 95%CI 4.7–70.9). Variables at baseline of BZF associated with the response were normalized AST, ALT and TBi. Using these variables, we constructed a score for predicting response to BZF (-3.19*Platelets+1.66*BiT+1.35*AST+1.22*ALT-3.27), which obtained an AUC of 0.874 (Se 71%, Sp 86%).

Conclusion: The Paris II has high sensitivity, so patients who respond rarely experience events. In non-responders according to Paris II, those with a Globe-score ≤0.35 have an excellent EFS; therefore, it may not be necessary to add a third-line treatment. Poise criteria had low accuracy to evaluate response after BZF. Variables associated with the response to BZF were AST, ALT, and TBi, but not ALP. We created a score to predict response to BZF, pending further validation.

OS-087

Amongst autoimmune liver diseases, primary sclerosing cholangitis demonstrates distinct methylation profiles on circulating DNA

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Background and aims: The autoimmune liver diseases— Primary Sclerosing Cholangitis (PSC), Primary Biliary Cholangitis (PBC), and Autoimmune Hepatitis (AIH) —are of unknown aetiology but have overlapping biology despite usually clinically distinct profiles. Methylation patterns on circulating DNA have been shown to be specific to different disease processes before. Our goal was to develop a machine learning biomarker integrating methylation patterns on circulating cell-free DNA (cfDNA) and clinical variables as a means to better understand autoimmune liver disease pathobiology.

Method: This pilot study included 63 patients clinically diagnosed with PSC (n = 21), PBC (n = 21), and AIH (n = 21). Methylation profiles of cfDNA plasma were analyzed using the MEDIPS package, and pairwise comparisons were performed using Quantitative Sequence Enrichment Analysis (QSEA) for MeDIP-seq data (False Discovery Rate, FDR < 0.01, Fold Change > 2). Pathway enrichment was conducted using Ingenuity Pathway Analysis (IPA). We applied the Boruta feature selection algorithm to identify key methylation sites across patient cohorts. A Support Vector Classifier (SVC) with a linear kernel was developed, using 101 bootstrapping iterations to classify patients into AIH, PBC, or PSC groups. SHAP (SHapley Additive exPlanations) analysis was utilized to identify the most significant methylation sites and 24 clinical variables, including age, sex, ALT, AST, ALP, bilirubin, medications, influencing model predictions.

Results: Our findings revealed a distinct separation in methylation patterns in the PSC group compared to AIH and PBC. Pathway analysis highlighted several activated pathways in PSC relative to the other groups, including the Gamma-Glutamyl cycle, NLR Signaling Pathway, JAK-STAT signaling, and IL-8 activation. The Boruta feature selection algorithm identified 182 key methylation sites predictive of disease group classification. By integrating these methylation sites with clinical variables, our Support Vector Classifier achieved a diagnostic accuracy of 90.46% (95% CI: 84.21–94.74%) and an AUROC of 0.9161 (95% CI: 0.9081–0.9167). The methylation patterns alone demonstrated strong classification capability with accuracy of 89.11% (95% CI: 78.95–94.74%) and an AUROC of 0.9131 (95% CI: 0.8974–0.9167), which was further augmented by the inclusion of clinical data. The SHAP analysis identified a locus on KLHL12 as a top predictive methylation site, effectively distinguishing PBC from AIH.

Conclusion: Our systematic investigation of cfDNA methylation profiles sheds light on distinct epigenetic alterations in autoimmune liver diseases. The machine learning diagnostic tool developed in this study, which integrates methylation data with clinical variables, demonstrates significant promise as a means to identify new disease biology for future targeted study.

OS-088

FiOCA study: comparative analysis of transplant-free survival in primary biliary cholangitis patients treated with obeticholic acid or fibrates

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Background and aims: The management of Primary Biliary Cholangitis (PBC) has become increasingly complex, with use of obeticholic acid (OCA) and fibrates as second-line therapy. Global practice is heterogeneous, and the lack of survival data on these patients increase the uncertainty in the second-line treatment allocation. Our study aims to compare the transplant-free survival in PBC patients on second-line treatment across the Global PBC cohort.
Method: We conducted a retrospective international cohort study involving PBC patients who initiated second-line treatment with either OCA or fibrates in 40 liver centers across Europe, Japan, South America, and North America. We collected clinical, biochemical, and treatment data at diagnosis and at the initiation of second-line treatment. Only patients exposed to single treatment (either OCA or fibrate) were included in this analysis. The Cox proportional hazards model was used to evaluate the hazard ratio (HR) for transplant-free survival.
Results: We accrued data on 1,333 patients, 646 on OCA and 685 on fibrates. 87.2% were women with an average age at the start of second-line treatment of 57.2 years (SD ± 11.15). Patients on OCA were more frequently cirrhotic (30.5% vs 19.4%, $p < 0.001$). The median alkaline phosphatase (ALP) at the start of second-line treatment was 2.09 times the upper limit of normal (ULN) (IQR 1.66–2.98) in patients on OCA and 1.72 times ULN (IQR 1.15–2.07) in patients on fibrates ($p < 0.001$). The median follow-up time was 30 months (IQR 12–55). The univariable Cox proportional hazards model showed a trend towards reduced survival in patients on OCA compared with fibrates (HR 1.46, 95% CI 0.97–2.20, $p = 0.06$). However, after adjusting for the presence of cirrhosis at the initiation of second-line treatment, no significant difference in survival was observed between the groups (HR 1.01, 95% CI 0.58–2.07, $p = 0.77$). In the multivariable Cox proportional hazards model, the presence of cirrhosis at the start of second-line treatment (HR 2.20, 95% CI 1.19–4.07, $p = 0.01$), higher ALP at second-line treatment (HR 1.23, 95% CI 1.06–1.43, $p < 0.01$), and the number of months before starting second-line treatment after the failure of UDCA (HR 1.01, 95% CI 1.01–1.02, $p = 0.02$) were found to be significantly associated with worse outcomes.
Conclusion: Our study demonstrated no difference in transplant-free survival in patients treated with either fibrates or OCA. The presence of established cirrhosis as well as more aggressive disease, documented by a higher ALP, were independently associated with worse outcomes. We provide further evidence that early access to second-line treatment in patients non-responsive to UDCA might improve outcomes.

OS-089

Elafibranor for primary sclerosing cholangitis: the ELMWOOD phase II randomised controlled trial

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Background and aims: Primary sclerosing cholangitis (PSC) is a rare, chronic, cholestatic liver disease characterised by progressive inflammation and fibrosis of the intra- and extra-hepatic bile ducts. The safety and efficacy of elafibranor (ELA), a PPAR alpha/delta agonist, were investigated in adults with PSC in the phase II ELMWOOD trial (NCT05627362).
Method: This 12-week, double-blind trial enrolled patients with large duct PSC and alkaline phosphatase (ALP) ≥ 1.5x the upper limit of normal, randomised 1:1:1 to daily oral ELA 80 mg, ELA 120 mg or placebo (PBO), stratified according to baseline ursodeoxycholic acid (UDCA) use. The primary endpoint was safety and tolerability of ELA vs PBO. Additional endpoints included least squares (LS) mean change from baseline (CfB) in ALP, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) values, enhanced liver fibrosis (ELF) score and pro-C3 levels, proportions of patients with ALP normalisation, and LS mean CfB in pruritus according to the Worst Itch Numeric Rating Scale (WI NRS).
Results: In total, 68 patients (male: 54.4%; mean age: 46.3 years) were randomised to ELA 80 mg (n = 22), ELA 120 mg (n = 23) or PBO (n = 23). At baseline, 55.9% had concomitant inflammatory bowel disease, 70.6% of patients were on UDCA, and 23.5% had an ELF score > 10.6. Liver biochemistries were elevated (mean: ALP: 369.5 U/L; ALT: 84.7 U/L; GGT: 447.2 U/L), and the mean (SD) WI NRS score was 1.9 (2.2). Overall, 68.2%, 78.3% and 69.6% of patients on ELA 80 mg, ELA 120 mg and PBO had treatment emergent adverse events (TEAEs), respectively; TEAEs that led to treatment discontinuation occurred in 4.5%, 4.3% and 8.7% of patients, respectively. Serious TEAEs occurred in 4.3% of patients on PBO and none on ELA. Patients on ELA 80 mg and 120 mg had significant reductions in ALP at Week 12 vs PBO (−103.2 U/L and −171.1 U/L vs 32.1 U/L; $p < 0.0001$), with improvements observed as early as Week 4 ($p < 0.0001$). Similar reductions were observed in ALT (−14.1 U/L and −27.4 U/L vs 8.9 U/L; $p < 0.05$) and GGT (−108.1 U/L and −135.2 U/L vs 54.3 U/L; $p < 0.0001$). At Week 12, ALP normalisation occurred in 9.1% and 17.4% of patients on ELA 80 mg and 120 mg, respectively, vs none on PBO. Patients on PBO had a relative increase in non-invasive markers of liver fibrosis vs stabilisation in patients on ELA 80 mg or 120 mg (ELF: 0.30 vs 0.12 and 0.02; pro-C3: 0.2 ng/ml vs −6.2 ng/ml and −2.6 ng/ml, respectively). Greater reductions at Week 12 in WI NRS were observed in patients on ELA 120 mg vs PBO (−0.96 vs −0.28; $p < 0.05$).
Conclusion: In ELMWOOD, ELA 80 mg and 120 mg were well tolerated in patients with PSC. At Week 12, patients on ELA had significant, dose-dependent reductions in biochemical markers of cholestasis. Patients receiving ELA 120 mg had improvements in pruritus. The effects of ELA 120 mg on liver fibrosis will be evaluated in an ongoing, 96-week open-label extension. These findings warrant further investigation of ELA in PSC.

Liver Transplantation

OS-090
A cfChIP-seq liquid biopsy for the diagnosis of acute cellular rejection following liver transplantation

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Background and aims: Liver transplantation (LTx) is a vital treatment option for patients with end-stage liver diseases. Acute cellular rejection (ACR) is a significant clinical diagnostic and therapeutic challenge at the post-transplant period. The clinical challenge lies in distinguishing ACR from other acute events, such as infections, vascular events, drug toxicity and biliary damage, which necessitates very different therapeutic modalities. Current diagnostic standards require liver biopsy for ACR diagnosis. This leads to a delay in diagnosis, is invasive, and with potentially complications. There is an urgent need for a simple, reliable, and reproducible non-invasive diagnostic test, which could be performed on daily basis, for monitoring post-LTx patients and diagnosing ACR.
Method: We utilized cell-free chromatin immunoprecipitation followed by sequencing (cfChIP-seq), a novel epigenetic-based liquid biopsy assay we recently introduced (Sadeh et al, *Nat. Biotech* 2001), to profile circulating cfDNA originating from active genes in plasma samples. The assay allows for interrogation of gene activity in the cell of origin. It provides insights into the extent of liver damage and the molecular states of dying liver cells and immune cells.
Results: We enrolled a cohort of >150 LTx patients and prospectively collected >4000 blood samples through their post-transplant hospitalization. We collected blood samples during 15 biopsy-verified ACR events and 14 non-ACT acute events for 20 patients. We developed a cfChIP-seq signature of genes that distinguish ACR samples from other acute liver damage events. We show that this signature allows the classification of ACR events with AUC of 0.94. This signature provides superior diagnostic performance compared to blood assay of liver enzymes (AUC of 0.75 for ALT and 0.48 for AST). We validated this signature in a follow-up LTx cohort.
Conclusion: We developed an ACR blood test using a cfDNA signature with high accuracy in patients post-LTx. The assay is highly

reproducible and robust, suggesting a path toward non-invasive detection, monitoring, and diagnosis of post-LTx ACR.

OS-091

AI-generated high-fidelity synthetic data enables privacy-preserving liver transplant research across liver disease subtypes: a study of the united network for organ sharing (UNOS) database

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Background and aims: Secure data sharing is crucial for cross-institutional collaboration in hepatology, but often hindered by stringent privacy regulations. Synthetic data—artificially generated datasets that replicate the statistical properties of real data without exposing confidential information—offer a promising solution. We aimed to implement and validate diffusion models, a state-of-the-art generative AI approach, to produce synthetic liver transplant datasets across various liver disease etiologies using the United Network for Organ Sharing (UNOS) database. Our focus was on preserving statistical fidelity, clinical utility, and ensuring robust patient privacy.
Method: We utilized the UNOS liver transplant dataset from 2019 to 2023, encompassing 35,374 patients. Diffusion models were trained to generate synthetic datasets for each liver disease category: alcohol (n = 14,772), metabolic (MASH, n = 10,311), viral (n = 2,545), autoimmune (n = 1,491), biliary (n = 3,350), cryptogenic (n = 2,161), and other (n = 744). We rigorously evaluated the synthetic data against the original using multiple metrics, including statistical fidelity by Wasserstein distances, clinical utility by the MELD score performance, correlation preservation, and privacy protection metrics such as Distance to Closest Record (DCR), Attribute Disclosure Risk, and K-anonymity violation rates.
Results: All synthetic disease subgroups achieved low multivariate Wasserstein distance <1.0, indicating excellent statistical fidelity with the original data. MELD score performance was consistently preserved, with negligible differences in AUC between synthetic and real datasets (0.004 to 0.033): alcohol (synthetic 0.845 vs. original 0.856), MASH (0.794 vs. 0.787), viral (0.814 vs. 0.827), autoimmune (0.814 vs. 0.827), biliary (0.768 vs. 0.800), cryptogenic (0.805 vs. 0.809), and other (0.832 vs. 0.809). Clinically significant correlations were maintained, such as between INR and bilirubin (R = 0.53 vs. 0.55), and the inverse relationship between sodium and creatinine (−0.15 vs. −0.13). In privacy assessments: DCR mean distances ranged from 0.75 to 1.22, ensuring synthetic patients were sufficiently distinct from real patients; Attribute Disclosure Risk was zero, and no K-anonymity violations were detected – meaning no actual patient data was present in the synthetic dataset.
Conclusion: Our study suggests that diffusion models can generate synthetic liver transplant data that retain essential statistical and clinical characteristics while providing strong privacy safeguards. This AI-driven method could enhance hepatology research by enabling more secure, privacy-compliant data sharing and collaboration across institutions. It may facilitate the augmentation of small patient cohorts and enable the use of "digital twins" for control arm simulations in trials. Future research is needed to validate this approach in multicenter studies and to explore its application in diverse clinical datasets.

OS-092-YI

The transcriptomic profile of antibody-mediated rejection is independent from the presence of donor specific antibodies

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Background and aims: The diagnosis of graft rejection after liver transplantation (LT) is based on light microscopy. Tissue transcriptomic signatures could help to clarify the alloimmune status of the graft, especially in cases where the diagnosis is unclear, such as chronic antibody mediated rejection (cABMR). CABMR, which leads to shorter graft survival after LT requires histologic criteria, the presence of donor specific antibodies (DSA), and the exclusion of other causes of liver injury. It is noteworthy that not all patients with cABMR fulfill all diagnostic criteria and the absence of DSA (cABMR-DSAneg) has been reported in other solid organ transplants and poses the same risk for adverse outcomes. We aimed to compare the transcriptomic signature of liver biopsies with cABMR and cABMR-DSAneg.
Method: All liver biopsies including surveillance and indication biopsies performed at the Hannover Medical School between 2018 and 2022 were screened. All biopsies with histologic criteria of cABMR (according to Banff 2016 criteria) and 20 liver biopsies with no histologic rejection (NHR) as controls were included. Biopsies with histological criteria for cABMR were divided into those with positive DSA within 3 months of the biopsy and classified as cABMR and those with negative DSA, classified as cABMR-DSAneg. RNA was extracted from paraffin-embedded tissue (FFPE) and sequenced. Downstream analyses explored the unique and shared molecular features of cABMR and cABMR-DSAneg. Differentially expressed genes were analyzed in comparison to biopsies with NHR.
Results: A total of 28 biopsies met the criteria for histologic cABMR, of which 7 (25%) had positive DSA (cABMR) and 21 (75%) had negative DSA (cABMR-DSAneg). Of these biopsies, 21 (6 cABMR and 15 cABMR-DSAneg) had sufficient tissue for RNA extraction. Most cases of cABMR (3/6, 50%) and cABMR-DSAneg (10/15, 66.7%) were found in surveillance biopsies, with no difference between groups (p = 0.83). When comparing the demographics of both groups, both had similar age at LT (47 vs 40 years, p = 0.88) and time after LT (149 vs 158 months, p = 0.88). The transcriptomic profile of cABMR was characterized by fibrogenesis, complement activation and TNF pathways. When comparing differentially expressed genes between cABMR and cABMR-DSAneg, both share the same transcriptomic profile with no up- or down-regulated genes that differ between the groups.
Conclusion: To our knowledge, this is the first report on the transcriptomic profile in liver biopsies with cABMR with and without DSA in the field of LT. Most of the liver biopsies compatible with cABMR do not have DSA, and the presence or absence of DSA does not influence the transcriptomic pathways at the tissue level. This implies that the presence of DSA, as described in other solid organ transplants, is not necessary for the diagnosis of cABMR.

OS-093

Inequalities in liver transplantation: data from the EPA-RITY study

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Background and aims: Social determinants of health (SDOH) are increasingly recognized as key drivers of health outcomes, including in transplantation medicine. Income inequality, in particular, has emerged as a critical factor influencing access to care and treatment

outcomes. Despite Italy's universal healthcare system, disparities persist, often challenging to quantify due to limited socio-economic data. Liver transplantation (LT) outcomes may be affected by factors such as income, education, and geographic location, influencing waitlist entry and progression. While these disparities are well-documented in countries with private or mixed systems, they remain underexplored in Italy. This study investigates, for the first time, the role of SDOH—particularly income—in shaping LT pathways, from waitlist enrollment to outcomes.

Method: This multicenter, retrospective study analyzed anonymized data from the national transplant database for patients listed for LT between 2010 and 2020. Income data were assigned to geographic areas based on postal codes. Linear and logistic regression models (odds ratios) were used to evaluate associations between income levels and LT outcomes, adjusting for individual and contextual confounders.

Results: We analyzed 9397 patients with complete postal code data from a total of 13947 listed for LT during the study period. Among these, 30.7% were under 50 years old, 40.6% were 51–60, and 28.7% were over 60; 73.6% were male. MELDNa scores at listing were 0–14 in 43.7%, 15–19 in 23.4%, 20–29 in 21.8%, and > 29 in 9.9%. Foreign-born patients were 33% more likely to have a MELDNa > 29 at listing (OR 1.33, p = 0.07). Patients from higher-income areas (> € 20,000) were 20% more likely to have a MELDNa <15. Waitlist durations were longer for women (+ 53 days) and residents of lower-income areas (+ 38–41 days). Organ failure at 6 months and 1 year increased with higher MELDNa scores but unexpectedly also with rising income levels.

Conclusion: Despite Italy's universal healthcare system, SDOH—especially income, gender, and migration status—significantly affect LT access and outcomes. These findings highlight the need for policies that integrate socio-economic factors into transplant planning to ensure equitable care. Addressing disparities through targeted interventions, improved outreach, and resource allocation adjustments is crucial for reducing barriers and achieving fair treatment outcomes.

OS-094

Donor derived cell free DNA can be used to tailor immunosuppression in liver transplant recipients - results of largest single center experience in the US

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Background and aims: Donor-derived cell-free DNA (dd-cfDNA) has emerged as a promising biomarker for detecting graft injury and early rejection in solid organ transplantation. However, data on its clinical utility in liver transplant recipients remains limited. We evaluated dd-cfDNA in liver transplant patients with both normal and abnormal liver function tests (LFTs) and assessed its utility in guiding immunosuppression (IS) titration in stable liver allografts.

Method: We retrospectively analyzed data from 68 liver transplant recipients with dd-cfDNA (AlloSure, CareDx Inc.) measurements from August 2021 to October 2023. The primary cohort included patients with at least one episode of rejection or stable allograft function. For the immunosuppression (IS) titration sub-analysis, we evaluated 13 stable patients who underwent IS modification based on dd-cfDNA levels. The IS regimen consisted of tacrolimus/sirolimus/cyclosporin with mycophenolate mofetil and/or prednisone. Statistical analyses included Wilcoxon rank-sum test for comparing stable versus unstable allografts, and Wilcoxon signed-rank test for evaluating changes after IS modification.

Results: Among 68 patients, 8 demonstrated evidence of rejection while 60 maintained stable allograft function. Median dd-cfDNA levels were significantly higher in unstable versus stable allografts (15% vs 2.8%, p = 0.0012). This correlated with significantly elevated liver enzymes in the unstable group (AST: 120 vs 25 U/L, p < 0.0001; ALT: 161 vs 24 U/L, p < 0.0001; ALP: 253 vs 81 U/L, p = 0.0004). In the IS titration sub-analysis (n = 13), mean initial dd-cfDNA was 3.78 ± 1.14%, with follow-up levels of 5.39 ± 1.42% (p = 0.241) after titration. Despite variable dd-cfDNA changes, LFT stability was maintained in 84.6% of patients after IS modification. Triple immunosuppression was more common in unstable patients (87.50% vs 51.67%).

Conclusion: Our findings demonstrate that in stable patients IS modification guided by dd-cfDNA levels -maintained allograft stability in vast majority of the cases. These results suggest that dd-cfDNA monitoring can effectively help down-titrate IS after liver transplantation while balancing their toxicity with risk of rejection. Larger confirmatory prospective studies are needed.

MASLD: Clinical and therapeutical aspects II

OS-095

Comparative analysis and cross-validation of artificial intelligence digital pathology (PathAI AIM-MASH and HistoIndex qFIBS) vs. expert hepatopathologist scoring in MASLD biopsies – results of the LITMUS study cohort

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Background and aims: The current regulatory approved surrogate endpoints for drug development in pre-cirrhotic Metabolic-dysfunction Associated Steatohepatitis (MASH) are histologically defined and require accurate measurement of disease activity using the MASLD Activity Score (MAS) and fibrosis stage (F) at trial entry and completion. Histopathologist scoring is subject to both inter- and intra-observer variation however, artificial intelligence (AI) models are a potential aid. The aim of this study was to independently assess performance of the latest iterations of the two best-evidenced quantitative AI approaches (PathAI AIM-MASH™ on H&E/MT stained digital slide images & HistoIndex qFIBS™ on unstained SHG/TPE laser microscopy images) vs. expert histopathologists.
Method: Centrally-evaluated MAS and F by the LITMUS Histopathology Group (LHG) served as the reference standard and were compared with ordinal outputs from each AI tool in 1360 liver biopsies from centres across Europe. Confusion matrices summarised agreement between methods, alongside standard measures of concordance. Accuracy of an AI-assisted histology screening pipeline for "at-risk MASH" (MAS≥4 + F≥2) was assessed.
Results: LHG central scoring (LHG-CS) considered 339/1360 cases to exhibit at-risk MASH and 524/1360 to be F≥3. A significant relationship was observed between LHG-CS and AIM-MASH for F (Kendall's tau 0.52, Cohen's Kappa 0.28) and MAS (0.65, 0.22), with high discriminatory power for diagnosing MAS≥4 (AUROC 0.87, Se/Sp 0.79/0.81), at-risk MASH (AUROC 0.79, Se/Sp 0.76/0.83) and F≥3 (AUROC 0.87, Se/Sp 0.77/0.84) by AIM-NASH. A significant relationship was also observed between LHG-CS and qFIBS for F (Kendall's tau 0.60, Cohen's K 0.29) and MAS (0.47, 0.10) with high discriminatory power for MAS≥4 (AUROC 0.79, Se/Sp 0.83/0.60) and F≥3 (AUROC 0.92, Se/Sp 0.86/0.84) by qFIBS. At-risk MASH performance was lower (AUROC 0.65, Se/Sp 0.36/0.94). Both AI methods showed similar overall concordance with LHG-CS for at-risk MASH (AIM-MASH 1106/1360 (81.3%), qFIBS 1081 (79.5%)), although the two differed in their relative Se/Sp for specific histological features. AIM-MASH considered a greater number of samples as at-risk MASH in disagreement with LHG-CS (172, 12.6% cases) compared to qFIBS (61, 4.5%).
Conclusion: This is the largest head-to-head study comparing the performance of AI digital pathology on MASLD biopsies centrally-scored by expert hepatopathologists. The results demonstrate substantial agreement between methods but highlight relevant differences in performance: AIM-MASH was superior at classifying at-risk MASH (AUROC 0.79 vs 0.65), with greater sensitivity but less specificity. In contrast, qFIBS was superior for staging F≥3 (AUROC 0.92 vs 0.87), due to greater sensitivity. Ongoing analysis with non-invasive biomarkers will examine the potential for AI as a complementary tool in trials.

OS-096

Alignment of response assessed by non-invasive fibrosis biomarkers and HistoIndex AI-based qFibrosis histology in metabolic dysfunction associated steatohepatitis (MASH) clinical trials: a new roadmap for robust drug efficacy assessment demonstrated in the HARMONY trial

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Background and aims: The current regulatory-approved reasonably-likely surrogate endpoints for MASH trials are histologically defined, yet expert hepatopathologist-based scoring is subject to inter- and intra-observer variation. This, combined with the heterogenous nature of liver tissue, potentially inflates placebo response rates, hindering drug development. In the absence of a single "perfect" response biomarker, assessing the extent of concordance of changes in multiple independent biomarkers could be an alternative approach to determine efficacy. Here, utilising the HARMONY Phase 2b trial (NCT04767529) dataset that established efficacy of Efruxifermin (EFX) using traditional histology endpoints, we explore novel response-biomarker strategies that combine non-invasive tests (NITs) and AI-based qFibrosis™ using SHG/TPE laser microscopy on unstained liver biopsies.
Method: This analysis included 104 patients at week 24 (W24: Placebo [PBO] n = 39, EFX = 65) and 76 at week 96 (W96; PBO = 29, EFX = 47). Concordance in fibrosis regression for PBO vs EFX (pooled doses) was assessed using: two NITs (ELF ≥0.5 absolute change and Liver Stiffness Measurement ≥30% change); central pathologist-scored fibrosis ([CPF] ≥1 stage change); categorical qFibrosis ([qF] ≥1 stage change), and continuous qFibrosis ([qFc] ≥ standard error of means).
Results: At W24, at least one NIT improved in 8/39 (20.5%) PBO vs. 47/65 (72.3%) EFX patients; both NITs showed regression in 0/39 (0%) PBO and 20/65 (30.1%) EFX (ChiSq P = 0.0001). At W96, at least one NIT improved in 12/29 (41.4%) PBO vs. 38/47 (80.9%) EFX; both NITs showed regression in 2/29 (6.9%) PBO and 23/47 (48.9%) EFX (ChiSq P = 0.0002). Factoring in liver biopsy assessment, dual-NIT response was concordant with CPF response in 0/39 (0%) PBO and 7/65 (10.7%) EFX cases at W24, and 0/29 (0%) PBO and 15/47 (31.9%) EFX cases (ChiSq P = 0.0007) at W96. Higher rates of dual-NIT concordance were observed with categorical qF response: 0/39 (0%) PBO and 13/65 (20.0%) EFX cases at W24, and 1/29 (3.4%) PBO and 20/47 (42.5%) EFX cases (ChiSq P = 0.0002) at W96. Concordance increased further with qFc response: 0/39 (0%) PBO and 15/65 (23.1%) EFX cases at W24, and 1/29 (3.4%) PBO and 22/47 (46.8%) EFX cases (ChiSq P = 0.0001) at W96.
Conclusion: Combining NITs with CPF appeared to supress PBO response (from 21%/41% at W24/W96 to 0% at both timepoints) whilst preserving clear efficacy signals, as seen by statistically significant superiority of EFX over PBO. Histopathological response as determined by qF/qFc exhibited greater concordance with dual-

NIT response, suggesting these approaches more closely track biological effect. These results demonstrate robustness of combined-NIT/AI-based histopathology and NIT-only biomarker strategies to assess treatment response and, with further validation, support the adoption of more robust reasonably-likely surrogate endpoints.

OS-097

Evaluating noninvasive diagnostic pathways for identifying MASH patients eligible for Resmetirom therapy: a real-world cohort analysis

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Background and aims: Resmetirom, the first FDA-approved medication for non-cirrhotic patients with metabolic dysfunction-associated steatohepatitis (MASH) with significant (F2) to advanced (F3) fibrosis, does not require liver biopsy for diagnosis. Current AASLD guidance recommend Vibration-Controlled Transient Elastography (VCTE) liver stiffness measurement (LSM) or the enhanced liver fibrosis (ELF) test for treatment consideration. In the real world, most patients with MASH do not undergo liver biopsy, and the diagnosis is predominantly based on noninvasive tests. This study aims to evaluate the performance of several noninvasive tests (NITs) diagnostic pathways that are proposed to be used in primary care to risk stratify patients with MASLD and determine who needs referral to hepatology care for treatment consideration.
Method: This retrospective study analyzed data from 424 MASLD patients treated with resmetirom at six U.S. tertiary hepatology clinics between March and November 2024. Demographics, laboratory results, liver stiffness measurements, and liver biopsies were recorded at baseline. Patient meeting one of the 3 AASLD guidance proposed criteria (1. LSM 8–20 kPa, or 2. ELF of 9.2–11.3, or 3. Liver biopsy fibrosis stage 2–3) were included in this analysis. The NITs diagnostic pathways that were evaluated included FIB4, SAFE score, Liver Risk Score, and ALADDIN-F2-Lab score.
Results: The cohort consisted of 424 patients with a median age of 58 years (IQR: 49–67), and 42.0% (179) were male. Diagnosis was established through liver biopsy in 20.8% of patients, with 45.5% demonstrating F2 fibrosis and 46.6% F3 fibrosis. Transient elastography was used in 88.9% of cases, with 69.8% of measurements falling within the AASLD-recommended range of 8–20 kPa. ELF testing was performed in 13.2% of patients, and 73.2% had levels between 9.2 and 11.3. A total of 337 patients meeting the AASLD guidance criteria were included in the analysis for NITs. Among the cohort, 45.8% had low-risk FIB-4 scores (<1.3). Results from alternative scoring systems showed varied proportions of patients classified as low risk: 80.2% for the Liver Risk Score, 13.0% for the SAFE score, and 12.5% for the ALADDIN-F2-Lab score.
Conclusion: This real-world analysis highlights the limitations of current AASLD and EASL guidelines, which rely on FIB-4, in identifying MASH patients with significant fibrosis. Nearly half of the eligible cohort would have been excluded from further evaluation based on low-risk classification using these tools. In contrast, novel scoring systems like SAFE and ALADDIN-F2-Lab, leveraging routine laboratory data, identified the majority of patients as intermediate or high risk, supporting the need for confirmatory testing with transient elastography or liver biopsy. These findings underscore the importance of developing alternative diagnostic strategies to optimize the identification and timely treatment of MASH patients.

OS-098

Direct effects of survodutide on liver endpoints beyond weight loss: insights from a phase 2 trial of the glucagon receptor/glucagon-like peptide-1 receptor dual agonist survodutide in people with metabolic dysfunction-associated steatohepatitis and fibrosis

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Background and aims: We evaluated weight-loss direct and indirect effects of survodutide, a glucagon receptor/glucagon-like peptide-1 receptor dual agonist, on liver endpoints in a phase 2 trial in people with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and F1 – F3 liver fibrosis.
Method: 295 patients were randomised to once-weekly subcutaneous injections of survodutide 2.4, 4.8, or 6.0 mg or placebo (NCT04771273). Patients with fibrosis stage F2/F3 and paired baseline and end-of-treatment biopsy readings (N = 170) were included, survodutide arms were pooled. Mediation analysis explores how an intermediate variable explains the pathway between an exposure and an outcome; we assessed the proportion of the effect of survodutide on liver endpoints that was attributable to a direct and indirect effect mediated by weight loss (WL). Liver endpoints assessed at Week 48 in this mediation analysis included resolution of MASH without worsening of fibrosis, improvement in fibrosis without worsening of MASH, absolute change in enhanced liver fibrosis (ELF™) score, relative change in propeptide of type III collagen (PRO-C3), FibroScan®-aspartate transaminase (FAST) score, liver stiffness measurement (LSM; FibroScan), and magnetic resonance imaging proton density fat fraction (MRI-PDFF). The model included treatment and percentage change in body weight, with baseline body weight, type 2 diabetes status, and fibrosis stage as covariates. We present the total treatment effect (TE) or total odds ratios (OR) and percentages mediated (% med), i.e., the proportion mediated by WL (the indirect effect of changes in body weight in relation to the total effect). Upper and lower limits presented are 95% confidence intervals.
Results: Changes in liver endpoints were mediated through WL with varying degrees of attribution. Liver endpoints that were highly mediated by WL were resolution of MASH without worsening of fibrosis (% med: 66.7% [41.3, 92.2%]; response rate: 62.9 vs 13.0% for placebo; OR: 14.70), or changes in MRI-PDFF (% med: 58.2% [43.5, 72.8%]; TE: −50.3 [−60.1, −40.5]). Endpoints for which WL had a

lower attribution were improvement in fibrosis without worsening of MASH (% med: 36.3% [−15.0, 87.7%]; response rate: 52.6 vs 25.9% for placebo; OR: 3.68), ELF score (% med: 38.6% [14.4, 62.7%]; TE: −0.64 [−0.83, −0.45]), PRO-C3 (% med: 25.2% [4.3, 46.1%]; TE: −28.63 [−36.38, −20.88]), FAST score (% med: 27.1% [10.6, 43.5%]; TE: −65.16 [−79.13, −51.18]), and LSM (% med: 35.1% [14.6, 55.7%]; TE: −38.78 [−49.08, −28.49]).
Conclusion: The results suggest that MASH resolution induced by survodutide was broadly mediated by WL. However, liver endpoints related to improvement in inflammation and fibrosis were less so, suggesting the reduction in these endpoints can be attributed to a direct effect of survodutide on the liver, likely via direct glucagon effect beyond WL.

OS-099

Personalised prediction of the individual risk of liver-related complications in MASLD using the dynamics of non-invasive tests of liver fibrosis

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Background and aims: Recent data suggest that monitoring the evolution of non-invasive tests of liver fibrosis helps to refine prognosis assessment in patients with MASLD. However, interpreting the variation of repeated non-invasive tests is challenging in clinical practice. We aimed to develop a model that uses the dynamics of non-invasive tests to provide a personalised prediction of liver-related events (LRE) in MASLD.
Method: We used an international multicentre cohort of MASLD patients with longitudinal follow-up data including liver stiffness measurements (LSM) by vibration-controlled transient elastography. The study outcome was LRE, a composite endpoint including decompensation of cirrhosis and/or hepatocellular carcinoma. Joint latent class modelling (JLCM), taking into account biomarker trajectory (longitudinal part of the model) and LRE occurrence (survival part), was developed to compute dynamic predictions resulting in a personalised prediction of the risk of LRE (0% to 100% at chosen time horizons). As repeated measurements were available during follow-up, JLCM was compared with FIB-4 and LSM at baseline and at each follow-up visit.
Results: 13,627 patients were included in the analysis, with 238 LRE occurring during a median follow-up of 4.0 years (IQR: 2.1–5.9). LSM trajectory adjusted on FIB-4 and gender (longitudinal part) and age with platelets (survival part) were selected by JLCM for LRE prediction. Calibration plots showed very good agreement between the predicted risk of LRE by JLCM and the observed incidence of LRE during follow-up. JLCM provided the highest discrimination for LRE: integrated AUROCs calculated at baseline and the different follow-up visits ranged 0.872–0.888 and were significantly higher than those obtained with LSM alone (0.853–0.864, all $p < 0.034$) or with FIB-4 alone (0.829–0.847, all $p \leq 0.001$). We calculated thresholds to delineate three risk groups according to the 5-year risk of LRE: low risk (≥ 80% sensitivity for LRE), intermediate risk, and high risk (≥ 95% specificity for LRE). These thresholds were 0.45%/1.51% per year for JLCM, 10/17 kPa for LSM, and 1.73/3.35 for FIB-4. At baseline and at each follow-up visit, JLCM included 85–89% of the patients in the low-risk group. 67–72% of the patients who experienced LRE during the follow-up were included in the high-risk group with JLCM, compared to 54–56% with LSM and 46–50% with FIB-4.
Conclusion: By automatically integrating and interpreting the dynamics of non-invasive tests of liver fibrosis, a new model provides an accurate and personalised assessment of the individual risk of liver-related complications in patients with MASLD.

Viral Hepatitis General

OS-100

Long term clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective study

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Background and aims: The long-term clinical outcome following direct acting antivirals for hepatitis C virus infection has not been yet documented despite the fact that they have been widely used. A total of 14,495 CHC patients received treatment in outreach program "Educate, Test and Treat" among 73 villages in Egypt since 2015. Our aim was to report the incidence of decompensated cirrhosis, hepatocellular cancer, and all-cause mortality in addition to fibrosis changes among patients received direct-acting antiviral therapy over a 10-years period.
Method: We conducted a prospective study including patients who received DAAs since 10 years enrolled from eleven Egyptian villages up till now. Patients with a history of decompensated cirrhosis, hepatocellular cancer, liver transplantation, or chronic hepatitis B were not included in our analysis, nor were those receiving interferon-ribavirin treatment. Our primary aim was to report the incidence of decompensated cirrhosis, hepatocellular cancer, and all-cause mortality. Secondary objective was detection of liver fibrosis changes, by FibroScan or FIB-4 and FIB-6.
Results: 1603 patients were eligible for the study, with available follow-up information and were included in analyses. Median follow-up was 98.0 months (IQR 71.0–105.0). During follow-up, 377 patients

died, 32 reported decompensated cirrhosis and 41 reported hepatocellular carcinoma. Exposure to direct-acting antivirals was associated with all-cause mortality rate of 3.42/100 py (95% CI 3.08–3.77), decompensation of 0.26/100 py (95% CI 0.18–0.36), and hepatocellular carcinoma of 0.51/100 py (95% CI 0.11–0.25). In cirrhotic patients, 17% showed reversal of cirrhosis, 19.1% showed fibrosis regression while 63.8% remained stationary. F3 patients showed reversal of fibrosis in 44.4%, 19.8% showed fibrosis regression and 19.8% remained stationary while 16.0% progressed to F4.
Conclusion: This is the first study to document the long-term outcomes for patients treated with direct-acting antivirals (DAAs) for hepatitis C virus infection in Egyptian patients with genotype 4. Our findings demonstrate that DAAs are associated with a decreased risk of decompensation and hepatocellular carcinoma, and often lead to improvements in liver fibrosis. Further studies involving different ethnicities and genotypes are needed.

OS-101-YI
Concomitant diabetes mellitus in untreated chronic hepatitis B with low-level viremia is associated with increased risk of hepatocellular carcinoma: validating the world health organization 2024 recommendations
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Background and aims: The World Health Organization (WHO) 2024 guidelines recommended antiviral therapy in chronic hepatitis B (CHB) patients with diabetes mellitus, regardless of hepatitis B virus (HBV) DNA, fibrosis status or alanine aminotransferase (ALT) levels. The benefits of treatment expansion to these patients have not been well defined.
Method: We enrolled CHB patients, defined via hepatitis B surface antigen positivity or ICD-9 coding, who newly presented to a population-wide electronic health registry between 2011 to 2015. Patients with concomitant liver diseases (other than metabolic associated steatotic liver disease), history of hepatocellular carcinoma (HCC), or HCC diagnosed within 6 months after the entry date were excluded. Diabetes mellitus was defined as glycosylated haemoglobin ≥ 6.5%; fasting serum glucose ≥ 7 mmol/L, use of antidiabetic medications or ICD-9 coding. The primary outcome was incident HCC development, and multivariate Cox regression models were applied to calculate adjusted hazard ratio (aHR) and 95% confidence intervals (95%CI).
Results: Among 38979 CHB patients (mean age 47.5 +/− 15.4 years; 41.9% male, 43.3% on antiviral therapy for a median of 5.2 years, 24.3% with newly diagnosed diabetes during study period). Diabetes was an independent predictor of HCC (aHR 1.53, 95%CI 1.29–1.82), and this association remained robust after stratification by age, sex, antiviral treatment, Fibrosis-4 score, AST to platelet ratio index, HBV DNA levels, and alanine aminotransferase levels (aHR: 1.34–4.91). Among the 22096 untreated patients, diabetes was associated with a 1.5-fold increased risk of HCC (aHR 1.50, 95% CI 1.07–2.10), with the association remaining significant in patients with baseline HBV DNA <2000 IU/mL (aHR 1.53, 95%CI 1.09–2.14) or FIB-4 ≤ 3.25 (aHR 1.94, 95%CI 1.24–3.04). When focusing on patients with concomitant CHB and diabetes, antiviral treatment was independently associated with reduced HCC risk (aHR 0.76, 95%CI 0.68–0.84), with more prominent risk reduction in patients < 65 years (aHR 0.64, 95% CI 0.56–0.74); as compared to age ≥ 65 years (aHR 0.91, 95% CI 0.78–1.07) ($P_{interaction}$ for age <0.001).
Conclusion: Concomitant diabetes mellitus was associated with increased HCC risk in CHB, including in untreated patients with low-level viremia or non-advanced liver fibrosis. The risk reduction effects of antiviral treatment were more pronounced in younger patients. These findings support the WHO 2024 recommendations in expanding CHB treatment to patients with concomitant diabetes mellitus.

OS-102
Mortality benefits of a national program of supported, active care in the treatment of marginalised people with chronic HCV infection
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Background and aims: Chronic hepatitis C infection is common in marginalised, deprived communities, including those actively using drugs. Given the high mortality in these populations the benefits of treating hepatitis C are unclear. The English Hepatitis C Elimination program focussed on providing holistic care and support to deprived people with hepatitis C and here we report on its impact.
Method: Retrospective review of National Health Service England Hepatitis C Registry data and United Kingdom Health Security Agency mortality data between 2015 and 2022. Standardised mortality ratios (SMR) of the observed number of deaths in people treated and cured of hepatitis C who did not have significant liver disease were compared to the expected number of deaths using general population mortality rates by age, sex, year, and Index of Multiple Deprivation (IMD) were calculated.
Results: Between 2015 and 2022, following the introduction of the comprehensive hepatitis C elimination program 38,429 individuals without evidence of cirrhosis were successfully treated, a large proportion were from deprived communities and 15.7% had a history of homelessness. 1548 (4.0%) died. 23,718 had sufficient data to assign an index of deprivation at diagnosis, of which 67% resided in the 2 most deprived quintiles when first diagnosed. Post treatment mortality, assessed by SMRs, did not differ significantly in affluent cohorts (IMD 4 SMR = 1.2 (1.0–1.5), and 5 (SMR 0.9 (0.6–1.1) and was marginally increased in highly deprived cohorts (IMD 1 = 1.2 (1.1–1.3), IMD 2 = 1.1 (1.0–1.2)). However during the first three years of the program SMRs in the most deprived cohorts were substantially reduced when compared to untreated controls but this benefit reduced with time and, during COVID, SMRs increased, peaking in 2021 before falling again in 2022. The reductions in benefits of the program seen over time may reflect either engagement of a more marginalised cohort in the later years of the program or a reduction in support provided as commitment to the program reduced.
Conclusion: Mortality in people with hepatitis C, who do not have cirrhosis and are effectively treated in a supportive holistic program is not increased compared to appropriate control populations. A comprehensive package of care for people with hepatitis C is associated with beneficial effects on mortality but the impact reduces over time.

OS-103
The nucleoside analogue NITD008 strongly suppresses viral replication in immunodeficient humanized mice stably infected with the hepatitis E virus
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Background and aims: Hepatitis E virus (HEV) infection has an emerging clinical relevance for patients worldwide, but there is currently no approved antiviral therapy. For immunosuppressed people with chronic hepatitis E, off-label treatment with ribavirin is used in daily clinical practice, but ribavirin can cause serious side effects and resistance does emerge. Therefore, there is an urgent need for new and effective antiviral drugs against HEV infection. The adenosine nucleoside analogue NIDT008 is one such candidate that has been shown to be effective in preclinical studies against a broad range of RNA viruses. The aim of this study was to evaluate the efficacy of NITD008 in vivo in human liver chimeric mice stably infected with HEV.
Method: Immunodeficient human-liver chimeric mice were infected with hepatitis E virus (genotype 1) via the co-housing fecal-oral route. After a stable infection was achieved (6–8 weeks), median HEV RNA viremia was 1.5×10^7 IU/ml, mice received 20 µg/g of NITD008 by oral gavage daily for up to 2 weeks, while a control group received mock treatment. Viral changes were determined by qPCR in faeces and blood. Mice were sacrificed after 1 or 2 weeks of treatment, while a subgroup was observed for a 3-week rebound phase. Intrahepatic analysis including immunohistochemistry, multiplex RNA in situ hybridization (RNA-ISH) and qPCR was performed in all mice at sacrifice.
Results: NITD008 effectively reduced fecal HEV loads by up to 4log already in the first week of treatment, with some mice showing no detectable virus shedding. All mice had undetectable serum HEV titers (LLoQ) after 7 days, while vehicle-only controls showed no decrease in fecal and serum viral titers (median 7.7×10^6 IU/mL and 1×10^6 copies/ml, respectively). Intrahepatic analysis showed a 1.5 log reduction in HEV RNA/human housekeeper levels in treated mice compared to controls after 1 week of treatment and a 2.5 log reduction after 14 days of treatment. Consistent with the qPCR data, RNA-ISH analysis confirmed the presence of only a few weakly HEV-RNA-positive human hepatocytes in treated mice, whereas approximately 95% of human liver cells were strongly positive in control animals. Two weeks of NITD008 administration did not induce ALT elevation or significant weight loss in treated mice. Despite the strong reduction in HEV infection, HEV rebound was observed after 3 weeks of treatment cessation in this immunodeficient system.
Conclusion: This study demonstrates the efficacy and non-toxicity of the adenosine nucleoside analog NITD008 towards human hepatocytes after only 2 weeks of treatment in HEV infected human-chimeric mice. Longer treatment periods and/or combination regimens with ribavirin are needed to further optimize results and eventually achieve complete viral clearance even in the absence of a humoral immune response.

OS-104

Outcomes beyond 10 years in entecavir or tenofovir treated Caucasian chronic hepatitis B patients of the real-life PAGE-B cohort

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Background and aims: There is very few data from trials or real-life cohorts about the long-term outcomes of chronic hepatitis B (CHB) patients treated with a high-genetic barrier nucleos(t)ide analogue (NA). We assessed the incidence of major outcomes in the real-life PAGE-B cohort focusing on patients treated for >10 years.
Method: The PAGE-B cohort included 1951 adult Caucasians with CHB, with or without compensated cirrhosis, who were treated with entecavir/tenofovir being followed at 10 centers. Eight centers which originally included 1644 (84%) of the 1951 patients participated in the follow-up study beyond year 10. Cumulative incidence rates were assessed from both Kaplan-Meier curves and Fine & Gray's models taking into account relevant competing risks.
Results: Of the 1644 patients (baseline age: 53 ± 14 years, 72% males, 17% HBeAg+, 28% cirrhotics), 842 cases (51%) (baseline age: 51 ± 13 years, 71% males, 19.5% HBeAg+, 31% cirrhotics) were followed beyond year 10 for a mean of 14 ± 2 years. Hepatocellular carcinoma (HCC) developed in 174 (10.6%) patients (157 until and 17 after year 10). The 5-, 10- and 15-year cumulative HCC rates (95% CI) were 6.8% (5.6–8.1), 10.8% (9.2–12.5) and 13.7% (11.8–15.8), respectively (Fine-Gray), whereas the HCC incidence rate (95% CI) per 100 patient-years was 1.25 (1.07–1.46) until and 0.83 (0.55–1.23) after year 10 ($p = 0.073$). There were 176 deaths until and 63 deaths after year 10 (liver related deaths: 77 and 19), whereas 18 and 4 patients underwent liver transplantation (LT), respectively. Death/LT incidence rate (95% CI) per 100 patient-years was lower until than after year 10 [1.50 (1.30–1.72) vs 2.21 (1.74–2.80), $p = 0.008$], but liver related death/LT rate did not differ between the two periods [0.73 (0.60–0.90) vs 0.76 (0.50–1.14), $p = 0.872$]. HBsAg loss was observed in 191 (11.6%) patients. The 5-, 10- and 15-year cumulative HBsAg loss rates (95% CI) were 5.0% (4.0–6.1), 9.4% (8.0–11.1) and 17.0% (14.6–19.6), respectively (Fine-Gray), whereas the HBsAg loss incidence rate (95% CI) per 100 patient-years was 1.06 (0.89–1.25) until and 2.04 (1.58–2.64) after year 10 ($p < 0.001$). NA was discontinued in 218 (13.3%) patients [125 (7.6%) before and 93 (5.7%) after HBsAg loss]. NA discontinuation before HBsAg loss was the main factor associated with higher HBsAg loss rates [Crude Hazard Ratio (95% CI) vs patients remaining on NA: 5.58 (3.80–8.28), $p < 0.001$]. The 1-, 3- and 5-year cumulative HBsAg loss rates after NA discontinuation were 5%, 14% and 24%, respectively.
Conclusion: CHB patients remain at risk for HCC after 10 years of NA therapy with a numerical but not significant decline in the annual HCC incidence over time. A small proportion (<10%) of patients who remain HBsAg positive discontinue NA therapy, which is associated with significantly increased HBsAg loss rates.

EASL JOURNAL OF HEPATOLOGY

Late-breaker Posters

LBP-001

Preclinical profiling of ABI-6250, a first-in-class oral therapeutic candidate for chronic hepatitis

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Background and aims: Chronic hepatitis D virus (cHDV) infection is the most severe form of viral hepatitis, resulting in aggressive progression of liver disease, with limited treatment options. Bulevirtide (BLV), an injectable peptide inhibiting HDV entry via binding to the sodium taurocholate co-transporting peptide (NTCP) receptor (a bile acid [BA] transporter) is approved in Europe for the treatment of cHDV. Here we report the preclinical profiling of ABI-6250, a novel orally bioavailable small-molecule HDV entry inhibitor targeting NTCP, which offers a potential oral alternative to the current injectable therapy.
Method: The half maximal effective concentration (EC_{50}) of ABI-6250 was determined in NTCP-expressing cells and primary human hepatocytes (PHHs) infected with patient or cell culture-derived HDV or hepatitis B virus (HBV), respectively. Virus specificity was evaluated in cell culture by testing against different viruses. The half-maximal cytotoxic concentration (CC_{50}) was determined in a panel of cell lines and primary cells. NTCP-specificity of ABI-6250 was evaluated in vitro by measuring the half maximal inhibitory concentration (IC_{50}) across multiple cellular transporters. Dose-escalating pharmacokinetic/pharmacodynamic (PK/PD) studies were conducted with ABI-6250 in cynomolgus monkeys and drug exposure, BA elevations, and coproporphyrin I (CP-I) plasma levels were measured.
Results: ABI-6250 potently inhibited 18 European HDV-patient isolates with a median EC_{50} of 21.1 nM in HepG2-NTCP cells, as well as cell culture-derived HDV genotype (GT) 3-D and HBV GT A, C, and D with a mean EC_{50} of 19.5 (HDV) and 23.9 nM (HBV) in PHHs, respectively. The mean CC_{50} was > 26 µM in seven different human cell lines, as well as in human peripheral blood mononuclear cells and PHHs. ABI-6250 demonstrated high HDV-specificity with a mean fold-selectivity ratio ($EC_{50,virus}/EC_{50,HDV}$) > 830 when tested against HCV, HSV-1/2, HCMV, and RSV. In addition, ABI-6250 had a 13 to 2425-fold NTCP-selectivity ratio ($IC_{50,transporter}/IC_{50,NTCP}$) when tested against 14 different transporters including MDR1, BCRP, OAT1/3, and OCT1/2. Furthermore, PK/PD studies in monkeys revealed dose-dependent ABI-6250 plasma exposure and increased BA levels starting at a single oral dose of 0.03 mg/kg, while OATP1B function remained unaffected up to 10 mg/kg, as evidenced by unchanged CP-I levels, a biomarker for OATP1B inhibition.
Conclusion: ABI-6250, a highly potent and selective orally bioavailable first-in-class HDV entry inhibitor, has demonstrated promising preclinical results. ABI-6250 elevates total BAs in monkeys at projected clinically-relevant concentrations without raising CP-I plasma levels, indicating selective NTCP target engagement. ABI-6250's preclinical PK profile supports once-daily oral dosing for cHDV treatment, and a Phase 1a clinical trial is currently ongoing.

LBP-002

High-throughput combinatorial CRISPR screening in hepatic progenitor cell-derived organoids reveals genetic determinants of response to standard-of-care chemotherapy in cholangiocarcinoma

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Background and aims: Cholangiocarcinoma (CCA) is a genetically heterogeneous malignancy characterized by complex co-occurring mutations, limited treatment options, and chemotherapy resistance. Traditional single-gene CRISPR screens fail to capture its full mutational landscape, while combinatorial approaches face scalability challenges. To overcome these limitations, we developed a combinatorial method to generate organoid models using multiplexed CRISPR knockout screening, which is a high-throughput platform that enables the simultaneous knockout of frequently mutated CCA genes to study tumor evolution and resistance to therapy.
Method: A lentiviral library encoding guide RNAs for 5,929 gene knockout combinations from the 10 most frequently mutated CCA genes was transduced into human chemically derived hepatic progenitor cells (hCdHs) to generate organoids, which were then validated against patient-derived CCA organoid subtypes. Genetic and transcriptomic profiles were analyzed using next-generation sequencing (NGS) and bulk RNA sequencing. High-throughput pharmacogenetic profiling was performed by exposing organoids to standard CCA chemotherapies—gemcitabine, cisplatin, oxaliplatin, and docetaxel—both as monotherapies and in combination.
Results: Organoids evolved from multi-luminal structures at passage 0 (T0) into poorly differentiated, grape-like forms by passage 7 (Tlate), losing apicobasal polarity and acquiring phenotypic traits characteristic of intrahepatic CCA. RNA sequencing revealed greater transcriptional aberrations in Tlate than in T0, indicating a pronounced gene expression shift. NGS analysis showed that, of the 5,929 gRNA combinations tested, 29.62% exhibited high alpha-robust ranking aggregation scores, suggesting potential CCA drivers. Further analysis identified 16 knockout combinations that enhanced proliferation, with PBRM1-ARID1A knockout promoting the most growth, whereas PBRM1-KMT2C knockout reduced proliferation. Pharmacogenetic profiling revealed two distinct drug response

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clusters: Cluster A (gemcitabine-based) and Cluster B (cisplatin/docetaxel-based). CDKN2A and KMT2C mutations increased sensitivity to Cluster A and B therapies, respectively, while APC and SMAD4 mutations conferred resistance. ARID1A-related knockout combinations exhibited broad drug sensitivity. Transcriptomic analysis of Tlate organoids treated with drugs revealed mutation-dependent RNA expression patterns that are linked to drug sensitivity and resistance.
Conclusion: The platform enabled high-throughput studies of CCA evolution and chemotherapy responses across diverse mutational landscapes. These findings underscore the potential for personalized CCA treatment by integrating this platform with patient-derived organoid biobanks and clinical trial data, accelerating targeted therapy development.

LBP-003

DR10624, a first-in-class, FGF21 receptor (FGF21R)/glucagon receptor (GCGR)/GLP-1 receptor (GLP-1R) triple agonist rapidly and significantly reduced liver fat in obese subjects with modest hypertriglyceridemia: a 12-week randomized, placebo-controlled, double-blind, multi-center trial

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Background and aims: DR10624 is a first-in-class (FIC) long-acting FGF21R/GCGR/GLP-1R triple agonist. The study aims to explore DR10624 as a novel biologic treatment for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH).
Method: The Phase 2a trial was a 12-week randomized, placebo-controlled, double-blind, multi-center, multiple ascending dose study in obese adults with modest hypertriglyceridemia (BMI 30-45 kg/m^2, fasting triglycerides (TG): 1.7 to 5.7 mmol/L at screening). Subjects were randomized in a 5:1 ratio to be dosed weekly of DR10624 (12.5 mg, 25 mg, 50 mg, or 75 mg titration) or placebo for 12 weeks. The efficacy endpoints included changes in liver fat content (assessed by magnetic resonance imaging – proton density fat fraction [MRI-PDFF]), lipid profile, and insulin resistance (measured by homeostatic model assessment index of insulin resistance [HOMA-IR]) from baseline.
Results: 49 subjects were randomized and 27 (55.1%) were White. After 12 weeks, DR10624 showed profound therapeutic efficacy on key metabolic markers. The least squares mean (LSM) relative reduction from baseline in liver fat were significantly greater with DR10624 (51.9%, 77.8%, 79.0%, and 75.8% in 12.5 mg, 25 mg, 50 mg, and 75 mg titration, respectively) than with placebo (26.3%). The proportions of subjects receiving DR10624 (12.5 mg, 25 mg, 50 mg, and 75 mg titration) that achieved ≥50% relative reductions in liver fat were 66.7%, 88.9%, 100%, and 85.7%, respectively. Among subjects with baseline liver fat ≥8% (MRI-PDFF), 94.7% of those across all DR10624 treatment groups (n = 19) achieved a ≥ 50% relative reduction in liver fat, compared to 16.7% of those receiving the placebo (n = 6). The study showed statistically significant reductions in geometric LSM TG from baseline in DR10624-treated subjects across all doses compared to placebo. The LSM relative reductions from baseline in TG were 31.3%, 58.9%, 70.2%, and 55.2% with DR10624 (12.5 mg, 25 mg, 50 mg, and 75 mg titration), respectively, and 6.9% with placebo. Statistically significant reductions in geometric LSM VLDL-C, total cholesterol, non-HDL-C, and HOMA-IR were observed in subjects receiving 50 mg and 75 mg titration of DR10624 compared to placebo. Remarkably, the LSM relative changes from baseline in HOMA-IR were -42.7% and -35.9% with DR10624 (50 mg and 75 mg titration, respectively), and 5.8% with placebo, suggesting greatly improved insulin sensitivity. DR10624 was well tolerated in the study, with no serious adverse events related to the drug.
Conclusion: DR10624, administered weekly for 12 weeks, resulted in rapid and clinically significant reduction in liver fat, along with remarkable improvements in lipid profiles and insulin sensitivity. The Phase 2a data further underscore DR10624's strong potential as an innovative and promising treatment for MASLD/MASH.

LBP-004

Primary analysis of a phase 2b open-label study demonstrates VTP-300 administered with low-dose nivolumab is associated with meaningful reductions of HBsAg in chronic hepatitis B participants with HBsAg less than 200 IU/mL

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Background and aims: There is significant unmet need to induce functional cure (FC) of chronic hepatitis B virus (CHB) to limit duration of nucleos(t)ide analogue (NUC) therapy and reduce the risk of hepatocellular carcinoma. VTP-300, an antigen-specific investigational immunotherapy, has been shown to induce sustained CD8+ T cell responses to HBV as well as meaningful HBsAg reductions, including HBsAg loss, in patients with CHB. We report efficacy and safety data from the primary analysis of HBV003, an open-label Phase 2b study (NCT05343481).
Method: HBV003 enrolled participants with CHB, on NUC therapy, with an HBV-DNA viral load of ≤ 1000 IU/mL and HBsAg of ≥ 10 IU/mL and ≤ 4,000 IU/mL, subsequently amended to HBsAg ≤ 200 IU/mL at screening. Participants were randomised to three groups to investigate different VTP-300 and low dose nivolumab (LDN) regimens and then followed up for 12 months, unless they discontinued NUC therapy (optional) where follow-up continued for a further 48 weeks. Follow-up has been completed for the primary endpoint which is the percentage of participants with ≥ 1 log HBsAg reduction 6 months after initiation of therapy (Day 169). Follow-up for safety and immunogenicity continues until the end of the study.
Results: 121 participants were enrolled with 70 (58%) having HBsAg levels ≤ 200 IU/mL at screening. 97 (80%) were HBeAg negative and 95 (79%) were male. HBsAg declines ≥ 1 log at Day 169 across all three groups were observed in 16/121 (13%) of all participants and in 15/69 (22%) of those with baseline HBsAg levels ≤ 200 IU/mL. Preliminary results of the best treatment arm reveal that, for participants with baseline HBsAg ≤ 200 IU/mL who received modified vaccinia Ankara (MVA) and LDN together, 8/23 (35%) achieved HBsAg reductions of ≥ 1 log; subsequently, 6/23 (26%) were reported with total HBsAg loss, on or after Day 169. Results corresponding to functional cure, immunogenicity, genotype data that include all treatment groups will be presented at the meeting. VTP-300 administered with LDN was generally safe and well tolerated and no participants discontinued the study due to adverse events.
Conclusion: VTP-300, a novel antigen-specific investigational immunotherapy, administered in combination with LDN results in meaningful reductions of >1 log in HBsAg at D169 in all 3 treatment groups; all 3 regimens were well tolerated. It is in patients with HBsAg ≤ 200 IU/mL that HBV directed immunotherapy with the combination of VTP-300 and LDN can achieve HBsAg loss in a meaningful proportion of patients. Further studies investigating sequential therapy of HBsAg lowering agents and VTP-300/LDN in CHB patients are warranted.

LBP-005

DA-1241, a GPR119 agonist, demonstrates hepatoprotective and glucose-regulating effects in a 16-week randomized placebo-controlled trial in presumed metabolic dysfunction-associated steatohepatitis (MASH) patients

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Background and aims: DA-1241 is a potent and selective agonist for G protein-coupled receptor 119 (GPR119). It showed target engagement by increasing glucagon-like peptide-1 (GLP-1) secretion and demonstrated post-prandial glucose-lowering efficacy by directly stimulating insulin secretion in type 2 diabetic patients (NCT03646721). Preclinical studies have shown that GPR119 agonism has potent anti-MASH effects. This phase 2a trial (NCT06054815) evaluated the efficacy and safety of DA-1241 as a potential treatment for MASH, alone and in combination with a dipeptidyl peptidase 4 inhibitor (DPP4i) to augment endogenous GLP-1 action.
Method: Total 109 subjects with presumed MASH and qualifying baseline alanine transaminase (ALT) and imaging analysis were randomized to receive DA-1241 50 mg, DA-1241 100 mg alone, DA-1241 100 mg with a DPP4i, or placebo (PBO) in a 1:2:2:2 ratio, once daily for 16 weeks. The primary efficacy endpoint was the change from baseline in ALT after 16 weeks of treatment.
Results: In the subgroup with 40 ≤ ALT < 200 U/L at baseline, DA-1241 treatment resulted in dose-dependent reductions in ALT, with the 100 mg dose demonstrating a significant decrease of 22.8 U/L at week 16 ($p < 0.05$ vs. PBO). The mean FibroScan-aspartate aminotransferase score improved from 0.559 to 0.371, indicating reductions in liver fibrosis and steatosis. Liver fat content decreased by 23.0 dB/m in Controlled Attenuation Parameter, along with a mean relative reduction of 19.9% in Magnetic Resonance Imaging-Proton Density Fat Fraction. Cytokeratin 18, a marker of hepatocyte apoptosis, was significantly decreased by 30.5% ($p < 0.05$ vs. PBO). Plasma lipidomics profiles were analyzed before and after treatment. Administration of DA-1241 100 mg reduced both plasma glycerolipids such as DG36:4, TG52:4, and glycerophospholipids including PE38:4 and PE38:5, which are known to be potential pathogenic lipids ($p < 0.05$ vs baseline). Interestingly, DA-1241 100 mg increased sphingomyelin levels, which were reported to be decreased in MASH patients, compared to baseline ($p < 0.05$). Notably, on top of the hepatic effects, DA-1241 100 mg rapidly and markedly lowered mean hemoglobin A1c (HbA1c) by 0.37, 0.41, and 0.54%p at week 4, 8, and 16 from the baseline of 6.99%, despite nearly half of them being non-diabetic ($p < 0.05$ vs. PBO). Additionally, co-administration with DPP4i augmented metabolic effects, including further reduction from baseline in HbA1c (-0.66%p, $p < 0.001$ vs. PBO) and plasma triglycerides levels (-0.35 mmol/L, 95% CI -0.57 to -0.12), though no further improvement was observed in hepatic parameters.
Conclusion: DA-1241 is the first oral GPR119 agonist to demonstrate both hepatoprotective and glucose-regulating effects in presumed MASH patients. These findings support its further development as a potential monotherapy or combination therapy for MASH and metabolic disorders.

LBP-006

MELD 3.i: a bayesian approach for consecutive updates to model for end-stage liver disease

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Background and aims: The Model for End-Stage Liver Disease (MELD) score has been a cornerstone of liver transplant (LT) allocation, with iterative updates culminating in the implementation of MELD 3.0. However, evolving factors such as changes in liver disease epidemiology, organ allocation policies, and clinical practices necessitate ongoing model refinement. To address these dynamics, we applied a Bayesian framework to recalibrate MELD 3.0 using contemporary data.
Method: This retrospective cohort study included all US adult liver transplant (LT) candidates listed between July 13, 2023 to June 30, 2024. Candidates from the first two-thirds of listing dates formed the training set, while the last third comprised the validation set. We employed a Bayesian proportional hazards model, incorporating MELD 3.0 as informative priors to generate posterior distributions of the coefficients. Model performance was assessed using concordance (C-) statistics, and reclassification analyzed patient redistribution and mortality risks across MELD tiers.
Results: The cohort included 13,764 candidates (41.1% female). The updated score, MELD 3.1 showed improved C-statistics for 90-day waitlist mortality in the validation set (0.7195 vs. 0.7152 for MELD 3.0, $p = 0.036$). Reclassification analysis revealed that MELD 3.1 up-categorized 5.9% of patients and down-categorized 2.8%, resulting in a net gain of 3.1% among decedents. This net gain was entirely observed among female candidates, reflecting the more favorable score in MELD 3.1, which assigned a higher coefficient for female sex and a lower coefficient for creatinine. MELD 3.1 also demonstrated net gains across different age groups and liver disease etiologies.
Conclusion: Our findings support the need for periodic MELD updates using contemporary data to maintain predictive accuracy and improve LT allocation. An iterative update framework ('MELD 3.i') could help the system adapt to evolving demographics and clinical practices, optimizing transplant fairness and effectiveness.

LBP-007-YI

Macrophage Nrf1-Foxo1 axis controls liver fibrosis by modulation of mitochondrial reprogramming

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Background and aims: Liver fibrosis is a progressive condition driven by chronic injury, ultimately leading to cirrhosis. Immune dysregulation, particularly macrophage polarization, plays a crucial role in fibrosis progression. Pro-inflammatory M1 macrophages worsen inflammation and fibrosis, with their polarization influenced by metabolic shifts between glycolysis and oxidative phosphorylation. Nuclear factor erythroid 2-related factor 1 (Nrf1), a key redox-sensitive factor essential for mitochondrial homeostasis, has been extensively studied in hepatocytes but remains largely unexplored in

macrophages in the context of liver fibrosis. This study aims to elucidate the immunoregulatory role of macrophage Nrf1 in liver fibrosis, potentially identifying novel therapeutic targets to mitigate or reverse fibrosis progression.

Method: Myeloid-specific Nrf1-knockout ($Nrf1^{M-KO}$) mice and Foxo1 knockout ($Foxo1^{M-KO}$) mice were developed to investigate the role and underlying mechanisms of macrophage Nrf1-Foxo1 axis across three murine models of liver fibrosis induced by a high-fat diet, carbon tetrachloride injection or bile duct ligation. Bone marrow-derived macrophages (BMDMs) were isolated from conditional mice, then stimulated with lipopolysaccharide (LPS, 100 ng/mL, 6 hours). CRISPR/Cas9 and siRNA approaches were used to assess downstream targets.

Results: Nrf1 expression was significantly reduced in macrophages from fibrotic liver tissues, as confirmed by qRT-PCR and immunofluorescence staining in both human and murine models. $Nrf1^{M-KO}$mice exhibited exacerbated liver fibrosis, characterized by elevated serum ALT/AST levels, increased collagen deposition, and upregulated fibrotic markers (TGF-β, Col1a1, TIMP1). Loss of Nrf1 promoted M1 macrophage polarization, enhanced inflammatory responses (elevated TNF-α, IL-1β, iNOS), and impaired mitochondrial function (reduced ATP production and increased mitochondrial ROS). In contrast, $Foxo1^{M-KO}$ mice exhibited attenuated fibrosis, reduced inflammation, and improved mitochondrial integrity. Mechanistically, Nrf1 directly interacted with Foxo1 to regulate the transcription of KLF6, a key mediator of mitochondrial function and macrophage polarization. These findings underscore the pivotal role of the Nrf1-Foxo1-KLF6 axis in macrophage-driven inflammation and fibrosis, highlighting potential therapeutic targets for liver fibrosis.

Conclusion: Our study highlights the functional properties of macrophage Nrf1-Foxo1 axis in controlling mitocondrial reprogramming and liver fibrosis progression.

LBP-008

Safety, tolerability, and remarkable hepatitis B surface antigen reduction in chronic hepatitis B patients treated with BW-20507

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Background and aims: BW-20507 is an N-acetylgalactosamine conjugated small interfering RNA (siRNA) designed to target the hepatitis B virus (HBV). Preclinical studies have demonstrated its distinct antiviral activity and promising potential for the treatment of HBV infection. Here, we present preliminary data from an ongoing study evaluating the safety, tolerability, and antiviral activity of BW-20507 in patients with chronic HBV infection (CHB).

Method: This is a randomized, open-label, multiple- ascending dose study to evaluate the safety and tolerability in CHB patients without advanced liver fibrosis or cirrhosis. CHB patients who were nucleotide/nucleoside analogs (NUCs) naïve or on NUCs (HBV DNA < 90 IU/mL) with hepatitis B surface antigen (HBsAg) > 50 IU/mL were randomized to 4 cohorts [100 mg (on NUCs), 200 mg (on NUCs), 200 mg (NUCs naive), 400 mg (on NUCs)] to receive BW-20507 subcutaneously every 4 weeks for a total of 3 doses. Participants who were NUCs naïve will take NUCs by the investigators' discretion on Day 1.

Results: Thirty-one patients with CHB were enrolled with 8 participants in 100 mg (on NUCs), 200 mg (on NUCs), 400 mg (on NUCs) cohorts and 7 in 200 mg (NUCs naive) cohort. Four participants in 200 mg (naive) started NUCs on Day 1. Up to the cutoff date, all participants had completed the D225 visit (24 weeks after the 3rd dose). All participants tolerated well with a good safety profile. No participants discontinued the study, and no serious adverse events or deaths have been reported. The follow-up visits are still ongoing. Baseline characteristics including the HBsAg levels were generally well balanced across NUCs experienced cohorts (HBsAg: 3.2 ± 0.5, 3.0 ± 0.4, and 3.1 ± 0.4 $\log_{10}$ IU/ mL for 100 mg, 200 mg, and 400 mg, respectively) and 200 mg NUCs naïve cohort (HBsAg 3.3 ± 1.2 $\log_{10}$ IU/ mL). The maximal reduction from baseline were -2.4, -3.0 and -3.2 $\log_{10}$ IU/mL for NUCs experienced cohorts (100 mg, 200 mg, and 400 mg, respectively) and -2.9 $\log_{10}$ IU/ mL 200 mg NUCs naïve cohort. Overall, 16.1% (5/31) for all participants received BW-20507 achieved HBsAg loss at the nadir. In participants who received 200 mg or 400 mg BW-20507, the HBsAg loss rate was 100% (2/2), 67% (4/6) and 56% (5/9) in participants with baseline HBsAg < 100 IU/ mL, < 500 IU/mL, < 1000 IU/mL, respectively. The 3 NUCs naive participants who never take NUCs also demonstrated HBV DNA reduction which was consistent with the reduction in HBsAg. Two participants with low HBV DNA at baseline (30 IU/mL and 388 IU/mL) achieved HBV DNA below lower limit of quantification. The maximal reduction of HBV DNA was -2.5 $\log_{10}$ IU/mL in a participant with high HBV DNA (5.4 $\log_{10}$ IU/mL) at baseline.

Conclusion: Three subcutaneous doses of BW-20507 were well tolerated and demonstrated a favourable safety profile in patients with CHB. Significant dose-dependent HBsAg reductions have been observed. BW-20507 also has high potency in decreasing HBV DNA.

LBP-009

Globally derived and externally validated cut offs for liver failure and inclusion of infections improve prognostication for inpatient death: towards ACLF harmonization

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Background and aims: Liver failure (LF) in patients with ACLF is defined variably or not included as a requisite for ACLF. Since the major outcome is inpatient death, criteria to define LF are required for harmonization of criteria globally. Aim: To assess the relative contribution of individual laboratory values or complication towards inpatient mortality prediction using a global cohort with external validation.

Method: 2 cohorts, derivation (CLEARED consortium) & validation (multi-center Mayo) were used. *Derivation cohort*: CLEARED includes >7000 cirrhosis patients admitted non-electively globally. Patients were followed till death/discharge. Admission labs [INR, bilirubin (bili), creatinine (SCr)], & complications (infection, HE)] were used to create a decision rule to classify inpatient death. We used cut-offs to

maximize negative predictive value (NPV) & assessed labs/complications individually or in combination. We then swapped labs for admission MELD3.0 /original MELD. Then, we fit decision tree models (XGBoost) using the cut-offs & sorted each predictor's relative contribution based on increase in information gain & defined AUCs. *External Validation*: Similar analyses were performed on data from 3 Mayo centers on cirrhosis inpatients being considered for listing with similar eligibility as CLEARED.
Results: *Derivation cohort: CLEARED*: 7239 pts from 115 ctrs across 6 continents of whom 808 (11.2%) died in-hospital were included. Individual labs: With bili, a 7.5 mg/dL cutoff maximized NPV (93%). For SCr & INR alone, cutoffs of 1.5 were optimal. Combined 3 labs cutoffs NPV was 91%. MELD: MELD 27 yielded NPV 92.1% while MELD 3.0 28 had NPV 94.0%. Decision Tree Analysis: Individual Labs: INR had the highest contribution (71.1%), then bili (16.7%), & SCr(12.2%), with AUC of 0.698. With complications, the relative contribution became: HE (42.2%), infection (22.2%), INR (18.6%), bili (12.7%), & SCr(4.3%) w/ AUC of 0.765. Using MELD instead of individual labs: AUC with individual cut-offs + HE/Infection (0.765) was superior to models with labs swapped for MELD 3.0/original MELD + HE/Infection (AUC: 0.748/0.726). *External Validation: Mayo*: 1,682 inpatients with a 12.2% mortality rate were included. NPV: for 3-labs NPV was 89.4% similar to MELD 91.1% & MELD 3.0, 92.4%. Decision tree analysis, individual labs + HE/Infection model (AUC: 0.808) again outperformed the MELD 3.0/MELD + HE/Infection models (AUCs: 0.797/0.796).
Conclusion: Using a large inpatient global cirrhosis cohort with external validation, admission lab cut-offs with highest NPV for inpatient death were individually admission bilirubin>7.5 mg/dl, creatinine>1.5 mg/dl and INR>1.5, while for MELD was ≥27 and MELD3.0 was ≥28; these values may be used to define liver failure in patients with ACLF. Decision tree analysis showed that admission HE and infections significantly added to mortality risk contribution.

LBP-010-YI
Short-term intravenous albumin administration increases serum sodium levels in hospitalized patients with decompensated cirrhosis and dilutional hyponatremia. A randomized, multicenter, controlled trial (ALBUCAT)
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Background and aims: Dilutional (hypervolemic) hyponatremia is common in decompensated cirrhosis and associated with high short-term mortality. Currently, there is no effective treatment available, and therapy is based on fluid restriction and diuretic withdrawal. Findings from small cohorts and retrospective studies suggest that intravenous (iv) albumin administration may be effective in improving serum sodium concentration, but definitive data from specific randomized controlled trials is lacking. We therefore aimed at investigate the effects of iv albumin therapy in hospitalized patients with decompensated cirrhosis and dilutional hyponatremia.
Method: We performed a multicenter, open-label, randomized, controlled trial, in patients with serum sodium ≤133 mEq/L. Patients were randomized 1:1 to receive either iv albumin for a maximum of 10 days (1 g/kg the first day, followed by 40 g/day) or placebo. The primary outcome was resolution of hyponatremia (increase of serum sodium ≥5 mEq/L with a final value > 130 mEq/L), while secondary outcome was overall survival. Here we report results with modified full analysis set (mFAS) for the primary outcome: resolution of hyponatremia.
Results: During a 5-year period (2019 to 2024), 52 patients were randomly assigned to receive either iv albumin (n = 25) plus standard of care (fluid restriction and diuretic withdrawal) or standard of care alone (n = 27). Median age was 61 years, and most patients were male (69%) and had alcohol-related cirrhosis (73%). Median MELD at inclusion was 17 (14 - 21) and median serum sodium was 128 mEq/L (123 - 131), with 17 patients (33%) having severe hyponatremia (<125 mEq/L). Both groups had similar baseline characteristics. Resolution of hyponatremia was achieved in 12 patients (48%) from the albumin group compared to only 4 patients (15%) from the control group [RR 3.39 (95%CI 1.27 - 9.05), p-value = 0.0145]. During treatment period, median serum sodium increased to 133 mEq/L (131 - 135) in the albumin group vs 129 mEq/L (128 - 131) in the control group
Conclusion: In patients with cirrhosis and dilutional hyponatremia administration of iv albumin is associated with increased serum sodium and resolution of hyponatremia. Intravenous albumin appears to be beneficial in the treatment of dilutional hyponatremia in cirrhosis.

LBP-011
Modeling the epidemic of metabolic dysfunction associated steatohepatitis in Europe shows a growing clinical and economic burden in France, Italy and United Kingdom
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Background and aims: Metabolic Dysfunction Associated Steatohepatitis (MASH) is responsible for significant clinical, economic and humanistic burden and is increasing alongside type 2 diabetes (T2D) and obesity. We used a Markov model to project the comprehensive burden of MASH in France, Italy, and United Kingdom (UK) over the next 2 decades.
Method: Using a Markov Model, disease states for prevalent (2020) and incident cases of MASH (2021-2040) were projected over 20 years. We included 9 disease states [MASH without fibrosis (F0), fibrosis stage 1 (F1), stage 2 (F2), stage 3 (F3), compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), first-year post-liver transplantation (LT), and post-liver transplantation after 1 year and onwards (PLT)] and 3 competing mortality states (cardiac-specific, liver-specific, and other). Transition probabilities were extrapolated from the literature, and calibrated using national prevalence estimates for T2D and obesity, ensuring alignment with observed incidences of DCC, HCC, and LTs. Cost data were collected from country-specific sources. MASH-related direct medical costings, indirect costs related to work productivity (WP) losses, and health-related quality-of-life (HRQL) were updated annually based on disease progression. Future economic burden estimates were inflation-adjusted annually using country-specific rates as per the International Monetary Fund.
Results: From 2021 to 2040, MASH prevalence is expected to rise from 4.03% to 4.20% in France, 4.58% to 4.97% in Italy, and 4.74% to 4.87% in the UK. More importantly, the prevalence of advanced MASH per 100,000 is projected to increase in all 3 countries (2021-2040) with advanced fibrosis (F3-CC) rising by +30%, while more advanced liver disease (DCC, HCC, and LTs) are expected to increase by +60%, respectively. Finally, MASLD-related liver mortality (per 100,000) is projected to increase from 7.88 (2021) to 11.52 (2040) in France, 9.38 (2021) to 14.21 (2040) in Italy, and 10.57 (2021) to 14.65 (2040) in the UK. Direct annual medical costs are also expected to also increase (2021-2040), rising from $1.28 billion to $2.96 billion in France, $1.34 billion to $3.00 billion in Italy, and $2.47 billion to $6.19 billion in the UK. Additionally, there will be substantial increases in WP losses and impairment of HRQL related to MASH.
Conclusion: The clinical, economic and humanistic burden of MASH is projected to substantially increase in 3 major European countries. Developing country-specific policies to target the burden of this important non-communicable disease will be important.

LBP-012

Multicenter, open-Label, randomized non-inferiority study comparing 8-week vs 12-week Sofosbuvir/Ravidasvir treatment for non-cirrhotic chronic hepatitis C patients (EASE trial)

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Background and aims: Hepatitis C virus (HCV) remains a significant global health challenge, exacerbated by high treatment costs associated with direct-acting antivirals (DAAs). There is a pressing need for more affordable and efficient treatment options. This study compared the effectiveness of an 8-week versus a 12-week regimen of sofosbuvir/ravidasvir in non-cirrhotic patients with chronic HCV infection.
Method: A randomized, open-label, non-inferiority clinical trial was conducted across nine hospitals and 17 primary healthcare centers in Malaysia. Non-cirrhotic adults (18–69 years) with chronic HCV of all genotypes were randomly assigned (1:1) to receive either 8 or 12 weeks of sofosbuvir/ravidasvir using a permuted block randomization. The primary endpoint was the sustained virologic response 12 weeks post-treatment (SVR12), while secondary outcomes included SVR12 across demographic and clinical subgroups and the incidence of treatment-emergent adverse events (TEAEs). Non-inferiority was established with a 5% margin, and analysis was conducted using the intention-to-treat population. The trial is registered at ClinicalTrials.gov (NCT04885855).
Results: From March 1, 2021, to March 31, 2023, a total of 322 participants were randomized to either the 8-week (n = 161) or 12-week (n = 161) regimen. The majority of participants were aged 40–49 years (42.2% vs. 41.0%) and had genotype 3 infections (58.4% vs. 61.5%). The 8-week regimen achieved an SVR12 rate of 93.42% (142/152), while the 12-week regimen had an SVR12 rate of 93.46% (143/153), demonstrating non-inferiority (difference: -0.04%; 90% CI: -4.94%, 4.85%; p = 0.047). SVR12 rates were consistent across baseline HCV RNA levels, genotypes, and HIV co-infection status. Adverse events were similar between both treatment groups, with hypertension (6.2% vs. 5.6%), headache (2.5% in both groups), and arthralgia (0.6% vs. 3.1%) being the most common.
Conclusion: The 8-week sofosbuvir/ravidasvir treatment regimen demonstrated non-inferior efficacy compared to the 12-week regimen, indicating that it could be a shorter, more cost-effective option for treating non-cirrhotic individuals with chronic HCV infection.

LBP-013

Novel hepatitis B virus biomarkers-guided nucleos(t)ide analogues withdrawal strategy promotes hepatitis B surface antigen clearance in chronic hepatitis B patients: results from a randomized controlled trial (BIO-STOP study)

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Background and aims: Nucleos(t)ide analogues (NAs) discontinuation was reported to promote hepatitis B surface antigen (HBsAg) clearance among European patients with chronic hepatitis B virus (HBV) infection. However, whether Asian patients benefit from finite NAs treatment remained obscure. Recently, novel biomarkers involving HBV RNA and hepatitis B core-related antigen (HBcrAg) are reported to be superior predictors for off-treatment durability.

This study aimed to evaluate the efficacy and safety of a novel strategy of NAs cessation for Asian patients based on integrative biomarkers.
Method: A multicenter, randomized controlled trial (NCT04519359) was conducted at 9 centers in China from July 2020 to January 2025. Non-cirrhotic patients with long-term first-line NAs treatment who were HBV DNA undetectable, HBsAg < 200 IU/mL together with novel biomarkers (HBV RNA or HBcrAg) undetectable were randomized at a 2:1 ratio to stop or continue NAs therapy. The primary endpoint was the cumulative incidence of HBsAg loss until week 144. Secondary endpoints included levels of HBsAg decline from baseline as well as the cumulative rates of virological relapse (VR) and clinical relapse (CR) at the end of the study. NAs-stoppers with continuous CR (defined as HBV DNA rebound > 2,000 IU/mL and ALT elevations > 2 × upper limit of normal) after NAs cessation were reintroduced to NAs therapy. Safety assessments including nonserious and serious adverse events as well as subgroup analyses were also performed.
Results: Totally, 90 patients were included in the final modified intention-to-treat analysis (60 in NAs-Stop group and 30 in NAs-Continue group). Patients enrolled had a mean age of 45.9 ± 10.2 years, with a median NAs treatment duration of 9.4 (6.0, 13.0) years. Baseline characteristics between two groups were balanced, with both 50% hepatitis B e antigen (HBeAg) negative prior to treatment, median HBsAg level of 1.69 $\log_{10}$ IU/mL in NAs-Stop group and 1.76 $\log_{10}$ IU/mL in NAs-Continue group, respectively. Compared with patients in NAs-Continue group, NAs-stoppers showed an increased 144-week cumulative incidence of HBsAg clearance (25.9% vs. 4.2%, p = 0.013) and more profound HBsAg decline during follow-up (0.90 vs. 0.46 $\log_{10}$ IU/mL, p = 0.056). Cumulatively, 38.6% and 20.2% patients experienced VR and CR after stopping NAs. Sixteen patients were retreated and no serious adverse events occurred. Initially HBeAg-negative patients with baseline HBsAg < 100 IU/mL was considered the favourable candidates for NAs withdrawal with the HBsAg loss rate reaching 40.0%.
Conclusion: Non-cirrhotic CHB patients with long-term viral suppression could benefit from integrative HBV biomarkers-guided NAs discontinuation strategy, especially for those with prior HBeAg-negative and lower baseline HBsAg levels, which potentially provides a new paradigm of finite NAs treatment for Asian patients in the future.

LBP-014

HBsAg loss and seroconversion after 16-week or 24-week AHB-137 treatment in HBeAg-negative chronic hepatitis B participants on NA therapy: results from an ongoing multicenter, randomized phase IIb study

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Background and aims: AHB-137, an unconjugated antisense oligonucleotide (ASO), has shown a favourable safety profile and a high HBsAg loss rate with seroconversion following 24-week of AHB-137 treatment in HBeAg-negative chronic hepatitis B (CHB) participants in an ongoing Phase IIa study. An ongoing Phase IIb study is being conducted to assess the efficacy and safety of 16-week versus 24-week AHB-137 regimens.
Method: HBeAg-negative CHB participants, with baseline HBsAg > 100 to 3,000 IU/mL (inclusive) and under nucleos(t)ide analogue (NA) treatment, were enrolled in a multicenter, randomized, Phase IIb study (NCT06550128). Participants were randomized to receive weekly subcutaneous doses of either 24 weeks of 300 mg AHB-137 or 8 weeks of placebo followed by 16 weeks of 300 mg AHB-137. After AHB-137 treatment, a 24-week on-NA follow-up and an additional 24-week follow-up were scheduled. The primary endpoint is the proportion of participants achieving HBsAg loss (HBsAg < 0.05 IU/mL) and HBV DNA < lower limit of quantification (10 IU/mL), at the end of AHB-137 treatment (EOT).
Results: To date, a total of 64 participants have been enrolled, with 31/32 completing the 16-week AHB-137 treatment and 32/32 completing the 24-week treatment without AE-related dropouts. At the EOT, 66% (21/32) and 75% (24/32) of the participants achieved the primary endpoint in the 16-week arm and the 24-week arm, respectively. Rapid HBsAg loss (≤12 weeks) was observed in the majority of participants who achieved primary endpoint, with 81% (17/21) in the 16-week arm and 83% (20/24) in the 24-week arm. Notably, 45% (9/20) of participants with baseline HBsAg levels >1,000 IU/mL attained this rapid HBsAg Loss. At the EOT, seroconversion (anti-HBs ≥10 mIU/mL) was achieved by 33% (7/21) and 54% (13/24) of participants who achieved primary endpoint in the two arms, respectively. Safety profiles were comparable between the two arms, with no treatment-related serious adverse events, drug discontinuations, or deaths. Consistent with observations in the Phase IIa study, most TRAEs were Grade 1-2. Grade 3 TRAEs included injection site erythema and laboratory abnormalities. A case of Grade 4 ALT flare occurred concurrently with rapid HBsAg decline and HBsAg loss and resolved spontaneously with no direct bilirubin elevation or prolonged prothrombin time. In general, ALT flares were highly associated with HBsAg loss. Platelet count decreased was reported in 4 participants (6.3%), and all were Grade 1.
Conclusion: In this ongoing Phase IIb trial, high rates of HBsAg loss and seroconversion have been achieved following either 16 or 24 weeks of treatment with 300 mg AHB-137. Both regimens demonstrated favourable safety and tolerability profiles. These efficacy and safety results are consistent with the observations from the previous Phase IIa study, further supporting AHB-137 development for HBV functional cure.

LBP-015

Comparison of endoscopic ultrasound portosystemic gradient with HVPG and direct porto-systemic pressure gradient measurements

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Background and aims: Endoscopic ultrasound (EUS) has emerged as a valuable tool for assessing portal hypertension (PH). No prior comparative assessment of direct portal pressure gradient (PPG) as measured by EUS versus the transjugular route exists. Our study aimed to compare the values of EUS-PPG and HVPG with direct PPG measurements during transjugular intrahepatic portosystemic shunt procedures (TIPS).
Method: All consecutive patients scheduled for elective TIPS were included. Exclusion criteria were platelet <50,000/µL and an INR > 2.5. EUS was performed using a 22-gauge FNA needle attached to an invasive pressure measurement module for HVPG measuring. Three measures were taken, and the mean was noted. TIPS placement and HVPG was performed according to the standard method. All EUS, HVPG, and direct PPG measurements were performed under general anesthesia during the same session and under similar conditions.
Results: We prospectively enrolled 25 patients between January 2023 and October 2024, with an average age of 50 ± 14 years (72,7% male). The underlying causes of PH were porto-sinusoidal vascular disease (n = 2, 8%), alcohol-related cirrhosis (n = 17, 68%), viral-related cirrhosis (n = 3, 12%), MASLD cirrhosis (n = 1, 4%), and Budd-Chiari (n = 1, 4%), autoimmune cirrhosis (n = 1, 4%). Indication for TIPS consisted of variceal hemorrhage in n = 9 (36%) of cases, refractory ascites in n = 14(56%), refractory hydrotorax in n = 1 (4%) and Budd-Chiari syndrome in n = 1(4%). EUS-PPG was technically successful in 23 patients (92%), with two failures attributed to either obesity or significant ascites, which impeded profound needle advancement into the portal vein (PV). HVPG was successful in 24 of 25 patients (96%), while direct PPG measurements were available for all patients. The mean EUS-PPG was 14.8 ± 3.8 mmHg. The mean T-PPG was 16,8 ± 4. There was a strong correlation between EUS-PPG and T-PPG (r = 0.86, p < 0.01 and ICC = 0.894 (95% CI: 0.744 - 0.956). The mean HVPG was 16,1 ± 4,3mmHg and showed a moderate correlation with EUS-PPG (r, 0.55, p < 0.05, ICC = 0,66; 95%CI: 0.200-0.867). In 2 patients, major discrepancies were seen (>5 mmHg). However, clinically significant portal hypertension (PPG > 10mmHg) was correctly assessed in 100% of cases using both methods. HVPG and T-PPG showed good correlation (r = 0,667, ICC = 0,734 (95%CI: 0,455-0,908).
Conclusion: EUS-PPG measurement using a 22G needle has proven to be an accurate and safe technique, reliably diagnosing CSPH.

LBP-016

Efficacy and safety of elebsiran and pegylated interferon alfa combination therapy versus pegylated interferon alfa in participants with chronic hepatitis B virus infection: follow-up results from the ongoing phase 2, randomized, open-label ENSURE study

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Background and aims: Sustained hepatitis B surface antigen (HBsAg) loss post the end of treatment (EOT) is critical for functional cure in patients with chronic hepatitis B virus (HBV) infection. The ENSURE study (NCT05970289) is an ongoing phase 2, randomized, pegylated interferon alfa (PEG-IFN alfa) controlled study to delineate the contribution of an HBV targeting small interfering ribonucleic acid (siRNA) elebsiran (aka BRII-835) and PEG-IFN alfa, respectively, to HBsAg loss and curative outcomes. Week(W) 48 data have demonstrated that compared with PEG-IFN alfa alone, the addition of elebsiran resulted in much greater HBsAg loss at EOT with most of these participants also achieving HBsAg seroconversion. Here, post EOT follow-up results are summarized.
Method: Virologically suppressed non-cirrhotic participants with chronic HBV infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy, with screening HBsAg > 100 and ≤ 3,000 IU/mL, were randomized at a ratio of 1:1:1 to one of three cohorts: PEG-IFN alfa alone, elebsiran 200 mg + PEG-IFN alfa, or elebsiran 100 mg + PEG-IFN alfa. Elebsiran and PEG-IFN alfa were administered subcutaneously every 4 weeks and weekly for 48 weeks, respectively. NRTI was given daily until NRTI stopping criteria were met at W72.
Results: A total of 55 participants were enrolled. All participants completed W64 (16 weeks post EOT) follow-up visit. The baseline characteristics were generally well balanced across the cohorts. Up to W64, the incidence of adverse events (AEs) was comparable across cohorts and most AEs were consistent with the known side effects of PEG-IFN alfa. No new ≥ Grade 3 AEs or serious AEs were reported during post EOT follow-up. 11/12 participants who achieved HBsAg loss at EOT were sustained at W64. In total, HBsAg loss was observed in 4/19 (21.1%) and 7/18 (38.9%) participants from the elebsiran 200 mg or 100 mg plus PEG-IFN alfa cohorts respectively at W64, compared with 1/18 (5.6%) in the PEG-IFN alfa alone cohort. Of note, one participant from elebsiran 100 mg plus PEG-IFN alfa cohort achieved HBsAg loss post EOT at W56.
Conclusion: Elebsiran and PEG-IFN alfa combination therapy was generally well tolerated. Compared with PEG-IFN alfa alone, the addition of elebsiran resulted in greater HBsAg loss through 16 weeks post EOT, supporting the additive benefit of siRNA. The results at 24 weeks post EOT follow-up will be presented at the conference.

LBP-017

SCG101 HBV-specific TCR-T cell therapy demonstrates dual antiviral and antitumor activities, achieving HBV clearance in liver biopsies and functional cure in HBV-related hepatocellular carcinoma patients

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Background and aims: SCG101, a first-in-class autologous HBV-specific TCR-T cell therapy utilizing a natural, high-affinity TCR, has completed enrollment in its IND phase I trial (NCT06617000)

evaluating its safety and efficacy as a monotherapy in patients with HBV-related HCC. Here, we present the key findings of the study.
Method: The trial enrolled 18 HLA-A*02:01(+), serum HBsAg(+) patients with advanced HBV-related HCC (BCLC B/C) who had received 2-5 prior systemic therapies. Seventeen patients completed SCG101 infusion at 5×10^7 or 1×10^8 cells/kg intravenously 3 days after lymphodepletion (Cyclophosphamide 500 mg/m²/day, and Fludarabine 25 mg/m²/day). Safety, pharmacokinetics, pharmacodynamics, and efficacy of SCG101 were evaluated.
Results: Following infusion, SCG101 exhibited dose-dependent proliferation measured by vector copy number. Serum HBsAg declined in all 17 treated patients, with 16 (94.1%) achieving a 1.0-4.6 $\log_{10}$ reduction within 28 days, persisting < 100 IU/mL for up to 1 year. Notably, 4 patients (23.5%) achieved HBsAg loss. Two patients underwent liver biopsies pre- and post- infusion. Immunohistochemistry showed complete HBsAg clearance in hepatocytes and/or HCC cells at 69 and 486 days. In one patient, paired in situ hybridization confirmed HBV-DNA elimination, while the other (tested only at day 486) also showed full clearance of HBV-DNA. In addition to its antiviral activity, SCG101 also demonstrated antitumor potential. By data cutoff, 16 patients eligible for efficacy analysis had a median follow-up of 10.6 months; median overall survival was not yet reached. One patient achieved a partial response (PR) lasting 7 months and remains under follow-up. Six patients had decrease in sum of diameters of target lesions ranging from -3.6% to -58%, with 2/6 achieving ≥30% reduction. Sixteen patients exhibited transient ALT elevation concurrent with HBsAg reduction, beginning within 1-2 days post-infusion. Grade ≥3 ALT elevation (per CTCAE v5.0) occurred in 88.2% of patients but resolved to baseline/Grade ≤1 within 14 days, indicating SCG101's cytolytic mechanism in eliminating hepatocytes and HCC cells harboring integrated HBV-DNA. Other common treatment-related adverse events (TRAEs) included CRS (100%), elevated AST (82.4%), neutropenia (82.4%) and thrombocytopenia (76.5%), mostly resolving to Grade 1/baseline levels within 1-13 days.
Conclusion: SCG101 achieved HBV clearance serologically and histologically. The rapid, sustained HBsAg reduction and virological clearance of HBV markers in biopsies support SCG101's cytolytic mechanism of HBsAg-targeted immune activation and subsequent elimination of infected hepatocytes and HCC cells. These findings underscore SCG101's potential to achieve a mechanism-driven functional cure for chronic HBV infection and long-term tumor control via its unique dual activities.

LBP-018

Chronic hepatitis B virus infected participants responding to prior BRII-179 treatment achieved faster and higher rate of hepatitis B virus surface antigen seroclearance on elebsiran plus peginterferon-alfa: end of treatment data from ENSURE study

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Background and aims: In a previous phase 2 study (NCT04749368), BRII-179, a recombinant protein based immunotherapeutic, induced robust hepatitis B virus specific immune responses in a notable proportion of, but not all, participants. We hypothesized that those with BRII-179 induced anti-HBs antibody responses have a less impaired intrinsic immune profile and may be more responsive to curative therapies.
Method: Eligible participants from a previous study who completed BRII-179 and elebsiran (an HBV-targeted siRNA) for at least 1 year were enrolled into this open label phase 2 ENSURE study (NCT05970289). In this study, participants received elebsiran 100 mg and peginterferon alfa-2a (PEG-IFN alfa) over a 48-week treatment period. End of treatment (EOT) data analyzed by anti-HBs response to prior BRII-179 treatment are reported.
Results: A total of 28 participants with baseline HBsAg ≥ 100 IU/mL were analyzed. 18 and 10 participants had peak anti-HBs antibody titer ≥ 10 IU/L (defined as anti-HBs responders) and < 10 IU/L (defined as non-responders) induced by BRII-179 in the previous study. Median (range) HBsAg at the time of initiating elebsiran + PEG-IFN alfa was numerically higher in anti-HBs responders (539.4 [106.7-2165.0] IU/mL) than in non-responders (219.3 [106.7-671.5] IU/mL). At EOT (Week 48), 11/18 (61%) of anti-HBs responders achieved HBsAg seroclearance, compared to 1/10 (10%) of non-responders. Among the anti-HBs responders who lost HBsAg, 10/11 (91%) had anti-HBs antibody titers > 100 IU/L at EOT, and notably 9/11 (82%) achieved seroclearance before Week 24. Elebisiran + PEG-IFN alfa was generally safe and tolerated. The majority of AEs were consistent with the known side effects of PEG-IFN alfa.
Conclusion: After receiving elebsiran plus PEG-IFN alfa treatment, a substantially higher rate of HBsAg seroclearance was achieved in participants who had BRII-179 induced anti-HBs response (responders) than in those who did not (non-responders). These responders also achieved faster HBsAg seroclearance compared to those without prior BRII-179 treatment, most of whom achieved HBsAg seroclearance after 24 weeks of elebsiran + PEG-IFN alfa (Jia, 2024; Yuen, 2022). These data suggest that BRII-179 induced immune responses may identify patients who are more responsive to curative treatments. Furthermore, rapid HBsAg seroclearance with higher anti-HBs titers may translate into durable functional cure or potentially shorter treatment duration. Post treatment follow-up is ongoing.
Reference: Jia J, et. al. Efficacy and safety of elebsiran and PEG-IFN alfa combination therapy vs PEG-IFNα in participants with chronic HBV infection: preliminary EOT results from ENSURE study. AASLD 2024. Yuen MF, et. al. Preliminary 48-week safety and efficacy data of VIR-2218 alone or in combination with pegylated interferon alfa in participants with chronic HBV infection. AASLD 2022.

LBP-019

Semaglutide-treated participants in the phase 3 ESSENCE trial (part 1) have greater concordance of non-invasive test improvements compared with placebo

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Background and aims: In this secondary analysis of part 1 of the ESSENCE trial (NCT04822181), we evaluated treatment response at week 72 through assessment of histology and non-invasive tests (NITs) in participants with biopsy-defined metabolic dysfunction-associated steatohepatitis and fibrosis stage 2 or 3.
Method: Of the first 800 randomised participants, those with available measurements for considered NITs and histology results at week 72 (N = 394) were assessed for on-treatment response related to disease activity, defined by having histological resolution of steatohepatitis and no worsening of liver fibrosis, a decrease in alanine transaminase (ALT) levels (≥ 25% from baseline) or improvement in FibroScan-AST (FAST) score (≥ 0.22 points from baseline). For NITs and histology related to fibrosis (N = 494), response was assessed by histological improvement in liver fibrosis and no worsening of steatohepatitis, decrease in liver stiffness measurement by vibration-controlled transient elastography (LSM-VCTE) ≥ 30% from baseline or enhanced liver fibrosis (ELF) score decrease (≥ 0.5 units from baseline).
Results: Considering measures of disease activity in the semaglutide (n = 269) and placebo (n = 125) arms, 90.3% vs 59.2% met at least one treatment response criteria, respectively. In the semaglutide arm, 45.7% of participants met all response criteria (ALT, FAST and histology) vs 10.4% in the placebo arm. ALT criteria were met by 75.8% of participants in the semaglutide arm vs 37.6% in the placebo arm. Response criteria for any two measures were met and overlapped in 75.1% of participants in the semaglutide arm vs 30.4% in the placebo arm; ALT and FAST responders overlapped in 62.5% in the semaglutide arm vs 20.0% in the placebo arm. In the semaglutide arm (n = 332), 84.3% met at least one of the treatment response criteria related to fibrosis, compared with 54.9% in the placebo arm (n = 162). Overall, 16.0% of participants in the semaglutide group met all response criteria (ELF, LSM-VCTE and histology) vs 5.6% for placebo. LSM-VCTE criteria were met by 53.6% of participants in the semaglutide arm vs 30.9% in the placebo arm. Response criteria for any two measures were met and overlapped in 53.9% of participants in the semaglutide arm vs 19.2% in the placebo arm; ELF and VCTE-LSM responders overlapped in 37.7% in the semaglutide arm vs 10.5% in the placebo arm.
Conclusion: A higher proportion of participants who received semaglutide met the NIT and histology-based definitions of treatment response compared with placebo. This suggests that more participants may be experiencing improvements in NITs beyond those captured by histology alone. However, the study remains ongoing for clinical outcomes to validate long-term clinical benefit.

LBP-020

Off-treatment antiviral efficacy and safety of repeat dosing of imdusiran followed by VTP-300 with or without nivolumab in virally-suppressed, non-cirrhotic subjects with chronic hepatitis B (CHB)

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Background and aims: Reaching functional cure (defined as sustained HBV DNA ≤ LLOQ and HBsAg loss 24 weeks after HBV treatment cessation) of CHB requires suppression of viral replication, reduction of HBsAg and stimulation of host HBV-specific immunity. Imdusiran (IDR) is a GalNAc-conjugated single trigger siRNA therapeutic and VTP-300 is an HBV-specific immunotherapeutic consisting of a chimpanzee adenoviral vector (ChAdOx1-HBV) dose followed by a Modified Vaccinia Ankara (MVA-HBV) dose delivering HBV antigens. IM-PROVE II is an ongoing Phase 2a study assessing the safety, pharmacodynamics and immunogenicity of repeat doses of IDR followed by VTP-300 (Group A), placebo (Group B) or VTP-300±low dose nivolumab (LDN; Group C) in nucleos(t)ide analogue (NA) suppressed CHB subjects. End of treatment results (Week[W] 48) from Groups A, B & C have been reported previously. End of study results for A & B and preliminary results up to W72 for C is reported here.
Method: CHB subjects in Groups A (n = 20), B (n = 20) and C (n = 22) with HBsAg ≥100 but <5000 IU/mL received IDR 60 mg every 8 weeks × 4 doses. At W26 and W30, subjects received VTP-300 (A & C) or placebo (B). Subjects in C also received LDN (0.3 mg/kg) at W30 if they did not have risk factors for immune related thyroiditis. Subjects could receive a 2nd MVA-HBV dose (± LDN in C) at W38 if protocol criteria were met. Eligible subjects discontinued (d/c) NA at W50. Safety, HBV parameters and immunology samples were assessed at multiple timepoints. HBsAg was assessed via Diasorin Liaison XL assay (LLOQ = 0.05 IU/mL) and results ≤ LLOQ were subsequently analyzed by Abbott HBsAg Next Qualitative assay (cutoff = 0.005 IU/mL).
Results: All Group A & B subjects have completed the study (In B, 1 subject was lost to follow-up at W48 and 1 withdrew consent after NA restarted). NA therapy was d/c in 16/20 (80%) subjects in A and 10/19 (53%) subjects in B. 3/16 (13%) and 4/10 (40%) subjects in A & B respectively restarted NA due to elevated HBV DNA. None achieved functional cure. Of the 22 subjects in Group C, 13 received IDR + VTP-300 + LDN (C + LDN) and 9 received IDR + VTP-300 alone (C-LDN). NA was d/c in 9/13 (69%) subjects in the C + LDN group and 6/9 (67%) subjects in the C-LDN group, with 1 subject in each group restarting NA due to elevated HBV DNA. Two of 13 (15.3%) subjects in C + LDN

have HBsAg levels ≤ LLOQ 22W post-NA d/c and are approaching functional cure, and both subjects have detectable anti-HBsAb levels (31.6 & 5.6 mIU/mL). A third subject in C + LDN had HBsAg ≤ LLOQ at W48 and was just above LLOQ (0.051 IU/mL) at 22W post-NA d/c. There have been no Serious Adverse Events (SAEs), Grade 3 or 4 AEs, serious ALT flares or treatment discontinuations.
Conclusion: Preliminary off NA treatment follow-up data suggest that repeat dosing of IDR followed by VTP-300 + LDN was well-tolerated and led to HBsAg loss in 3 out of 13 subjects, with 2 approaching functional cure. Additional follow-up data will be presented.

LBP-021
Prolonged reduction of hepatitis B surface antigen in virologically suppressed participants treated with concurrent or sequential use of pegylated interferon alpha with xalnesiran-based therapy: results after 120 weeks of follow-up of an observational study
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Background and aims: Treatment with xalnesiran (a small interfering ribonucleic acid) plus an immunomodulator led to substantial percentages of hepatitis B surface antigen (HBsAg) loss in participants (pts) with chronic hepatitis B. However, challenges in the sustainability of HBsAg loss were identified. This observational study aims to describe the real-world treatment patterns and associated long-term outcomes after the end of xalnesiran-based therapy (EOT) period in the Piranga study (N Engl J Med. 2024, NCT04225715). This abstract reports results at 120 weeks (wks) of follow-up (FU).
Method: This study (NCT05977283) enrolled pts recruited at the Nanfang Hospital in the Piranga study and who had an HBsAg reduction ≥0.5 log10 IU/mL at EOT. Pts were prospectively followed up for 144 weeks after EOT. Three treatment patterns can be described. Arm 1 comprised pts treated with a xalnesiran-based therapy + nucleos(t)ide analogue (NUC) without pegylated interferon alpha (IFN) in the Piranga study for an average of 42 wks who were subsequently treated with NUC in this study. Arm 2 comprised pts treated with xalnesiran, NUC, and IFN concurrently in the Piranga study for 48 wks who were subsequently treated with NUC. Arm 3 comprised pts treated with a xalnesiran-based therapy and NUC without IFN for an average of 26 wks who were subsequently treated with IFN + NUC for 24 to 48 wks in this study and then with NUC. The primary endpoint was the rate of HBsAg loss (<0.05 IU/mL) at 48 wks of FU.
Results: Overall, 47 pts treated with xalnesiran-based therapy for 12 to 48 wks in the Piranga study were enrolled. Before treatment with xalnesiran, pts had: mean age, 36.7 years; mean HBsAg, 2.9 $\log_{10}$ IU/mL; HBsAg <100 IU/mL in 10.6%; HBeAg + in 42.6%; previously on NUC in all. The percentage (n) of pts achieving HBsAg loss in Arms 1 (n = 28), 2 (n = 9), and 3 (n = 10) were 10.7% (3), 55.6% (5), and 0% (0) at EOT, 14.3% (4), 22.2% (2), and 30% (3) at FU wk48, and 0% (0), 22.2% (2), and 10% (1) at FU wk120, respectively. However, among those with HBsAg loss, one pts remained HBeAg positive in Arm 2. The percentage (n) of pts achieving HBsAg <100 IU/mL in Arms 1 to 3 were 89.3% (25), 66.7% (6), and 80% (8) at EOT, and 32.1% (9), 55.6% (5), and 60% (6) at FU wk120, respectively. The mean HBsAg levels at FU wk120 remained statistically lower than those before xalnesiran-based therapy. However, compared to EOT, they had increased by 1.0, 1.4, and 0.3 $\log_{10}$ IU/mL, in Arms 1 to 3, respectively. Among all pts, 51.3% and 0% of those with HBsAg <100 IU/mL and >100 IU/mL at EOT had HBsAg <100 IU/mL at FU wk120, while 73.9% and 12% of those with HBsAg <1000 IU/mL and >1000 IU/mL before xalnesiran-based therapy had HBsAg <100 IU/mL at FU wk120, respectively.
Conclusion: Concurrent or sequential use of IFN in combination with a finite treatment of xalnesiran resulted in a prolonged reduction of HBsAg 120 wks after EOT. The sustainability of HBsAg loss after EOT still needs to be improved.

LBP-022
Treatment options to support the elimination of hepatitis C: an open label, factorial randomised controlled trial
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Background and aims: WHO recommends treating Hepatitis C infection with one of three antiviral combinations for 8 to 12 weeks, two of which (sofosbuvir/velpatasvir and sofosbuvir/daclatasvir) are widely used in low-income settings. No randomised trials have compared these treatments, data is limited in rare viral genotypes, and high cure rates may be achievable with shorter durations of therapy.
Method: We conducted a multi-arm, randomised controlled trial in Vietnamese adults with chronic hepatitis C infection, with mild-moderate liver fibrosis. Recruitment was stratified by viral genotype (1-5 versus 6) with 1:1 random allocation to sofosbuvir 400 mg/daclatasvir 60 mg (SOF/DCV) or sofosbuvir 400 mg/velpatasvir 100 mg (SOF/VEL). Participants were simultaneously factorially randomised to one of four treatment strategies: (i) 12 weeks standard-of-care (SOC) (ii) four weeks' therapy with additional weekly PEGylated interferon (4w-DAA/IFN) (ii) induction/maintenance therapy with two weeks' standard therapy followed by 10 weeks' therapy 5 days/week (weekends off) and (iv) response-guided therapy for either 4,8 or 12 weeks determined by quantitative viral load on day 7. Primary outcome was sustained virological response 12 weeks after treatment completion (SVR12).
Results: 624 participants were randomised: 296 (47.4%) genotype 6, 328 (52.6%) genotypes 1-5). Primary outcome was assessable for 609/624 (97.6%). SVR12 was 294/302 (97.4%) for SOF/DCV and 292/307 (95.1%) for SOF/VEL (difference +2.2% (90%CrI -0.2%,+4.8%) vs 5% non-inferiority margin). There was a 93% probability that SOF/DCV had higher efficacy than SOF/VEL. For the strategies tested SVR12 was (i) 148/150 (98.7%) in SOC (ii) 143/152 (94.1%) with 4w-DAA/IFN (-5.7% (-9.6%,-2.3%) (iii) 151/152 (99.3%) with induction/maintenance (+0.6% (-1.1%,+2.7%)), and (iv) 144/155 (92.9%) with response-guided therapy (-4.5% (-8.3%,-1.3%)). Serious adverse events were rare (2.7%). 21/23(91.3%) not achieving first-line SVR achieved SVR12 following retreatment.

Conclusion: SOF/DCV is non-inferior to SOF/VEL and is likely to have higher efficacy in this study. High efficacy was seen with three novel strategies that could improve treatment access for harder-to-reach populations. (Funding Wellcome Trust, ISRCTN 61522291).

LBP-023-YI

Validation of quantitative magnetic resonance cholangiopancreatography metrics in the prediction of event-free survival in primary sclerosing cholangitis: an International PSC study group collaboration

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Background and aims: Quantitative magnetic resonance cholangiopancreatography (MRCP) metrics have shown promising results in predicting event-free survival in primary sclerosing cholangitis (PSC). However, larger multi-center cohorts with longer follow-up are necessary to provide further validation and establish its prognostic role. We conducted the first multi-center study across members of the International PSC Study Group to assess the prognostic value of quantitative MRCP metrics in PSC.

Method: Data were collected retro- and prospectively from five tertiary and transplantation centers in England, Italy and the Netherlands. Postprocessed quantified MRCP data (MRCP+, Perspectum Ltd.) was combined with clinical data including PSC type, time- and age-related variables and the Amsterdam Oxford Model (AOM) risk score as covariates. The primary outcome was event-free survival, a composite endpoint of PSC-related mortality, (listing for) transplantation or hepatic decompensation. Cox proportional hazard regression models, using a 70:30 derivation to validation split, were used to assess the predictive performance of quantitative MRCP metrics and AOM, quantified as hazard ratios (HR) and C-statistic with confidence intervals (CI). A 5-fold cross validation (5-fold CV) was included in the derivation set.

Results: A total of 399 patients were included with a median follow-up of 5.9 (Q1-Q3: 4.3-8.5) years and 96 events, including 52 signs of hepatic decompensation, 42 liver transplantations and 4 deaths. The 270 available AOM risk scores indicated a low-risk population with a mean risk score of 1.6 ± 0.7. Multivariable analysis identified the total number of candidate strictures (HR 1.04, 95% CI: 1.02-1.06; $p < 0.001$) and time from diagnosis to MRCP + (HR 1.05, 95% CI: 1.02-1.08; $p = 0.003$) to be associated with event-free survival. Total number of candidate strictures alone showed a c-statistic of 0.66 (95% CI: 0.57-0.72) in the derivation set, 0.67 in 5-fold CV and 0.71 in the validation set. The AOM risk score was also associated with event-free survival (HR 3.49, 95% CI: 2.27-5.35; $p < 0.001$) and showed a reasonable c-statistic of 0.77 (95% CI: 0.63-0.8) in the validation set, while the combination of total number of candidate strictures and AOM risk score showed a strong c-statistic of 0.83 (95% CI: 0.76-0.89) in the derivation set and 0.82 in both 5-fold CV and the validation set, outperforming the AOM risk score alone.

Conclusion: This study confirms the prognostic value of total number of candidate strictures by MRCP + for the prediction of event-free survival in PSC, as well as its added value to the Amsterdam Oxford prognostic model. Further studies on clinical incorporation of quantitative MRCP metrics for risk monitoring and as surrogate endpoint in clinical trials are therefore warranted.

LBP-024

Metabolic dysfunction- and alcohol-associated steatotic liver disease is associated with higher risk of advanced fibrosis and mortality than metabolic dysfunction-associated steatotic liver disease: data from a large global biopsy-proven cohort

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Background and aims: Metabolic dysfunction- and alcohol-associated liver disease (MetALD) is increasingly being recognized as an important subtype of steatotic liver disease (SLD). We compared clinical profiles and outcomes of patients with MetALD with metabolic dysfunction-associated steatotic liver disease (MASLD) patients from a large global biopsy-proven SLD cohort.
Method: The Global NASH Council collaboration enrolled patients with biopsy-proven SLD from more than 40 countries. Patients' self-reported amount of weekly alcohol consumption was used to separate MASLD from MetALD (20-50 g/30-60 g per day for female/male).
Results: We included 8,808 participants with self-reported alcohol use data. The mean (SD) age was 49 (14) years, 50% were male, and

11% were current drinkers. Mean body mass index was 33 (8) kg/m2, 67% had obesity, 43% type 2 diabetes (T2D), 46% hypertension, and 55% hyperlipidemia. Furthermore, 44% had significant histologic fibrosis (≥F2), 26% advanced fibrosis (≥F3), and 9% histologic cirrhosis (F4). No patient had enough alcohol use to meet the definition of alcohol-associated liver disease (ALD) (>50/60 g female/male). A total of 170 patients (1.9%) met the criteria for MetALD. Those with MetALD were more commonly enrolled from European countries (75% vs. 32%), were older [mean age 57 (11) vs. 49 (14) years] and predominantly male (68% vs. 50%) with a higher rate of hypertension (64% vs. 46%) than MASLD (all $p < 0.01$). However, rates of obesity, T2D, and hyperlipidemia were similar ($p > 0.05$). MetALD patients also had higher rates of cardiovascular disease (16% vs. 5%), significant histologic fibrosis (57% vs. 44%), and histologic cirrhosis (16% vs. 8%) (all $p < 0.05$). Furthermore, MetALD patients had more fibrosis based on non-invasive tests: FIB-4 2.04 (1.36) vs. 1.43 (1.37), liver stiffness by vibration-controlled transient elastography (VCTE) 13.5 (10.9) vs. 10.9 (8.7) kPa, Agile-3 + score 0.645 (0.292) vs. 0.522 (0.315) (all $p < 0.01$). The performance of FIB-4 and VCTE for predicting advanced fibrosis was similar in Met-ALD and MASLD (AUC = 0.82 and 0.86, respectively). In follow-up of 4.9 (4.0) years (available for 6,427 patients), MetALD patients had significantly higher cumulative all-cause mortality: 11% vs. 2%, with the hazards ratio (HR) of 4.93 (95%CI: 2.80-8.70; $p < 0.0001$). After adjustment for other potential drivers of mortality (age, sex, obesity, T2D, hypertension, hyperlipidemia, histologic fibrosis stage) in a Cox proportional hazard model, having MetALD was independently associated with higher all-cause mortality [adjusted HR 2.78 (95%CI: 1.49-5.19; $p = 0.0013$].

Conclusion: Compared to MASLD, Met-ALD patients have a more severe liver disease and are at three-time higher risk of all-cause mortality. Consistently applying the new nomenclature for MetALD is essential to better understand the impact of the spectrum of steatotic liver disease.

LBP-025

Elafibranor impacts inflammatory, fibrotic and symptom-associated markers in patients with primary biliary cholangitis: Proteomic results from the ELATIVE® trial

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Background and aims: Primary biliary cholangitis (PBC) is a rare, cholestatic liver disease, characterised by inflammation, fibrosis and destruction of intrahepatic bile ducts. Elafibranor, a peroxisome proliferator-activated receptor (PPAR) agonist exerting effects on PPAR alpha and delta, was efficacious and well-tolerated in patients with PBC in the phase III ELATIVE® trial (NCT04526665). Here, longitudinal protein expression profiles were evaluated in serum samples from patients in ELATIVE®, to provide insights into the immunoregulatory mechanism of elafibranor in PBC.

Method: For patients in ELATIVE® who consented, serum samples were collected at baseline, Week 26 and Week 52. Longitudinal protein expression profiles were analysed using Olink® Proximity Extension Assay technology. Two Olink® panels, Target 96 Immune Response and Explore HT, were used, covering >5,500 proteins. Quality control and data normalisation were conducted by Olink®. Linear mixed models were fitted to each protein from baseline to Week 52. Statistically significant changes in protein expression were identified using the Benjamini-Hochberg method with a 5% false discovery rate. Proteins with statistically significant changes in expression were assessed in elafibranor-treated patients with and without biochemical response, according to the primary endpoint of ELATIVE®. Pathway analyses were conducted using QIAGEN® Ingenuity Pathway Analysis (IPA®).

Results: Serum samples were analysed from 121 patients, of whom 87 received elafibranor; 46 with and 41 without biochemical response at Week 52. Expression of control proteins, gamma-glutamyl transferase-1 (GGT1) and 5'-nucleotidase (NT5E), decreased with elafibranor treatment when measured by Olink® and standard methodologies, validating the use of Olink®. A network of >20 proteins involved in hepatic inflammation had statistically significant changes of expression in elafibranor-treated patients with biochemical response at Week 52. IPA® revealed a novel inflammatory signature, including downregulation of intercellular adhesion molecule 1 (ICAM-1), dipeptidyl peptidase 4 (DPP4) and SerpinA3. This network is known to be implicated in immune cell adhesion and inflammatory regulation, and maps to immunomodulation and fibrosis pathways. Similarly, biomarkers associated with itching and fibrosis, such as bone marrow stromal cell antigen 2 (BST2) or solute carrier family 39 member 14 (SLC39A14), were significantly downregulated.

Conclusion: This is the first longitudinal proteomic analysis to characterise proteins with modulated expression in patients with PBC treated with elafibranor. The findings provide novel mechanistic insights into the anti-inflammatory effect of elafibranor in PBC, as well as impact on proteins associated with PBC symptoms, through effects on PPAR alpha and delta.

LBP-027

Elafibranor improves fatigue versus placebo in patients with primary biliary cholangitis, with limited correlation with pruritus: analyses from the phase III ELATIVE® trial

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Background and aims: Fatigue and pruritus are common symptoms in primary biliary cholangitis (PBC). While their underlying mechanisms are unclear, it has been hypothesised that fatigue may be exacerbated by pruritus in some patients (pts). In the phase III ELATIVE® trial (NCT04526665), elafibranor (ELA) significantly improved biomarkers of cholestasis in PBC. Here, the impact of ELA

vs placebo (PBO) on fatigue to Week (Wk) 52 is reported, as well as the association between fatigue and pruritus.
Method: Pts with PBC were randomised 2:1 to ELA 80 mg (n = 108) or PBO (n = 53). Fatigue was assessed via the Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a) and PBC-40 Fatigue domain. Data are reported for pts with moderate-to-severe (mod-to-sev) fatigue at baseline (BL; PFSF 7a score ≥ 60; PBC-40 Fatigue domain score ≥ 29). Changes in PFSF 7a and the PBC-40 Fatigue domain were summarised from BL to Wk 52, with respect to categorical changes, percentage change, and minimal clinically important differences (MCIDs; PFSF 7a: ≥ 3; PBC-40 Fatigue domain: ≥ 5). Spearman's correlation coefficients were calculated between fatigue (PFSF 7a and PBC-40 Fatigue domain) and pruritus (5-D Itch and PBC-40 Itch domain) PROs for scores at BL and change from BL to Wk 52. Pts with missing data at BL and/or Wk 52 were excluded.
Results: For PFSF 7a, 42/95 (44.2%) pts receiving ELA and 16/46 (34.8%) receiving PBO had mod-to-sev fatigue at BL. By Wk 52, 18/42 (42.9%) of these pts receiving ELA vs 5/16 (31.3%) receiving PBO improved to mild/normal fatigue. Mean (95% CI) percentage change from BL to Wk 52 in PFSF 7a score was larger for pts receiving ELA vs PBO (−9.5% [−12.9%, −6.2%] vs −4.2% [−9.6%, 1.2%]). At Wk 52, 28/42 (66.7%) pts receiving ELA had an improvement ≥ MCID vs 5/16 (31.3%) pts receiving PBO. For the PBC-40 Fatigue domain, 53/95 (55.8%) receiving ELA and 26/46 (56.5%) receiving PBO had mod-to-sev fatigue at BL. By Wk 52, 12/53 (22.6%) of these pts receiving ELA vs 4/26 (15.4%) receiving PBO improved to mild/no fatigue. Mean (95% CI) percentage change from BL to Wk 52 in PBC-40 Fatigue domain score was larger for pts receiving ELA vs PBO (−9.8% [−15.4%, −4.1%] vs −5.8% [−12.0%, 0.4%]). At Wk 52, 21/53 (39.6%) pts receiving ELA had an improvement ≥ MCID vs 7/26 (26.9%) pts receiving PBO. At BL, fatigue and pruritus PRO scores had a weak correlation (r = 0.25–0.35), suggesting pruritus was not a main driver of fatigue. Similarly, changes in fatigue and pruritus PROs from BL to Wk 52 did not demonstrate a strong correlation (r = 0.26–0.33), and they could improve independently of one another.
Conclusion: Treatment with ELA resulted in clinically meaningful improvements in fatigue, with greater improvements vs PBO. A weak correlation between fatigue and pruritus PROs at BL, and in improvements over time, suggests that ELA can improve these debilitating PBC symptoms independently of each other.

LBP-028
Variceal hemorrhage outcomes are worse in patients with prior decompensating events. Systematic review with individual patient data meta-analysis

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Background and aims: We investigated the effect of prior decompensation on outcomes of patients with variceal hemorrhage (VH) on non-selective beta-blockers (NSBB) plus endoscopic variceal ligation (EVL) to prevent recurrent VH.
Method: Individual patient data (IPD) were obtained from studies (Cochrane Library, PubMed, Embase, 2000-2024) including patients treated with NSBB + EVL to prevent recurrent VH, stratified by presence or absence of decompensation (VH, ascites, encephalopathy, jaundice) prior to index VH. Death was the primary outcome. New decompensating events (rebleeding, new or worsening ascites or hepatic encephalopathy, new jaundice) were secondary outcomes. Competing-risk analysis on the whole cohort was performed to assess the cumulative incidence function (CIF) of events (death and/or LT competing) and adjusted effects (by Child-Pugh score (CPS), creatinine and hepatocellular carcinoma) were assessed by the Fine and Gray model. Subgroup analysis was performed according to pre-emptive TIPS (pTIPS) eligibility at time of VH. Risk of bias was assessed by adapted PROBAST tool. Random effects IPD meta-analysis (inverse variance weights) was performed (two stages approach) to assess single study effects and heterogeneity.
Results: 2679 participants from 14 studies were included: mean CPS 8.1 ± 2.2, 27% females, 52% alcoholic etiology, 24% viral and 6% MASH. In 1364 (51%), VH was the first decompensating event while 1309 (49%) had prior decompensation (60% had prior ascites). Overall, 923 were p-TIPS eligible and 1756 were not (only 28 because of a CPS of 14-15). Two-year mortality: In the overall population, two-year mortality was significantly higher in those with prior decompensation vs. those without prior decompensation (36% vs. 19%; p = 0.0001; adjusted SHR by IPD meta-analysis 1.37, CI 1.11-1.68, I2 = 0.0%). In participants ineligible for pTIPS because of CPS of A, or because they had a CPS of B without active bleeding, mortality was also higher in those with prior decompensation (adjusted SHR 1.31, 95%CI 1.04-1.650). In participants eligible for pTIPS or not eligible because of CPS 14-15, there were no differences in mortality with or without prior decompensation. Two-year new decompensation: In the overall population, the development of a new decompensating event was higher in patients with vs. those without prior decompensation (SHR 1.33, 95% CI: 1.04-1.70, I2 = 55%). Risk for new decompensation was also significantly higher in patients ineligible for p-TIPS, independent of CPS, but not in p-TIPS candidates.
Conclusion: In patients with VH treated with NSBB + EVL to prevent recurrent VH, outcomes are worse in those with a history of a decompensating event prior to VH. Alternative therapies for these patients should be explored.

LBP-029-YI

Spatial transcriptomics of the tumor microenvironment discriminates inflamed tumors responsive or resistant to atezolizumab + bevacizumab in patients with advanced HCC

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Background and aims: The combination of atezolizumab + bevacizumab (atezo + bev) is the standard of care for advanced hepatocellular carcinoma (aHCC), with ~30% of patients achieving an objective response. Single-cell RNA sequencing identified $CD8^+$ T effector cells (CD8_Teff) and pro-inflammatory $CXCL10^+$ macrophages (Macro_CXCL10) as key players in inflamed tumors responding to atezo + bev, while their coexistence with immunosuppressive myeloid cells, such as $TREM2^+$ macrophages (Macro_TREM2) and $CD14^+$ monocytes (Mono_CD14) was a trait of resistance (Cappuyns et al., *JHEP* 2024). We hypothesized that the spatial distribution (location and distance among immune populations), as captured by spatial transcriptomics, plays a crucial role in treatment response.

Method: We used the Xenium Prime 5.000-gene panel (10x Genomics), customized with 100 additional genes, to profile 10 inflamed tumor samples (5 atezo + bev responsive and 5 resistant) and 3 non-inflamed resistant tumors. We further characterized these samples by multiplexed immunohistochemistry staining of $CD8^+$ T cells and Macro_TREM2, using a density-based algorithm to identify clusters of at least 3 immune cells ($CD8^+$ T cells, Macro_TREM2) with a maximum distance of 100 μm between neighboring cells.

Results: Among 13 samples, a total of 2.4 million cells were analyzed. The distribution of CD8_Teff and Macro_CXCL10 cells within inflamed samples differed between responsive and resistant tumors. In responsive tumors, cancer cells were significantly closer to CD8_Teff and Macro_CXCL10. Conversely, resistant tumors were characterized by a) Macro_CXCL10 being restricted to the tumor periphery and b) significantly higher levels of infiltrating immunosuppressive myeloid cells compared to responders. At the multiplex/protein level, inflamed atezo + bev resistant tumors showed: a) higher prevalence of clusters containing both immune cell types ($CD8^+$ T cells and Macro_TREM2) indicating closer proximity (38% in resistant *vs.* 18% in responsive; $p = 0.027$); b) lower prevalence of clusters with only $CD8^+$ T cells (36% in resistant *vs.* 81% in responsive; $p = 0.018$); and c) the presence of clusters with only Macro_TREM2 (26% in resistant *vs.* 0% in responsive; $p = 0.015$).

Conclusion: Single-cell spatial transcriptomics data from aHCC tumors confirmed a distinct immune landscape in atezo + bev resistance, marked by the intra-tumoral exclusion of pro-inflammatory macrophages and closer spatial proximity between immunosuppressive myeloid cells and CD8+ T cells, effectively blocking the immune response to checkpoint inhibitors.

LBP-030-YI

Pitfalls in creatinine measurement and their impact on model for end stage liver disease score

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Background and aims: The Model for End-Stage Liver Disease (MELD) score is affected by bilirubin interference in creatinine measurement, particularly with the Jaffé assay. This study evaluates this interference and develops a correction model to adjust for method- and bilirubin-dependent effects.

Method: A serum-free matrix containing only the analyte and interferent was used to systematically generate samples with varying creatinine (0–5 mg/dL) and bilirubin (0–35 mg/dL) levels. Creatinine was measured using Jaffé and enzymatic assays, and a 3D-reference model was developed to estimate true creatinine values. Validation was performed with independent patient samples, using gas chromatography-isotope dilution mass spectrometry (GC-IDMS) as the reference. MELD, MELD-Na, ReMELD-Na and MELD 3.0 scores were recalculated for 1,332 end stage liver disease (ESLD) patients

from our tertiary care center and liver allocation data from the Scientific Registry of Transplant Recipients (SRTR) registry.
Results: The Jaffé assay systematically overestimated creatinine, leading to artificially elevated MELD scores, whereas this effect was not prominent in enzymatic assay. The correction was applied in ESLD patient samples (N = 18,981), affecting all four MELD scores investigated. The deviation ranged from +2 to -1, occurring in 7.9–8.7% of all patient samples, depending on the MELD-score investigated. Corrected MELD scores > 10 are associated with significantly longer survival in deceased patients ($P < 0.001$) for all MELD derivates, except MELD 3.0, indicating the increased accuracy. In SRTR (N = 20,444) data, -1 deviations were most frequent at MELD ≥11, reaching almost 50% at some MELD scores >25. However, after correcting for creatinine bias, the overall predictive performance of the MELD scores for 3-month survival remained unchanged.
Conclusion: Jaffé-derived creatinine overestimates MELD, potentially affecting liver allocation decisions. Bias correction using a validated experimentally derived adjustment model effectively mitigates this error. However, to ensure fairness and equity in transplantation, the exclusive use of enzymatic creatinine assays is strongly recommended.

LBP-031
Advancing prime editing for Wilson disease: precise and durable in vivo Correction of ATP7B mutations
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Background and aims: Wilson disease (WD) is a rare disorder caused by ATP7B loss of function mutations, leading to hepatic and systemic copper accumulation, progressive liver disease with neuropsychiatric manifestations. Current therapies require lifelong management with compliance and tolerability challenges. Prime Editing (PE) is a next generation gene editing technology that precisely corrects mutations in DNA without DNA double strand breaks. PE offers precise correction of ATP7B mutations, restoring native gene function. The ATP7B p.H1069Q and p.R778L mutations are highly prevalent, found in >40% of WD cases. Here, we report the development of Prime Editor drug candidates with in vivo validation in humanized WD mouse models and non-human primates which show efficient, precise gene and disease correction when delivered using liver-targeted lipid nanoparticles (LNPs).
Method: We optimized PE components in vitro using a high-throughput screening platform. Lead Prime Editors targeting ATP7B p.H1069Q and p.R778L were selected for in vivo validation. Humanized ATP7B WD mouse models, recapitulating key human disease phenotypes, received a single intravenous (IV) dose of LNP-formulated RNA Prime Editor components. Editing efficiency, phenotypic rescue, and durability were assessed. To improve liver targeting, a GalNAc-conjugated PEG-lipid was incorporated into LNPs.
Results: A single IV administration of LNP-encapsulated Prime Editor in humanized ATP7B p.H1069Q mice resulted in >70% precise hepatocyte correction of H1069Q, leading to >75% reduction in hepatic copper accumulation and improved copper homeostasis. Gene correction and phenotypic rescue persisted for at least 12 weeks, the latest time point assessed. No off-target edits were detected genome-wide in human hepatocytes or WD patient-derived cells. Compared to unconjugated LNPs, GalNAc-conjugated LNPs administered to rats enhanced liver specificity, reducing mRNA distribution to other organs such as gonads by 8-fold, and increasing hepatic mRNA delivery by 60%. Surrogate Prime Editors targeting ATP7B p.H1069 or the glucose-6-phospate transporter, SLC37A4 p.L348 in cynomolgus monkeys achieved 40-80% precise hepatocyte editing, supporting the translational potential of the Prime Editor candidates.
Conclusion: Prime Editors, delivered via liver-targeted LNPs, enable efficient, precise and durable correction of pathogenic ATP7B mutations causing WD. The high levels of gene correction achieved in humanized WD mouse models resulted in lasting phenotypic rescue, supporting the potential of an LNP delivered Prime Editor as disease-modifying therapy. GalNAc-conjugated LNPs further enhance liver specificity. Based on these findings, IND-enabling studies for PM577, our Prime Editing drug candidate for WD, are underway, highlighting its potential as a one-time, curative treatment for WD patients.

LBP-032
Sustained long-term clinical improvement in Wilson disease patients on tiomolybdate choline
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Background and aims: Wilson disease (WD) is a rare disorder of copper disposition. ALXN1840 (tiomolybdate choline, TMC) is a novel copper binding agent under investigation for the treatment of WD. ALXN1840 rapidly forms inert tripartite complexes with copper and albumin to prevent the toxicities associated with excessive free copper. To characterize the effects of extended ALXN1840 treatment over years, long-term neurologic and hepatic outcomes of WD patients on ALXN1840 were assessed across its completed Phase 2 and Phase 3 clinical trials.
Method: For efficacy, data from the Phase 2 WTX101-201, Phase 2 ALXN1840-WD-205, and Phase 3 WTX101-301 trials were pooled and analyzed (n = 255). Endpoints such as cooper mobilization, neurologic and hepatic assessments, and overall clinical status were evaluated. For safety, data from the Phase 2 ALXN1840-WD-204 trial were also included (n = 266). Median duration on ALXN1840 treatment was 961 days (max 2,781 days) for the efficacy dataset and 943.5 days (max 2,781 days) for the safety dataset.
Results: Directly measured non-ceruloplasmin bound copper (dNCC) daily mean area under the effect-time curve (AUEC) showed an increase in Cu mobilization was sustained over 6 years of treatment. Statistically significant improvements from baseline were observed on Unified Wilson Disease Rating Scale (UWDRS) Part II (patient-reported symptoms) and Part III (clinician-reported symptoms), CGI-S (Clinical Global Impression – Severity), and CGI-I (Clinical Global Impression – Improvement). Hepatic status, as measured by Model for End-stage Liver Disease (MELD) and Modified Nazer Score, trended towards improvement through the duration of treatment. Most AEs were mild and reversible with less than 5% of patients having a drug-related serious adverse event (SAE), and with none having a drug-related renal or urinary system SAE.
Conclusion: Pooled analysis of clinical trial data from 255 WD patients on ALXN1840 treatment shows sustained clinical

improvement over 6 years of treatment. Combined with long-term safety, this analysis supports the potential use of ALXN1840 as a therapy for Wilson disease.

LBP-033

Rapid HBsAg declines and HBsAb seroconversion observed with a single dose of VRON-0200 plus Tobevibart and Elebsiran: preliminary results of a VRON-0200 combination treatment from a phase 1b study for functional cure in chronically HBV-infected patients

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Background and aims: Sustained off tx responses (Functional Cure) have been observed with EOT HBsAg loss and HBsAb seroconversion. VRON-0200 is a therapeutic vaccine for CHB functional cure that expresses a genetically encoded checkpoint modifier, fused with HBV core and pol (but not S) antigens, designed to enhance, broaden, and prolong $CD8^+$ T cell responses. In an ongoing Phase1b study (n = 27), a single VRON-0200 dose, when added to SOC nucleos(t)ide therapy, previously reported a promising safety profile, positive HBV immunogenicity, and HBsAg declines starting after D28. Here we report the first safety, immunogenicity, HBsAg and HBsAb data from a Combination Cohort, in this study, investigating VRON-0200 plus the addition of Tobevibart and Elebsiran.

Method: 8 CHB patients(pts), virologically suppressed on NUCs, with HBsAg ≤1,000IU/mL, randomized to i.m. VRON-0200 5×10^{10}vp prime on D1, followed by 6 mthly doses of Tobevibart and Elebsiran starting on D28, alone, or, with a VRON-0200 boost on D196. Safety, virologic, and immunologic assessments are performed. Sera collected at multiple timepts and HBsAg (via ELISA; LLOD: 0.05IU/mL) and HBsAb levels (detectable at ≥10mIU/mL) are assessed. T cell frequencies measured pre-tx (2 timepts) and multiple post-tx timepts, via IFN-γ ELISpot analysis from PBMCs using 3 peptide pools (core, pol, and S antigen).

Results: As of Feb 20, 2025, 4 pts were included: 3(75%) male, all 4 (100%) Asian, median age, 46.5yrs, and median BL HBsAg, 197 IU/mL (range:28–627). In 420 pt safety days, no treatment-related SAEs or discontinuations were reported; the 8 AEs were in 2 pts:(1-SAE (GR3) and 7-AEs: GR2(n = 1); GR1(n = 6); 2 were TRAEs (GR1)). ELISpot results, at D28, just prior to Tobevibart and Elebsiran dosing, increased in all 4 pts following a single prime VRON-0200 dose. At D28, HBsAg levels were similar to BL, but declined -3.1, -2.6, -2.4, and -1.3 $\log_{10}$IU/mL at D35 (7 days post first dose of Tobevibart and Elebsiran) and -3.5, -3.2, -3.0, -2.2 $\log_{10}$IU/mL at D84 (post 2 doses of Tobevibart and Elebsiran), respectively. In addition, at D35, all 4 pts (100%) seroconverted from HBsAb negative to positive. Additional safety, HBsAg, HBsAb, and ELISpot responses will be reported.

Conclusion: These initial data of the combination of a single i.m. VRON-0200 dose plus Tobevibart and Elebsiran had no observed safety concerns, was well tolerated, and displayed rapid (within 7 days of the addition of Tobevibart and Elebsiran) HBsAg declines and HBsAb seroconversions in all 4 (100%) patients. These initial responses appear promising, compared to investigational combination regimens, reported to date, including those containing PEG-IFN. These data, coupled with VRON-0200's safety, tolerability and ease of administration, may eventually support its use as an IFN-sparing immunotherapy, with the potential for shorter duration combination treatments for HBV functional cure.

LBP-034-YI

Genetic characterization of adult-onset cryptogenic cholestasis: a prospective multicentre study of 233 patients

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Background and aims: Inherited cholestatic liver diseases are rare disorders that impact the production or transport of bile, traditionally regarded as conditions of childhood. With the implementation of Next-Generation Sequencing (NGS) panels in clinical practice, there is growing interest in assessing the role of mutations in these genes in Adult-Onset Cryptogenic Cholestasis (AOCC) as well. We investigated a multigene panel, as these genes have been insufficiently studied in both young individuals and adults.

Method: From February 2017 to May 2023, all outpatients over 14 years old with AOCC were consecutively enrolled at four tertiary referral centres in Italy. We analysed the presence of mutations through high-throughput sequencing, including 36 genes: the detected variants were classified according to the American College of Medical Genetics and Genomics criteria.

Results: 233 patients with AOCC underwent molecular analysis. Among these, 108 (46.4%) were male, with a median age at presentation of 35.6 (± 15.2) years: Serum bile acids (16.2 ± 2.8 µmol/L) and alkaline phosphatase (154,6 ± 95,2 UI/L) were moderately elevated, and the patients exhibited liver stiffness consistent with mild liver fibrosis (6.7 ± 2.4 kPa). Out of 99 liver biopsies, 41 (41.4%) showed cholestasis on histology, including reduced expression of MDR3 and BSEP. Pathogenic (P) or likely pathogenic (LP) mutations were identified in 45 (19.3%) probands, either as single or compound heterozygosity. Including variants of uncertain significance (VUS), mutations occurred in 106 patients (45.5%). Considering all P/LP/VUS, the most recurrent genes were: ABCB4 (27 cases), TJP2 (18), SLC01B3 (10), ABCB11 (9), MYO5B (8), ABCC2 (7), VPS33B (6), and ATP8B1 (5). We compared the features of patients with P/LP mutations to those of others in the cohort study. No differences were observed in liver stiffness, itching history, choleretic drugs, or blood tests, except for bile acids (BAs). Female sex, BAs, age at testing, intrahepatic cholestasis of pregnancy (ICP), family history of liver disease, juvenile cholelithiasis, and low phospholipid-associated cholelithiasis occurred more frequently in patients with P/LP ($p < 0.05$). The multivariate analysis indicated that the only independent factors associated with disease-causing mutations were ICP and juvenile cholelithiasis.

Conclusion: Mutations in the genes responsible for inherited cholestasis were found to recur in AOCC in numerous cases with mild liver fibrosis, particularly in individuals with a history of juvenile cholestasis and ICP. The ABCB4 gene was the most frequently involved.

LBP-035

Addition of triple biomarkers and/or GALAD score to ultrasound enhances the sensitivity of HCC surveillance: a multi-centre randomised controlled trial

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Background and aims: Although alpha-fetoprotein (AFP), the lens culinaris-agglutinin-reactive fraction of AFP (AFP-L3), protein induced by vitamin K absence-II (PIVKA-II), and the GALAD score are valuable for hepatocellular carcinoma (HCC) detection, there is ongoing debate regarding the potential benefits of combining these biomarkers with ultrasound (US) to improve HCC surveillance. This study aimed to assess the HCC detection rate when using a combination of US with AFP, AFP-L3, PIVKA-II, and/or the GALAD score compared with US alone.

Method: This multi-centre, randomised controlled study enrolled patients with cirrhosis of any cause or high-risk chronic hepatitis B. The enrolled patients were randomly assigned to two groups and underwent HCC surveillance every six months for one year, either using a combination of US with the three biomarkers or US alone. CT or MRI was performed in all patients with a newly detected liver nodule larger than 1 cm or abnormal biomarker levels (cut-off values: 20 ng/mL for AFP, 10% for AFP-L3, and 40 mAU/mL for PIVKA-II). HCC diagnosis was confirmed based on imaging criteria or pathology.

Results: Among the 3,102 enrolled patients, the average age was 61 years, 62% were male, and 53% had cirrhosis, primarily Child-Pugh A. The main causes of chronic liver disease were hepatitis B (64%), hepatitis C (23%), and alcohol-related liver disease (5%). In our cohort, 55 patients developed HCC, with an annual incidence rate of 1.7%. HCC was detected significantly more frequently in patients who underwent surveillance with US combined with the three biomarkers compared with US alone (2.5% vs. 1.0%, $p = 0.002$). Among those diagnosed with HCC, the average tumour size was 2.5 cm, 95% were within the Milan criteria. In the combination group, 41% of HCC cases showed elevated biomarker levels despite negative US findings. Of these cases, 87.5% had elevated PIVKA-II, 56% had elevated AFP, and 31% had elevated AFP-L3. The sensitivity and specificity of US alone were 36.8% and 96.2%, respectively. When combined with AFP, sensitivity increased to 55.3%, while specificity remained at 96.3%. US combined with PIVKA-II showed a sensitivity of 67.6% and a specificity of 92.9%. The triple biomarker combination with US increased sensitivity to 74.1%, similar to the GALAD score combined with US, but specificity dropped to 92.3% and 88.0%, respectively. The receiver operating characteristic (ROC) values for AFP, AFP-L3, PIVKA-II, and the GALAD score in HCC surveillance being 0.81, 0.77, 0.73, and 0.85, respectively.

Conclusion: The addition of triple biomarkers and/or the GALAD score to US significantly enhances the sensitivity of HCC surveillance compared with US alone. Notably, 41% of HCC cases were detected through abnormal biomarker levels and/or the GALAD score, underscoring the potential for early HCC detection using biomarker-enhanced surveillance strategies.

LBP-036-YI

Suboptimal performances of Baveno VII and AASLD 2024 criteria for detecting clinically significant portal hypertension with varices in untreated patients with HDV cirrhosis

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Background and aims: Presence of gastroesophageal varices (EV) on esophagogastroduodenoscopy (EGD) results from clinically significant portal hypertension (CSPH) and are associated with an increased risk of liver decompensation. Non-invasive tests (NITs) are increasingly used in clinical practice for assessing the risk for CSPH with EV, but disease-specific cut-offs for chronic hepatitis Delta (CHD) are missing. We investigated the performances of NITs-based criteria to predict EV in CHD patients.
Method: Untreated patients with HDV-related compensated cirrhosis and available liver stiffness measurement (LSM) and EGD from the multicenter European SAVE-D and D-SHIELD cohorts were included. EGD and LSM were performed prior to Bulevirtide (BLV) start. Baveno VII (LSM $\geq$ 25 kPa) and AASLD (LSM >20 kPa + platelets [PLT] count $<150 \times 10^9$/L) criteria were applied to rule in and rule out (LSM $\leq$15 kPa plus PLT 150×10^9/L) CSPH. In a subgroup of patients, spleen stiffness measurement (SSM) was available for combined algorithms: "rule in" if at least 2 of LSM >20 kPa + PLT $<150 \times 10^9$/L + SSM >50 kPa; "rule out" at least 2 of LSM $\leq$ 15 kPa + PLT 150×10^9 + SSM <21kPa.
Results: Of the 660 compensated patients with cirrhosis included in the SAVE-D and D-SHIELD studies, 347 patients were included in this analysis 154 (44%) showed EV on EGD. 53 (62%) of 85 patients fulfilling Baveno VII "rule in" criteria had EV (62%), but 101 (66%) patients with EV had LSM <25 kPa. This criterion demonstrated a Specificity (Sp) of 83.4% and a Positive Predictive Value (PPV) of only 62.4%. 70 (65%) of the 108 patients fulfilling AASLD "rule in" criteria had EV, but 84 (55%) of patients with EV did not fulfill these criteria (Sp 80.3%, PPV 64.8%). 41/46 (89%) patients fulfilling the "rule out" criteria did not have EV on EGD, corresponding to Sensitivity (Sn) of 21.2% and Negative Predictive value (NPV) of 49.5%. 5 (11%) patients had missed varices according to "rule out" criteria. 216 (62%) and 185 (53%) patients fell in the "grey zone" according to Baveno VII and AASLD criteria, respectively, with a prevalence of varices of 44% and 41%, respectively. The addition of SSM (available in 74 patients) > 50 kPa to the "rule in" criteria improved Sn (72.7% *vs.* 45.5%) but reduced Sp (73.2% *vs.* 80.3%) while PPV remained substantially unchanged (68.6% *vs.* 64.8%). The corresponding positive likelihood ratio was 2.72. Conversely, incorporating SSM <20 kPa into the "rule out" criteria improved both Sn (32.6% *vs.* 21.2%) and NPV (53.2% *vs.* 49.5%).
Conclusion: Baveno VII and AASLD criteria based on NITs, including SSM, to identify CSPH with EV in CHD demonstrate suboptimal performances compared to other liver disease etiologies. Avoiding screening endoscopy based on NITs in CHD patients could lead to misclassify patients who have varices and are at higher risk of decompensating events.

LBP-038
Initial safety data from ELIMINATE-B, the first clinical trial of a gene editing treatment for chronic hepatitis B

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Background and aims: Chronic hepatitis B virus (cHBV) infection affects approximately 300 million patients world-wide and is responsible for 1.1 million deaths annually. Premature death in patients is predominantly due to complications of cirrhosis and hepatocellular carcinoma even with current standard of care therapies. Currently, there is no curative therapy for cHBV infection. Preclinical efficacy models across multiple species including non-human primates (NHPs) demonstrated that PBGENE-HBV eliminated covalently closed circular (cccDNA) and inactivated integrated hepatitis B virus (HBV) DNA, resulting in reductions of HBV DNA and HBsAg. PBGENE-HBV demonstrated cumulative editing at three dose levels tested in an NHP hepatitis B model, achieving 99% viral inactivation after multiple dose administrations.
Method: ELIMINATE-B is an ongoing, multicenter, global phase 1 first-in-human trial to evaluate the safety, pharmacokinetics, and antiviral activity of PBGENE-HBV, a first-in-class gene editing therapy in patients with cHBV infection being developed as a curative therapy. PBGENE-HBV consists of an ARCUS nuclease-encoding mRNA formulated in a lipid nanoparticle and optimized for safety and potency. PBGENE-HBV is designed to eliminate cccDNA, the source of viral replication and HBsAg production, and inactivate integrated HBV DNA, another source of HBsAg. Part 1 of ELIMINATE-B evaluates multiple ascending doses in HBeAg-negative patients controlled on nucleos(t)ide analogs.
Results: The first cohort, at the lowest dose level of 0.2 mg/kg, included three male participants enrolled at one study site in Moldova. Participants had a mean baseline HBsAg of 4387 IU/mL, with a duration of infection ranging from 8 to 39 years. Initial safety data demonstrated the treatment was well-tolerated with no dose-limiting toxicities (DLTs) and no serious adverse events, including no clinically significant laboratory abnormalities. Transient changes in AST/ALT and platelet counts were not clinically significant in any dosed participants. The first cohort indicates the translation of the PBGENE-HBV preclinical pharmacokinetic and safety data. The absence of significant laboratory abnormalities in the first cohort was consistent with preclinical studies in the NHP where multiple dose administrations of PBGENE-HBV resulted in no adverse effects at any of the evaluated dose levels.
Conclusion: Clinical safety data demonstrates that PBGENE-HBV was well tolerated with no DLTs and no serious adverse events. In combination with PK data, this validates the translation of the NHP model to the clinic, supporting the evaluation of multiple dose administrations and dose levels of PBGENE-HBV to achieve cumulative editing in support of cure. Comprehensive datasets of the tolerability and efficacy of multiple administrations are being collected and will be analyzed on full dosing of cohorts.

WEDNESDAY 07 TO SATURDAY 10 MAY

Acute liver failure and drug induced liver injury – Basic

TOP-249

Signaling interaction between TGF-β and EGF controls LPC proliferation and performing liver function in ALF

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Background and aims: In acute liver failure (ALF), massive hepatic necrosis (MHN) results in severe clinical manifestations and high mortality. Remarkably, liver progenitor cells (LPCs) can rescue ALF in patients through performing vital liver function. To date, key signaling inducing LPC proliferation and initiating liver functional gene expression remains largely unknown. This study aims to investigate how LPCs maintain quiescence under physiological conditions and how they are activated in ALF towards rapid proliferation and taking over liver-specific functions.
Method: SMAD7 transgenic mice were fed with DDC diet to examine the role of TGF-β signaling in LPC proliferation. Spatial transcriptomics was performed on 4 ALF patient liver samples to analyze cell-cell communication between LPCs, hepatocytes and macrophages. Mechanistically, integration of TGF-β and EGF signaling pathways was investigated in the LPC line HepaRG through multiple cellular and molecular approaches, including colony formation, cell cycle analysis, qPCR, immunoblot, immunofluorescence staining, and ChIP-qPCR.
Results: Cytostatic TGF-β signaling maintains LPC quiescence under physiological conditions through impeding G1-S phase transition. Overexpression of SMAD7 increases LPC proliferation in DDC-fed mice by inhibiting TGF-β-induced SMAD3 phosphorylation. In ALF, significant levels of TGF-β are still present, provided from activated macrophages, rather than hepatic stellate cells. Interestingly, despite the presence of TGF-β signaling, in this setting LPCs are proliferating. Mechanistically, EGF signaling effectively inhibits the anti-proliferative TGF-β effect through multiple mechanisms. EGF induces FOXO1 phosphorylation and nuclear exclusion, thereby preventing canonical SMAD-mediated transcription of the cell cycle inhibitors. Additionally, EGF promotes expression of c-MYC, which directly binds to CCND1 gene regulatory regions to drive cyclin D1 expression. Notably, while TGF-β signaling remains active in proliferating LPCs, it avoids the cytostatic outcome while initiating liver-specific gene expression. For example, canonical TGF-β/SMAD signaling and c-MYC synergistically regulate transcription of Apolipoprotein A (APOA) and Transferrin (TF) in LPCs.
Conclusion: Our study provides novel insights into how LPCs remain non-proliferative in healthy liver and how they may rapidly achieve proliferative activity and take over liver-specific functions following MHN. Cytostatic TGF-β-SMAD signaling physiologically keeps LPC quiescent. In ALF, EGF overrides TGF-β's growth-inhibitory effects. However, TGF-β-SMAD signaling is still required for liver functional gene expression in LPCs.

FRIDAY 09 MAY

FRI-136

Biomimetic ceria lipoprotein nanoparticle enable NAC-enhanced macropinocytosis-dependent liver-targeting delivery for the treatment of APAP-induced liver injury

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Background and aims: Drug-induced liver injury (DILI) is a severe liver disease mainly caused by the overdosed acetaminophen (APAP), resulting in excessive reactive oxygen species (ROS). N-acetylcysteine (NAC) is the currently only approved drug, but with limited application due to the short therapeutic time window and concentration-related side effects. Therefore, novel strategies to improve the therapeutic effect for DILI need to be explored. Ceria has the antioxidant effect with the potential for the treatment of DILI. Nevertheless, the bare forms tend to agglomerate and thus cause failure of lesion targeting, reduced biological activity, and potential toxicity. Therefore, we developed lipoprotein-based nanoparticle (CeO_2-rHDL) to achieve efficient DILI lesion accumulation of ceria to achieve synergic therapeutic effect.
Method: CeO_2-rHDL were successfully constructed. The electron microscopy and dynamic light scattering detector were utilized for the characterization. The liver-targeting capacity was evaluated via in vivo imaging system and confocal microscope. Therapeutic efficacy to improve the DILI prognosis was evaluated by in vitro studies, survival analysis, serum liver function indicators and immunohistochemical staining.
Results: The average size of CeO_2-rHDL was 32.87 ± 3.39 nm, presenting a spherical morphology. The in vivo distribution showed that the enrichment of CeO_2-rHDL in the liver can augment after APAP-induced liver injury, which was further enhanced by NAC. After the pre-treatment with inhibitors of various uptake pathways, the internalization of CeO_2-rHDL into hepatocytes was only inhibited via the macropinocytosis inhibitor by almost 70%, which can also effectively reduce the in vivo accumulation at the liver by 40%. CeO_2-rHDL was proved to reduce ROS and improve mitochondria function. In the DILI model, CeO_2-rHDL can significantly improve liver function with the reduction of liver necrosis. This therapeutic efficiency can be further improved by the combination with NAC with 100% survival rate for 72 h.
Conclusion: This study has developed CeO_2-rHDL for the treatment of DILI. Double-enhanced macropinocytosis-dependent uptake mediated the efficient liver targeting. CeO_2-rHDL rescued the injured mitochondria by reducing cellular ROS. It could improve the prognosis of DILI-bearing mice with the combination with NAC. Overall, this therapeutic nanoplatform provides a novel strategy for the DILI treatment.

FRI-137

Flavin-containing monooxygenase 3 (Fmo3) knockout mouse reveals the role of Fmo3 in female tolerance to acetaminophen-induced liver injury

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Background and aims: Sexual dimorphism causes significant differences in hepatic gene expression that considerably influence drug metabolism. Females are usually more susceptible to drug induced acute liver injury (ALI). Interestingly, female mice are more resistant to acetaminophen (APAP) induced hepatotoxicity. APAP, the most commonly used analgesic and antipyretic drug, causes about 50% of global cases of drug induced ALI. Flavin-containing monooxygenase-3 (Fmo3), predominantly expressed in human and mice female liver, oxygenate some drugs, xenobiotic and endogenous compounds containing nucleophilic heteroatoms. Fmo3 expression in mouse model of APAP autoprotection was associated with tolerance to APAP overdose in female mice. However, unequivocal evidence supporting the role of Fmo3 in protecting against APAP induced hepatotoxicity is unknown. This study explores possible mechanisms underlying Fmo3-mediated resistance to APAP overdose induced hepatotoxicity using Fmo3 knockout (Fmo3KO) mice.
Method: Fmo3KO and wildtype (wt) mice of both sexes were intraperitoneally injected with 250 mg/kg body weight of APAP. Liver tissue and plasma were collected at different time points until 72 h. Plasma aminotransferases (ALT & AST) were quantified using PiccoloXpress® Chemistry analyzed. Bile acids, APAP metabolites and glutathione (GSH) levels in liver were measured using LC/MS. Expression of key detoxification enzymes and transporters was analyzed using quantitative real-time PCR, Western blotting and immunochemistry. Tissue metabolites were investigated using MALDI imaging technique.
Results: Loss of Fmo3 expression was confirmed in Fmo3KO females. Baseline expression of APAP metabolizing enzyme, Cyp2e1 and plasma biochemistry were similar in both genotypes and sexes. Twenty-four hours after APAP injection, centrilobular necrosis was mild in the liver of wt female, but severe in the liver of female Fmo3KO, as well as in wt and Fmo3KO male mice. This was confirmed by ALT and AST plasma levels. Liver GSH levels at different time points after APAP treatment showed that female wt mice replenished GSH faster than female Fmo3KO mice. The upregulation of Fmo3 expression within pericentral region of the centrilobular necrosis correlated with faster GSH recovery. However, no alteration in mRNA expression of the GSH synthetic enzyme (Gclc) was observed. Plasma Bile acid did not differ significantly between groups. However, significant reduction of plasma APAP-GSH and APAP-NAC conjugates in wt female mice, correlated with lower expression of Abcc4 transporter gene.
Conclusion: The findings provide evidence for the role of Fmo3 in quick recovery from APAP-induced hepatotoxicity, via regulation of GSH biosynthesis and expression of detoxification enzymes and transporter molecules that limit intracellular accumulation of APAP toxic metabolites.

FRI-138-YI

Enhanced prediction of drug-induced liver injury in keratinocyte-based high-content single-cell screening integrating machine learning

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Background and aims: Idiosyncratic drug-induced liver injury (DILI) presents challenges for drug safety. A significant issue is the weak correlation between animal studies and clinical DILI, making effective in vitro models crucial for drug development. Although primary human hepatocyte cultures are standard for predicting hepatotoxicity, their extraction and maintenance present challenges limit assay types. Recent findings connect liver and skin, indicating keratinocytes might be a new tool for DILI prediction. This study enhanced a High-Content Single-Cell Screening (HCSCS) assay using keratinocytes with 20 control drugs from the ProEuroDILI Network. We aim to improve the predictive ability of this model through machine learning, enhancing in vitro DILI assessment systems.
Method: The HaCaT keratinocyte cell line was used in all experiments. Cells were seeded in a 96-well plate and, after 24 hours, exposed to 10 positive and 10 negative DILI compounds at varying Cmax concentrations. Cells were stained with fluorescent markers, and parameters such as morphology, cell cycle phase, count, mitochondrial potential, area, and oxidative stress were measured at population and single-cell levels. HCSCS imaging utilized the Operetta CLS system with automated analysis via Harmony 4.9, evaluating morphological, functional, viability, and mitosis endpoints. Additional single-cell analysis employed R, and machine learning algorithms classified DILI+ and DILI- compounds.
Results: DILI-positive drugs showed significant toxicity in HaCaT cells. Chlorpromazine and valproate reduced cell numbers at low concentrations (<30Cmax), increasing cell area and morphology. Tamoxifen had minimal impact on counts but increased ROS and altered mitochondrial potential. At intermediate doses (60–100Cmax), chlorpromazine was the most toxic, drastically lowering cell counts. Valproate caused nuclear enlargement but reversed changes at higher concentrations (>150Cmax). Tamoxifen produced smaller, round cells with increased ROS as mitochondrial function declined. DILI-negative drugs had limited effects; diphenhydramine slightly reduced cell numbers at high doses. Caffeine and lidocaine had mild impacts. These results provided robust datasets for toxicity classification, with machine learning models improving predictions for DILI-positive versus DILI-negative drugs. The SVM model trained on single-cell data at 150Cmax reached an F1-score of 0.813 and ROC-AUC of 0.89, highlighting the importance of morphological and functional parameters in drug toxicity classification.
Conclusion: Integrating keratinocytes with high-content screening and machine learning enhances DILI prediction and drug screening. This approach may significantly impact clinical practices, as keratinocytes are more accessible than hepatocytes, facilitating personalized patient models for disease study.
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FRI-139

Lipid metabolites in acute and chronic liver damage: Do N-acyl taurines protect the liver?

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Background and aims: N-acyl taurines (NAT) represent an understudied class of bioactive lipids composed of a fatty acid conjugated to taurine synthetized mainly by the liver and kidney. NATs are found in both plasma and bile, where they accumulate rapidly upon hydrolysis inhibition, a characteristic of many potent signaling molecules. Rodent models have shown promising effects of elevated levels of poly- and monounsaturated fatty acid containing NATs on metabolic health through improved insulin tolerance and resistance to liver steatosis. Interestingly, we observed that plasma NAT concentrations were increased in individuals 3 hours after lipopolysaccharide (LPS) stimulation as well as in non-cirrhotic metabolic dysfunction-associated steatotic liver disease (MASLD), suggesting NAT levels respond to both acute and chronic liver damage.
Method: To investigate if circulating NAT levels were also affected by more severe liver damage, NAT concentrations were measured in plasma from two independent clinical studies. The first study consisted of individuals with all-cause liver cirrhosis (compensated), chronic kidney disease (CKD) and matched controls. The second study consisted of individuals with acute decompensated liver cirrhosis and matched controls. To gain mechanistic insights into the causative role of NATs in liver damage development, *in vivo* rodent models with either elevated or reduced NAT abundance were treated with hepatotoxic doses of LPS or paracetamol and changes in plasma alanine transaminase (ALT) were assessed.
Results: Both compensated and decompensated liver cirrhosis patients had elevated levels of several species of NATs compared to matched controls, while levels were unaffected in CKD patients indicating the increase was specifically associated to damage of the liver. In mice, elevated NAT concentrations prevented LPS- and paracetamol-induced increases in plasma ALT, while reduced hepatic NAT synthesis caused an exaggeration of the response suggesting a protective role of NATs towards liver damage.
Conclusion: Impaired liver function leads to elevation of NAT levels in humans, but not impaired kidney function suggesting NATs are potentially relevant in human liver diseases. The ability of NATs to modulate liver damage severity in mice suggests this elevation potentially occurs as a compensatory mechanism in order to preserve liver function during acute and chronic injury.

FRI-140
Drug-induced hepatic sinusoidal obstruction syndrome: clinical characteristics analysis and preliminary exploration of mechanisms

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Background and aims: Drug-induced hepatic sinusoidal obstruction syndrome (DI-HSOS) refers to HSOS caused by pyrrolizidine alkaloids (PAs) of traditional Chinese medicine, chemotherapy mainly containing oxaliplatin (OX), and other drugs. DI-HSOS is a type of drug-induced liver injury (DILI) primarily characterized by damage to hepatic sinusoids and central veins in the liver. This study aims to analyze the clinical characteristics of DI-HSOS patients, explore characteristic differential genes and their potential regulatory pathways, and preliminarily investigate the mechanisms of DI-HSOS to provide a foundation for clinical diagnosis and treatment improvement.
Method: A retrospective study was performed on patients diagnosed with DI-HSOS and Non-HSOS-DILI at Zhongshan Hospital, Fudan University between January 1, 2014, and December 31, 2023. Clinical data were gathered. High-throughput gene expression analysis using the Gene Expression Omnibus database (GEO) and our model compared sequencing data from PA-HSOS and OX-HSOS mouse models with healthy controls through robust rank aggregation (RRA) analysis and Venn diagrams to identify differentially expressed genes. Enrichment analyses identified potential regulatory pathways. Experiments such as qPCR were conducted to validate main pathway genes, while further validation and mechanism analyses were performed using cell models, mouse models, and patient liver samples.
Results: Data from 54 DI-HSOS and 85 Non-HSOS-DILI cases were analyzed. Clinically, PA-HSOS primarily presented with abdominal distension (100%), while 74.1% of OX-HSOS exhibited no symptoms, contrasting with non-HSOS-DILI's predominant jaundice (57.6%). Laboratory findings showed more significant decreases in platelets, prolonged PT, and elevated D-dimer levels in DI-HSOS compared to Non-HSOS-DILI ($p < 0.05$). Imaging showed heterogeneous density or signal variations on scans, with features like inferior vena cava narrowing assisting differentiation. Pathologically, liver sinusoidal dilation was rare in Non-HSOS-DILI, whereas hepatocyte necrosis and inflammation were more pronounced. Analysis of DI-HSOS mouse models revealed 180 differentially expressed genes, with 62 common across studies. Enrichment analyses indicated roles for cell adhesion and apoptosis pathways. Experimental validation highlighted 4 significant genes, with increased Melanoma Cell Adhesion Molecule (MCAM) protein levels and decreased ST6 Beta-Galactoside Alpha-2,6-Sialyltransferase 1 (ST6GAL1) in DI-HSOS.
Conclusion: PA-HSOS shows prominent abdominal distension alongside platelet and coagulation changes while OX-HSOS often lacks symptoms. Imaging and pathology combined with medication history aid in distinguishing DI-HSOS from Non-HSOS-DILI. Cell adhesion and apoptosis pathways may contribute to both PA-induced and OX induced-HSOS pathogenesis. It shows notable MCAM protein elevation and reduced ST6GAL1 expression in the DI-HSOS model.

FRI-141
A comparison of the protective effects of Rimtoregtide (HTD4010) and DUR-928 on acute liver failure in mice

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Background and aims: Rimtoregtide (HTD4010) is a new 15 amino acid long synthetic peptide derived from the Reg3a protein with immunomodulatory, anti-inflammatory, and anti-apoptotic effects that was well tolerated in a first-in-human pharmacokinetic and safety study and is now being developed for acute inflammatory-related indications including acute liver failure and alcohol-related hepatitis. The intraperitoneal administration of lipopolysaccharide (LPS) alone or in combination with other hepatotoxins is a widely-used experimental model for inducing systemic and hepatic inflammation in rodents. The purpose of this study was 1) to test the potential protective effects of HTD4010 in an LPS-induced model mimicking acute liver failure in mice and 2) compare these effects to DUR-928, which is currently in late-stage development for the treatment of alcohol-associated hepatitis.
Method: In this study, male C57BL/6 mice were intravenously injected with 40 mg/kg LPS on Day 1 and divided into four groups including a model control (0.9% sodium chloride) group and a HTD4010 10 mg/kg/day group each dosed subcutaneously 1 hour and 8 hours after LPS injection on Day 1 then twice daily thereafter; and two DUR-928 50 mg/kg/dose groups, one dosed intravenously 1 hour after LPS injection; and the other, used to validate the DUR-928 results, was dosed 2 hours before LPS injection.

Results: HTD4010 10 mg/kg/day resulted in significant improvement in (greater than 2-fold) compared to the model control (87% vs 40%, $p < 0.01$). These protective effects of HTD4010 were significantly stronger than DUR-928 which showed some improvement in survival rates when administered 1 hour after the LPS injection (87% vs 53%, $p < 0.05$, respectively) but the fold-increase was less than that achieved with HTD4010. Of note, The protective effects of DUR-928 when treated prior to the LPS injection was consistent with what has been previously reported in the literature.
Conclusion: Treatment with HTD4010 resulted in significant protective effects in an LPS-induced mouse model mimicking acute liver failure. These findings provide evidence that HTD4010 may have a beneficial effect on acute liver conditions including alcohol-related hepatitis and other acute-inflammatory-related conditions.

FRI-142
ECM1 mitigates PAs-induced hepatic sinusoidal obstruction syndrome in mice by interacting with MMP9
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Background and aims: Hepatic sinusoidal obstruction syndrome (HSOS) is a rare yet life-threatening liver disease caused by pyrrolizidine alkaloids (PAs), hematopoietic stem cell transplantation, or chemotherapy drugs. The increase in hepatic matrix metalloproteinase 9 (MMP9) expression and activity is a significant contributor to the progression of HSOS. Nevertheless, the pathological mechanism and treatment strategies of HSOS remain unclear.
Method: RNA-sequencing analyse of liver samples from senecionine (SEN)-induced HSOS mice was performed. Wide type (WT) mice and hepatocyte-specific knockout of extracellular matrix 1 (ECM1) gene ($ECM1^{\Delta hep}$) mice were induced by SEN or monocrotaline (MCT), the classical PAs to induce HSOS. Furthermore, an adeno-associated virus vector (AAV) over-expressing ECM1 were injected by tail vein in HSOS mice. *In vitro*, SEN-induced AML12 cells injury and hepatic sinusoidal endothelial cells (HHSECs) injury were treated with ECM1 recombinant protein. Subsequently, the interaction between ECM1 and MMP9 was determined.
Results: RNA-sequencing results revealed that the signaling pathways of matrix metalloproteinases, platelet aggregation, inflammatory and immune response were significantly enriched in liver tissue of HSOS mice, whereas a decrease in oxidoreductase activities was noted. *Ecm1* was the most significantly down-regulated common gene in these pathways, along with an increase of *Mmp9* gene, which were further validated by western blot and qRT-PCR in both MCT- and SEN-induced HSOS mice. Moreover, a more severe pathological changes of hepatocyte necrosis, sinusoidal endothelial damage, inflammatory cell infiltration, and erythrocyte stasis was observed in $ECM1^{\Delta hep}$ HSOS mice compared with that in WT HSOS mice. However, hepatic ECM1 over-expression via AAV alleviated HSOS induced by SEN through down-regulating MMP9 expression and inhibiting MMP9 activity. In addition, PPI analysis and molecular docking analysis indicated a high-affinity protein/protein interaction between ECM1(amino acids 236–361) and MMP9 (catalytic domain). We further found that ECM1 bound directly to MMP9 and inhibited MMP9 activity through the experiments of the interaction between ECM1 and MMP9 protein. *In vitro*, the recombinant ECM1 protein enhanced the cellular viability in SEN- or MCT-induced AML12 cells and protected against SEN-induced HHSECs damage. In contact, knockdown of ECM1 in AML12 cells exacerbated SEN- or MCT-induced cell injury.
Conclusion: Hepatocyte ECM1 deletion aggravates the progression of HSOS, while ECM1 over-expression significantly attenuates HSOS induced both by SEN and MCT in mice by directly interacting with MMP9 to suppress MMP9 activity. This study reveals a previously unknown mechanism underlying the progression of HSOS and provides the experimental evidence for HSOS treatment through up-regulating ECM1.

FRI-143-YI
Metabolomic profiling to differentiate drug-induced liver injury from other liver diseases using machine learning models
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Background and aims: Idiosyncratic drug-induced liver injury (DILI) is an adverse reaction to various drugs. Diagnosing DILI is challenging as it mimics other liver injuries such as autoimmune hepatitis (AIH) and viral hepatitis (VH) and existing biomarkers cannot effectively differentiate it from other diseases. Thus, investigating DILI-specific mechanisms is essential for developing diagnostic tools. Analyzing the circulating metabolome may reveal disease mechanisms for biomarker discovery. This study compares the metabolomes and metabolic pathways in DILI patients with those of other acute liver injuries, and healthy volunteers.
Method: Metabolomic profiling analyzed serum from patients with DILI ($n = 49$), non-DILI acute liver injury (ALI) (AIH $n = 16$; VH $n = 27$; others $n = 11$), and healthy controls ($n = 48$) using ultra-high-performance liquid chromatography with mass spectrometry (UHPLC-MS). 15 machine learning classification models were developed based on the metabolomic dataset, to predict DILI vs. ALI, AIH, or VH. Cross-validation methods were used to mitigate the small sample size typical in low-incidence diseases. Pathway analysis included metabolites with VIP >1 and $p < 0.05$, using MetaboAnalyst 6.0. Spearman correlation determined associations between metabolites and clinical variables.
Results: Metabolomic analysis showed distinct patterns with 27 metabolites differing between DILI and ALI. Changes were more pronounced in DILI vs. AIH than between DILI and VH. Phe-Phe and valine were elevated in DILI vs. AIH, while fatty and bile acids were reduced. Pathway analysis highlighted altered Phe and fatty acid metabolism in DILI vs. AIH, but not with VH. Correlation analysis revealed links between metabolites and liver injury markers: Phe-Phe was negatively correlated with AST and ALT, while glycocholic acid was positively correlated with bilirubin. The full dataset was utilized to develop machine learning models using 10 metabolite panels for cohort differentiation. Phe-Phe and PC(18:3/0:0) were crucial for distinguishing DILI vs. ALI (Random Forest, AUC = 0.70), while serine and glycocholic acid were key for classifying DILI vs. AIH (Logistic Regression, AUC = 0.85). Metabolic similarities between DILI and VH resulted in lower classification performance (Extra Trees Classifier, AUC = 0.65), suggesting shared pathophysiology mechanisms.
Conclusion: Metabolomic analysis highlights relevant metabolic pathways that could be investigated in the search for biomarkers and non-invasive diagnostic tools. Our models were optimized using cross-validation techniques but require further validation. The use of

a reduced panel of metabolites would facilitate potential clinical application.
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FRI-144

Abrogation of hepatic TRb action protects the liver from acute liver injury

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Background and aims: Overdose of acetaminophen (APAP) is a well-known trigger for acute liver failure. Even if the underlying mechanisms of ALF are not yet fully understood, it is well known that triiodothyronine (T3) positively favors hepatocyte proliferation via thyroid hormone receptor β (TRβ) signaling. We observed that abrogation of hepatic TRβ action attenuates APAP-induced acute liver injury and that a crucial time-specific modulation of ALF through TH exists whereas T3 improved hepatocyte proliferation during liver regeneration.
Method: ALF was induced via i.p. injection of 300 mg/kg body weight of APAP (or solvent control) in male C57BL/6J mice w/o hepatocyte specific TRβ knockout. 1–24 h post APAP intoxication, liver function test, liver histology, proliferation and hepatic T3- and APAP-responsive markers were evaluated.
Results: APAP intoxication in hepatocyte-specific TRβ deletion mice (hepTRβKO) resulted in absence of pericentral hepatocellular necrosis and absence of elevated serum transaminases 24 hours post APAP intoxication as compared to WT mice. Interestingly, 12 hours after APAP application injured hepatocytes surrounding central veins could be observed in hepTRβKO mice.
Conclusion: We hypothesize a hepatocyte-intrinsic detrimental TH effect in disease development, whereas TH action during liver regeneration is beneficial. These findings harbor great translational potential for novel therapeutic strategies, e.g. to antagonize or agonize local TH action, depending on the disease status of patients suffering from ALF. It is of high clinical relevance if one could support the so far only therapeutic option NAC in the treatment of APAP-induced ALF, preferably with a prolonged therapeutic window.

FRI-145

miR148a-3p may play a direct role in regulating inflammatory responses in bacterial infection related acute-on-chronic liver injury

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Background and aims: Given their role as master regulators of many basic cellular processes, dysregulation of miRNAs have been linked to many abnormalities including liver diseases. A distinct expression pattern for miR148a-3p was previously identified in our bacterial infection related acute-on-chronic liver disease (BI-ACLF) mouse model. Herein, we aimed to study the *in vitro* effect of miR148a-3p on hepatic cytokines and chemokines in primary hepatocytes.
Method: Our group has previously established BI-ACLF mouse model using *Abcb4*$^{-/-}$ mice which were intraperitoneally injected with 4 mg/kg LPS. In the current study, mouse primary hepatocytes isolated from Abcb4$^{-/-}$ C57BL/6J mice by perfusion, were stimulated with 50 ng/ml LPS and transfected either with 50 nM miR148a-3p mimic or 50 nM miR-148a-3p inhibitor 6 hours post seeding. miRNA specificity and transfection efficiency was assessed by mock miRNA and GFP expressing plasmid transfections, respectively. Relative expression of *Il-6, Il-2, Il-22, Rantes, il-1β* and *Tnf-α* was determined by qRT-PCR using pre-designed TaqMan gene expression assays 48-hours after transfection. One-way analysis of variance (ANOVA), followed by Bonferroni's *post hoc* tests were applied as statistical tests.
Results: We have previously identified significant upregulation of miR148a-3p in our BI-ACLF model by screening of liver disease-related miRNAs using PCR arrays (miScript, Qiagen) together with differential expressions of *Il-6, Il-2, Il-22, Rantes, il-1β* and *Tnf-α*. Immunohictochemistry revealed a macrophage polarization in these mice with significant upregulation of M1 markers (CD64, CD86 and CCR7) while M2 markers either remained unchanged (CD206 and Arg1) or downregulated (CD163). *In vitro* LPS stimulation on the other hand, resulted in 35-fold overexpression of miR148a-3p. A more profound upregulation (580-fold) was observed after miR148a-3p mimic transfection, while anti-miR repressed the miR148a-3p levels (0.19-fold) *in vitro*. LPS-stimulated expressions before and after miRNA mimic transfection for *Il-6* (40.8-fold vs 13.2-fold), *il-1β* (53.9 fold vs 6.7-fold) and *Tnf-α* (52.2-fold vs 9.2-fold) suggest a significant repression effect of miR-148a-3p on these proinflammatory cytokines. On the other hand, inhibition of miR148a-3p expression by anti-mir transfection resulted in 6.3-fold, 9.2-fold and 4.5-fold upregulation for *Il-6, il-1β* and *Tnf-α* in the absence of LPS stimulation, respectively. Although similar upregulation was observed for *Il-2, il-22* and *Rantes* upon LPS stimulation, their expressions did not differ either by overexpression or inhibition of miR148a-3p.
Conclusion: miR148a-3p might play a direct role in regulating the observed acute inflammatory responses in pre-injured liver, which might lead to the transition from a stable chronic state to progressive liver damage after bacterial infection in BI-ACLF.

FRI-146-YI

Genetic polymorphisms associated with idiosyncratic drug-induced liver injury: a systematic review and bioinformatic analysis

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Background and aims: Despite being a multifactorial entity, individual genetics plays a crucial role in idiosyncratic drug-induced liver injury (DILI). This study performs a comprehensive systematic review and analysis of DILI and genetics literature, focused on elucidating relevant genes, drugs and functional enrichments.
Method: Using PRISMA 2020 Guidelines, we identified eligible literature published up to June 30, 2023, in four databases (Web of Science, EMBASE, Scopus, PubMed) with a refined search strategy for

liver injury and genetic-related terms. After screening, original articles on human patients with at least one control group, reported statistically significant variants between groups and indicated validated DILI biochemical criteria were included. Data extraction, bioinformatic and statistical analyses were performed using R v4.4.1, RStudio v2024.0 4.2 and Bioconductor v3.19 packages. Functional enrichment analyses were conducted using KEGG and Gene Ontology (GO) databases.

Results: A total of 25,874 records were screened, with 14,931 remaining for further evaluation after duplicate removal. Ultimately, 139 original articles were included: 124 studies involving variants associated to DILI susceptibility (DILI Risk set), 36 involving variants associated to DILI protection (DILI Protective set), and 21 for both. In the DILI Risk set 83 genes were included, being NAT2, HLA-B, HLA-DRB1, HLA-A, and HLA-DQB1 the most frequent. The DILI Protective set comprised 25 genes, of which MAFF, XRCC3, LTA, MTHFD1, UGT1A4, SLC22A2 and MIR1208 appeared exclusive to this set. The most common culprit drugs were antimycobacterials (46.7% for DILI Risk and 44.4% for DILI Protective), antineoplastics (21.0% and 27.8%) and amoxicillin-clavulanate (4.0%) for DILI Risk or systemic antivirals (11.1%) for DILI Protective. Hierarchical analysis performed with KEGG enrichment analysis revealed major pathway clusters in DILI Risk set corresponding to i) regulation of the adaptive immune response and cytotoxicity mediated by T and NK cells (HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DPB1, HLA-DQA1, HLA-DRB1, HLA-DQB1 and HLA-DRB5); ii) NF-κB pathway, cytokine signaling and general inflammatory response (NFKBIA, NFKB1 and RELA); iii) porphyrin, ascorbate and aldarate metabolism (UGT2B7, UGT1A1 and UGT1A9); iv) drug metabolism pathways mediated by cytochrome P450, in which CYP2E1, CYP3A4, CYP3A5, CYP2B6 and CYP2D6, GSTT1, GSTM1 and GSTP1 genes were involved, and v) biliary secretion and hepatic cellular transport (ABCG2, ABCB11, ABCC2, ABCB1, SLCO1B1 and CYP7A1). GO enrichment analysis showed consistent findings with previous KEGG results.

Conclusion: This work highlights the major role of the immune system and oxidative stress response in DILI, providing a solid basis for further studies focused on most reported genes, as well as on more infrequent genes with strong functional significance in hepatotoxicity.

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FRI-149

Serum levels of immune checkpoints in drug-induced liver injury and metabolic dysfunction-associated steatotic liver disease

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Background and aims: The adaptive immune system seems to play a significant role in the pathogenesis of drug-induced liver injury (DILI) and metabolic dysfunction-associated steatotic liver disease (MASLD). Due to its constant exposure to foreign antigens, the liver has developed a high capacity for immune tolerance. At this point, immune checkpoints control the immune system by preventing T-lymphocyte autoreactivity and promoting self-tolerance. Consequently, any alteration of these immune checkpoints may be related to a modification of immune activation, thus affecting the liver. The objective of this study was to analyse the levels of different immune checkpoints in the serum of control subjects, patients with DILI and patients with MASLD with significant liver fibrosis (MASLD F >2, n = 28) and without significant liver fibrosis (MASDL F ≤2, n = 10).

Method: Blood samples were collected from adjudicated cases of DILI within the first week of symptoms (n = 14), MASLD (n = 38) and healthy-liver controls (n = 28). Transient elastography (FibroScan®) was performed in MASLD and control cases. MASLD cases were divided into two groups according their fibrosis level (F0-F1-F2 (MASDL F ≤2) (n = 19) and F3-F4 (MASLD F >2) (n = 19)). Immune checkpoints were analyzed by ProcartaPlex™ Immunoassays.

Results: A similar profile of immune checkpoints without significant differences was identified between DILI and MASLD F >2 groups: BTLA (312 ± 59 and 250 ± 24 pg/ml), CTLA4 (46 ± 4 and 51 ± 3 pg/ml), CD28 (142 ± 11 and 138 ± 10 pg/ml), CD80 (84 ± 10 and 64 ± 4 pg/ml), PD-1 (24 ± 4 and 17 ± 2 pg/ml) and PD-L2 (1072 ± 102 and 1140 ± 65 pg/ml). However, the levels of these proteins are significantly higher in both groups than in the control and MASLD F ≤2 groups (BTLA: 121 ± 20 and 139 ± 33 pg/ml; CTLA4: 31 ± 2 and 29 ± 4 pg/ml; CD28: 101 ± 9 and 91 ± 9 pg/ml; CD80: 40 ± 4 and 44 ± 4 pg/ml; PD-1: 9 ± 1 and 7 ± 1 pg/ml; PD-L2: 639 ± 49 y 828 ± 87 pg/ml). With regard to PD-L1, significantly elevated levels were observed in the MASLD F >2 group (1.4 ± 0.4 pg/ml) in comparison to the other groups (DILI: 0.7 ± 0.1 pg/ml, MASLD F ≤2 groups: 0.6 ± 0.3 pg/ml, control: 0.1 ± 0.1 pg/ml).

Conclusion: The results indicate that the immune checkpoints under examination are capable of distinguishing between MASDL with or without significant fibrosis. Conversely, these markers are unable to differentiate between chronic liver disease (MASDL with significant fibrosis) and acute liver disease (DILI). The latter two diseases appear to exhibit similar immune tolerance mechanisms.

FRI-150

Dynamic transition of hepatocyte subtypes highlights novel repair pathways in acute liver failure after hBMSC transplantation

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Background and aims: Understanding the liver repair mechanisms in acute liver failure (ALF) mouse model following hBMSC transplantation is crucial. This study provides a comprehensive single-cell atlas to explore these regenerative processes.

Method: hBMSCs were transplanted into immunodeficient Fah-/-Rag2-/-IL-2Rγc-/- SCID (FRGS) mice with induced FHF. Single-cell

RNA sequencing (scRNA-Seq) was employed to map hepatic cell types, supplemented by bulk RNA sequencing and immunohistochemistry (IHC) for validation. Pseudotime analysis traced hepatocyte dynamics during regeneration.
Results: Regenerating livers contained two distinct hepatocyte subtypes: type-a and type-b hepatocytes. Type-b hepatocytes, marked by elevated Mlxipl expression, demonstrated superior transporter-like capabilities, particularly in bile acid transport and detoxification, and showed enhanced recovery after transplantation. Pseudotime analysis revealed a trajectory from classic to transporter-like hepatocytes, regulated by hepatic stem/progenitor cells (HsPCs). Multi-color IHC corroborated the existence of Mlxipl-high type-b hepatocytes in regenerating tissues.
Conclusion: This work reveals a dynamic hepatocyte subtype transition as a key driver of liver repair. The transporter-like hepatocytes, pivotal for restoring detoxification and bile acid transport, emerge through transformation from typical hepatocytes, shedding light on the mechanisms of liver regeneration.

FRI-151
Drug-induced liver injury in biopsy-scaled precision-cut liver slices
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Background and aims: Repeated consumption of drugs can lead to drug-induced liver injury (DILI), one of the major safety concerns for pharma companies and clinicians. An important challenge is the lack of methods to predict adverse effects of drugs on the liver. While rodent models are used for pre-clinical tests, these cannot predict DILI risk in humans. Human precision-cut liver slices (PCLS) have emerged as a promising ex-vivo model with great potential to replicate liver functionality. PCLS retains the liver's native micro-architecture and cellular diversity while offering a simpler preparation process than other 3D culture models. However, the usual diameter of PCLS cultures is rather big (5–8 mm) so large liver resections are needed to culture human PCLS which become scarce with the current evolution of parenchyma-sparing liver surgery. We aim to develop biopsy-scaled (1 mm) PCLS cultures for the evaluation of DILI.
Method: Healthy male BALB/c mice (Charles River) were used for baseline studies and an in-house bred BALB/c-Tg(Pdgfrb-GFP) strain for live imaging. Livers of mice were excised, cut in 250 um thick slices using a Leica 1200S vibratome, punched using 1/3 mm biopsy punchers (Kai®), and cultured in 24/96-well plates. Samples were snap-frozen at different times/conditions. RNA extraction was performed using TRIzol® followed by QuantSeq 3′ mRNA-Seq library preparation (Lexogen) and sequencing on a NovaSeq (Illumina). Whole-slice immunostaining was carried out on formalin-fixed samples. Imaging was done using a Zeiss LSM® 800 confocal and an EVOS M7000® microscope.
Results: Comparison of hepatocyte marker expression between 1 mm and 3 mm PCLS over 5 days suggests that a smaller diameter better preserves hepatocyte functionality in mouse cultures. GSEA analysis of RNAseq data on day 0 and 5 slices revealed high enrichment of ECM remodeling pathways and wound healing responses on day 5. Using BALB/c-Tg(Pdgfrb-GFP) mice we confirmed hepatic stellate cell activation over time demonstrated by an increase in the GFP signal. Exposure to pro-inflammatory cytokines further increased the signal showing the responsiveness of the cultures. Finally, 1 mm slices allowed paracetamol-driven liver damage observed on RNA and immunostainings. Optimized 96-well plate cultures of 1 mm PCLS facilitated the determination of IC50 concentrations of APAP and Omeprazole. Part of our findings in mice could be replicated in human 1 mm PCLS cultures.
Conclusion: PCLS of 1 mm diameter from both human and mouse liver samples demonstrated good preservation of hepatocyte functionality in culture compared to larger slices. The use of BALB/c-Tg (Pdgfrb-GFP) mice facilitates the evaluation of DILI drugs and fibrosis-inducing agents. 1 mm slices will allow for testing human liver biopsy-derived slice cultures for DILI and pro- and anti-fibrotic drugs and thus hold promise for personalized medicine approaches.

FRI-152-YI
Validation of markers of hepatocyte senescence for the prognosis of patients with severe acute hepatitis
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Background and aims: Severe acute hepatitis is a rare disease that can progress to acute liver failure (ALF) and associated mortality. Biomarkers defining prognosis early in the course of the disease are lacking making drug development and early selection for transplantation difficult. Hepatocyte senescence affects patients with severe acute hepatitis resulting in extrahepatic organ failure and poor survival (Kourtis et al. Nat. Cell Biol. 2024). The aim of this study was to validate these findings in real world clinical practice using traditional histopathological tools.
Method: Patients with severe acute hepatitis, due to autoimmune (AIH), drug-induced (DILI), or indeterminate hepatitis (IAH), presenting to a single centre (2010–2023) and undergoing a liver biopsy were studied. Archived FFPE liver biopsy samples were stained using immunohistochemistry to quantitate hepatocytes (HNF4alpha), senescent cells (P21, P16) and markers of regeneration (Ki67, and CCNA2). Quantifications of the positive cells were made using Image J.
Results: Data from 36-patients (AIH: 16, DILI: 13, DILI, IAH: 7; mean age: 46.9 years, bilirubin at admission: 329 µmol/L; INR at admission: 1.5) were analysed. 24-patients recovered spontaneously (survivors), and 12-patients developed ALF and either died (n = 2) or received transplant (n = 10) (non-survivors). The non-survivor group had higher bilirubin, creatinine, and INR levels at the time of liver biopsy. Hepatocyte expression of markers of senescence was significantly higher in the non-survivors (median p21 and p16 positive hepatocytes per tissue: 2.7% vs 7.5% (p = 0.03) and 24.9% vs 59.0% (p = 0.03) respectively). Regeneration markers were also markedly higher in non-survivors (median Ki67 and CCNA2 positive hepatocytes per tissue: 4.7% vs 14.9% (p = 0.05), and 1.0% vs 2.7% (p = 0.06) respectively), possibly representing ineffective regeneration. The expression of p21 was significantly higher in patients who developed renal dysfunction (median p21: 3.2% vs 10.5%, p = 0.04). In those that developed hepatic encephalopathy (HE), the expression of p21 as well as the markers of regeneration was significantly higher (median p21 3.1% vs 7.5%, p = 0.03; median CCNA2: 1.0% vs 3.7%, p = 0.01; median Ki67: 4.7% vs 11.9%, p = 0.06). Meanwhile p16 was only numerically higher in these groups (renal dysfunction: 28.9% vs 73.8%, p = 0.06; HE: 28.6% vs 71.8%, p = 0.16).
Conclusion: The results of this study validate the previous observations suggesting that expression of markers of hepatocyte senescence could serve as potential histological biomarkers to identify patients at high risk of progression to ALF, need for transplantation and mortality. Further validation and search for liquid biomarkers is underway.

FRI-153

Prognostic significance of very high and towering peak alanine aminotransferase (ALT) values with normal or near normal total bilirubin in patients with idiosyncratic drug-induced liver injury

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Background and aims: A high aminotransaminase (AT) level with concomitant jaundice in patients with drug-induced liver injury (DILI) is associated with worse outcomes. However, the prognostic significance of DILI with very high AT values but no jaundice is not known. We examined the prognostic value of a very high or towering alanine aminotransferase (ALT) value with normal or near normal total bilirubin (TBL) in well characterized DILI.
Method: 964 well-phenotyped DILI patients meeting predefined eligibility from the prospective US Drug Induced Liver Injury Network (DILIN) and Spanish DILI Registry were analyzed. We defined ALT 500 to ≤1000 U/L as very high, whereas ALT >1000 U/L as towering ALT. We then investigated five groups based on their peak ALT levels in U/L and serum TBL in mg/dL: Group A: peak ALT < 500 with accompanying TBL ≤1; Group B: very high peak ALT with accompanying TBL ≤1; Group C: very high peak ALT with accompanying TBL 1.1 to ≤2.5; Group D: towering peak ALT with accompanying TBL ≤1 and Group E: towering peak ALT with accompanying TBL 1.1 to ≤2.5. Primary outcome of interest is the number of cases fulfilling Hy's law criteria later in the injury course which was defined as ALT >150 U/L along with TBL >2.5 mg/dL. We also assessed for development of liver-related death or needing a liver transplant among the 5 groups.
Results: 692 patients from DILIN (mean age 49 yrs and 68% female) and 272 from the Spanish DILI Registry (mean age 50 yrs and 55% female) were included. There were 210 patients in Group A, 157 in Group B, 121 in Group C, 67 in Group D, and 137 in Group E from DILIN, while the Spanish Registry had 147, 40, 32, 24, and 29 in Groups A to E, respectively. The incidence of Hy's law in the DILIN cohort was 3.3% in Group A, 4.5% in Group B, 24% in Group C, 10.4% in Group D, and 28.5% in Group E, whereas in the Spanish Registry it was 2%, 5%, 22%, 25%, and 24% in Groups A-E, respectively. Furthermore, the percent of liver-related death or liver transplant in DILIN was 0.5% in Group A, 0% in Group B, 3.3% in Group C, and 1.5% in both Groups D and E, whilst in the Spanish Registry it was 0%, 2.5%, 0%, 8.4%, and 3.5% in Groups A to E, respectively.
Conclusion: In patients with DILI, a very high ALT is associated with poor liver outcomes only when accompanied by at least minimal TBL elevation, but a towering ALT is associated with poor liver outcomes with or without a minimal TBL elevation. These data assist in risk stratifying DILI presenting with very high ALT values without jaundice in clinical care and drug development.

FRI-154

Gadoxetate-enhanced MRI detects acute rifampicin-induced inhibition of hepatocellular transporter function in rats and normalization of function after chronic dosing

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Background and aims: Drug-induced liver injury (DILI) can be the result of impaired hepatobiliary transporters, with altered bile formation, flow, and subsequent cholestasis. Gadoxetate (Primovist, Bayer AB) is an hepato-specific paramagnetic gadolinium-based contrast agent. Dynamic gadoxetate MRI can detect acute rifampicin (RIF) induced changes in hepatobiliary transporter function in vivo in rats prior to established biomarkers of liver toxicity. Chronic dosing may lead to indirect changes in transporter function by affecting expression or degradation of transporters. In this study dynamic gadoxetate MRI was used to measure effects of acute and chronic dosing of RIF on hepatic plasma clearance (K^{trans}) and biliary efflux (k_{bh}) in mL/min/100cm3.
Method: All animal experiments were approved by the local animal ethics authorities. Male rats (Wistar Han, ~300 g) were separated in 3 groups (n = 4/group): vehicle, clinical RIF (10 mg/kg) and high RIF (67 mg/kg) and dosed daily. High RIF was designed to be an equivalent clinical dose, i.e. similar relation between the human steady state concentration and Ki for human OATP1/MRP2, and between rat steady state concentrations and rat Ki for Oatp1/Mrp2. Rats were imaged at 7 T on a Bruker Biospec MRI at 4 timepoints. Baseline and acute imaging (D1) were performed 3 h after oral dosing. Day 2 (D2) and Day 5 (D5) follow-up imaging were performed 24 h after the previous RIF dose.
Results: No adverse effects of rifampicin treatment or imaging were detected by clinical observation. At D1, RIF caused K^{trans} to drop by 49% in the clinical group (p = 0.009), and by 78% after the high dose (p = 0.001). This was followed by a gradual return to baseline values on D2 and D5. For k_{bh}, clinical RIF caused a non-significant reduction of 41% (p = 0.10) and high dose RIF caused a 69% reduction on D1 compared with baseline (p = 0.001) and there was a gradual return to baseline on D2 and D5.
Conclusion: Dynamic gadoxetate MRI shows potential as an early non-invasive marker of hepatobiliary transporter functionality. In this work, we found indications for normalized functionality after chronic rifampicin administration. This assay is fully translatable to the clinic as gadoxetate is an approved MRI contrast agent and may improve the risk assessment of DILI in humans.
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FRI-155-YI

The PPAR agonists Saroglitazar and Rosiglitazone provide hepatoprotection after APAP-induced liver injury in E2f1-/- mice

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Background and aims: Dysregulation of PPAR transcription-factors has been implicated with various metabolic disorders. In the context of acetaminophen (APAP)-induced hepatotoxicity, changes in PPAR-alpha(a) activation, fatty acid oxidation (FAO) and related lipophagy have been observed but treatments are still lacking. E2F transcription-factors are key regulators of both metabolism and the cell-cycle. Our preliminary results showed that *E2f1*$^{-/-}$ mice do not survive after APAP-induced liver injury, whereas *E2f2*$^{-/-}$ animals have a higher survival rate with increased FAO, PPARa and PPAR-gamma(g) levels when compared to wild-type (WT) and *E2f1*$^{-/-}$ mice. Therefore, the aim of this study was to investigate whether pharmacological activation of PPARa and PPARg, could improve the response to drug-induced liver injury (DILI) after APAP-induced liver damage.
Method: For this, *E2f1*$^{-/-}$, *E2f2*$^{-/-}$ and WT mice were used. Hepatotoxicity was induced by intraperitoneal injection of 360 mg/kg APAP. Mice were evaluated 6 and 48 h after treatment. Survival, liver-necrosis and proteome analysis were performed. Additionally, PPARg agonist (Rosiglitazone) and the dual PPARa/g agonist (Saroglitazar) were administered before and after APAP treatment.
Results: *E2f1*$^{-/-}$ mice exhibited reduced PPARa and PPARg levels, CREB activation and oxidative stress, which were linked to reduced FAO and levels of autophagy markers 6 hours post-APAP. Conversely, *E2f2*$^{-/-}$ mice had elevated activation of CREB and pathways involved in protection against oxidative stress, together with increased PPARa and PPARg levels. In addition, pretreatment with saroglitazar or rosiglitazone increased survival to 100%, reduced necrosis and normalized transaminase levels in *E2f1*$^{-/-}$ mice 48 h post-APAP, providing almost complete protection against toxicity. The dual agonist saroglitazar led to CREB activation, restored autophagy markers, redox homeostasis and increased FAO 6 h post-APAP. Rosiglitazone did not improve the effect of saroglitazar, but induced similar results in the protection against DILI and CREB activation. Given the importance of finding an antidote to APAP-induced hepatotoxicity, these drugs were also administered 1 and 3 h after APAP treatment. The results showed that after APAP treatment, the PPARa and/or PPARg agonists resulted in a 100% survival rate and were significantly associated with reduced liver damage. This protective effect was supported by a lower transaminase levels and less liver necrosis than in mice treated with APAP alone.
Conclusion: E2F1 deficiency increases hepatic vulnerability by impairing activation of the PPAR-CREB axis, dysregulation of lipid metabolism and increased oxidative stress. However, activation of this axis by PPAR agonists before and even after APAP-induced hepatotoxicity confers protection that may be valuable as a potential treatment in the future.

FRI-156
Coordinated liver tissue regeneration becomes ineffective with increasing injury in patients with acute indeterminate liver failure

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Background and aims: Severe indeterminate acute hepatitis (sIAH) represents a life-threatening condition without clear prognostic criteria or specific therapies, affecting patients without pre-existing liver disease. Recent studies have highlighted the significant role of p21 expression in the liver in driving disease progression and mediating interactions with extrahepatic organs through TGFβ signalling. This study aims to investigate the histopathological features associated with p21-expressing hepatocytes in patients with sIAH, with the goal of deepening our understanding of the disease's pathobiology and identifying potential predictors of patient survival.
Method: 34 patients with sIAH admitted to a single center between 2010 and 2019 that underwent liver biopsy were included. Severity of liver injury was assessed histologically in terms of confluent zonal, or panlobular/multilobular collapse as previously described. A multiplex immunofluorescence staining and an advanced single cell analysis protocol was employed to assess cellular pathomechanisms related to senescence and regeneration. Patients that died or underwent liver transplantation were analysed as non-survivors.
Results: The histopathology of non-survivors revealed more areas of multilobular necrosis with lower rates of hepatocyte proliferation and p62-expression and an increase in p21-expression in preserved hepatocyte islands. Interestingly, neighboring analysis revealed a close proximity of p21^{+} and Ki67^{+} hepatocytes in clusters. With a ratio of 1.59 between Ki67^{+} and p21^{+} hepatocytes compared to 5.76 in survivors, non-survivors showed a strong dysbalance towards p21 expression and lack of regeneration. Furthermore, regenerative dysbalance and p21 overexpression was associated extrahepatic organ failure in the form of renal impairment and hepatic encephalopathy (HE), with the percentage of p21+ hepatocytes positively correlating with serum creatine levels and of the patients developing HE, all showed increases in p21 expression. In the survivors, enhanced Ki67-expression coupled with an increase in p62^{+} hepatocytes hints at an autophagy mediated resolution of tissue injury and compensatory proliferation, notable since p62 expression was found to be distant to p21^{+} hepatocyte clusters. Furthermore, non-survivor patients revealed an elevation in tissue inflammation and damage with increases in yH2Ax and cleaved caspase 3 as well as an increased number of immune cells (IBA1 pos. macrophages, CD8 T-cells, CD45^{+} cells) both in necrotic areas and hepatocyte islands, while TGF-beta levels did not differ. This potentially resembles an exaggerated inflammatory response within the preserved hepatocyte areas in non-survivors.
Conclusion: sIAH non-survivor patients exhibit a regenerative dysbalance in favor of inflammation and hepatocyte senescence, the latter of which is linked to extrahepatic organ injury, underscoring its potential role in disease progression.

FRI-157
Longitudinal assessment of liver stiffness for up to 96 weeks by magnetic resonance elastography and correlation with fibrosis markers in alpha-1 antitrypsin deficiency-associated liver disease: results from phase 2 studies of fazirsiran

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease that may lead to the development of AATD-associated liver disease (AATD-LD). Imaging-based, non-invasive tests for liver fibrosis assessment of patients (pts) with AATD-LD,

including magnetic resonance elastography (MRE) and FibroScan®, are of interest. Cross-sectional and longitudinal analyses of liver stiffness measurement (LSM) via MRE in pts with AATD-LD are limited. Using data from phase 2 clinical trials of fazirsiran (an investigational small interfering RNA therapy for AATD-LD), we aimed to characterize LSM over time via MRE in pts with AATD-LD and to correlate findings with LSM via FibroScan and non-imaging fibrosis-related metrics.

Method: Baseline and post-baseline imaging data (MRE, FibroScan), and serum and histology data from pts with AATD-LD who received fazirsiran/placebo in the AROAAT-2001 (NCT03945292)/-2002 (NCT03946449) trials were included. LSM via MRE was an exploratory endpoint and optional at sites with MRE feasibility. MRE measurements were collected at baseline, and at Week 24/48/72 or Week 96. Change from baseline for MRE, correlation of MRE with FibroScan and correlation of imaging data with serum/tissue fibrosis measures were assessed. Further methodology is described in Strnad *et al. NEJM*, 2022 and Clark *et al. Gastroenterology*, 2024.

Results: Overall, 56 pts received placebo or fazirsiran (25/100/200 mg) in AROAAT-2001/-2002; of those, 22 and 46 pts had available baseline or post-dose MRE or FibroScan data, respectively. In most pts with baseline METAVIR fibrosis stage ≥1, LSM via MRE declined from baseline as early as Week 24 post-fazirsiran treatment; reductions were sustained up to Week 96. Versus baseline, LSM via MRE showed a statistically significant ($p < 0.05$, paired t-test) decrease of 18% with fazirsiran 200 mg at the last data collection; LSM via FibroScan declined by ~18% but changes were not statistically significant. Overall, 7/11 (64%) pts had >19% (cutoff for test-retest repeatability [TST]); range: 22–46%) decrease in LSM via MRE; 6/19 (32%) pts had a >35% (cutoff for TST; range: 36–70%) decrease in LSM via FibroScan. For pts with both MRE and FibroScan data, versus placebo, pts who received fazirsiran 200 mg had a greater decline in LSM via MRE than FibroScan (median change: –28% and –5%, respectively). LSM via MRE and FibroScan showed statistically significant correlations ($p < 0.05$) with most serum and liver histological markers, including serum Z-alpha-1 antitrypsin, Periodic Acid-Schiff stain with diastase globule burden and METAVIR fibrosis stage.

Conclusion: LSM via MRE demonstrated promising utility in monitoring fazirsiran treatment response in a small cohort of pts with AATD-LD. The utility of LSM via MRE and FibroScan will be further evaluated in ongoing phase 3 trials.

Study/writing funding: Takeda Development Center Americas, Inc.

FRI-158

Chronic plus binge ethanol feeding impact on cholesterol metabolism in liver- and intestine-specific Abcg5/g8 knockout mice

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Background and aims: The ABCG5/G8 heterodimer effluxes sterols including cholesterol from enterocytes and hepatocytes into the intestine and bile, respectively. In this study, we aim to adopt the chronic-plus-binge alcohol feeding diet (NIAAA mouse model) to liver *Abcg5/g8* knock-out (Hep-KO) and the intestinal *Abcbg5/g8* knock-out (Int-KO) mice to investigate the effects of alcohol on cholesterol metabolism.

Method: Total hepatic and ileal RNA was extracted from 15-week-old wild type (WT) C57BL/6J, Hep-KO and Int-KO mice, which were either fed with control diet (WT/Cont, Hep-KO/Cont and Int-KO/Cont groups) or liquid ethanol diet (5% v/v) followed by an acute ethanol binge (5 mg/kg, WT/EtOH, Hep-KO/EtOH and Int-KO/EtOH groups). Hepatic expressions of *Srebf2, Cyp7a1, Cyp8b1, Cyp27a1, Shp, Fxr, Abcg1, Pnpla3, Mboat7, Tm6sf2, Lxr, Acat2, Abca1*, and *Hmgcr* and ileal mRNA levels of *Fgf15, Lxr, Fxr, Shp, Npc1l1, Srebf2, Acat2* and *Abca1* were evaluated. One-way ANOVA test or Kruskal–Wallis test were used for the statistical analysis. $P < 0.05$ was considered as statistically significant. Liver and plasma total cholesterol levels were determined by colorimetric assay. Paraffin-embedded liver sections and frozen liver sections were stained with haematoxylin-eosin and oil red O, respectively.

Results: *Cyp7a1* suppression was observed in both Hep- and Int-KO groups independent of ethanol challenge ($p < 0.05$). Hepatic *Cyp27a1* levels were significantly downregulated in Hep-KO/EtOH compared to Hep-KO/Cont group. Hepatic mRNA levels of *Fxr* showed statistically significant suppression in ethanol challenged Hep- and Int-KO groups compared to WT/Cont group, and significant downregulation in Int-KO/EtOH group compared to others. Significant downregulation of hepatic *Acat2, Lxr* and *Hmgcr* expression in all groups was observed upon EtOH uptake. Among the genes evaluated in ileum, only *Acat2* showed significant downregulation in all KO groups and WT/EtOH group compared to WT/Cont. Among the well-known fatty liver associated genes, alcohol challenge resulted in the repression of *Pnpla3* and upregulation of *Tm6sf2* expression. Hepatic and plasma total cholesterol levels were not different. Histological staining of liver sections showed high numbers of lipid droplets indicating lipid accumulation and increased hepatic steatosis in mice challenged with EtOH regardless of the genotype.

Conclusion: Chronic-plus-binge ethanol-feeding markedly suppressed *Lxr, Acat2* and *Hmgcr* mRNA levels, suggesting its direct effect on cholesterol sensors LXR and ACAT2, and rate-limiting enzyme (HMGCR) for cholesterol synthesis. Moreover, the absence of both liver and intestinal *Abcg5/g8* gene expression resulted in downregulation of *Cyp7a1* expression independent of ethanol challenge, indicating a key role of bile acid synthesis in cholesterol metabolism.

FRI-159-YI

Adrenomedullin as an immunomodulator of CD14+MerTK+ circulating monocytes in liver failure syndromes

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Background and aims: Liver failure syndromes are characterised by dysfunctional immune response. This affects monocyte/macrophage phagocytic capacity and allows circulating microorganisms to disseminate and initiate sepsis. Adrenomedullin (ADM) is a potent vasodilator that contributes to immune regulation. We hypothesised that in liver failure there is a detrimental imbalance between ADM and Adrenomedullin binding protein (AMBP) - 1 that favours a dysfunctional monocyte/macrophage phenotype and function.

Method: Between April 2020 and June 2024, consecutive patients with acute liver failure (ALF = 54), Acute – on - chronic liver failure (ACLF = 25), Decompensated cirrhosis (DC = 9) and healthy controls (HC = 16) were recruited. ADM and AMBP - 1 concentrations were measured by ELISA, peripheral blood mononuclear cells (PBMCs)/monocytes were isolated and used for RNA sequencing and cell culture with ADM, adrenomedullin receptor antagonist (ADM 22–52), AMBP - 1.

Results: In the ALF group, the main aetiology was drug-induced liver injury 78% (n = 42), 43% of patients developed infection during the first 10 days of admission. In the ACLF group, the main cause of liver disease was alcohol-related liver disease in 88% of patients (n = 21) and the main precipitant was infection (n = 20). ADM expression in isolated monocytes was upregulated in ALF (log fold change = 5.88, p = 0.0002) and ACLF (log fold change = 4.62, p = 0.0006) compared to HC. Plasma ADM concentration was increased in ALF (1684 ± 1156 pg/ml) vs ACLF (836.1 ± 765.2 pg/ml) and HC (164.8 ± 62.73 pg/ml), Kruskal Wallis, $p < 0.0001$ (ALF vs HC). AMBP - 1 was decreased in ALF

(59.27 ± 44 ug/ml) vs ACLF (126.3 ± 72.23 ug/ml) and HC (252.8 ± 159.7 ug/ml) ($p < 0.0001$, ALF vs HC). In ALF, ADM was directly correlated with heart rate (HR, $r = 0.273$, $p = 0.04$), lactate, AST ($r = 0.6323$, $p < 0.0001$) concentrations and INR ($r = 0.352$, $p = 0.008$). No difference in ADM and AMBP - 1 concentrations was found between ALF patients who spontaneously survived or died/underwent transplantation. In patients, stimulation with LPS increased ADM production by PBMCs (ALF = 6; 561.4 ± 1038 pg/ml vs 259.2 ± 213.7 pg/ml, ACLF = 4, 3202 ± 491.2 vs 1757 ± 1689, HC = 7; 1920 ± 1184 vs 2299 ± 1188 pg/ml), (2 - way ANOVA $p = 0.0151$). The immunophenotyping of PBMCs after culture (HC n = 6 and ALF n = 6) showed that among CD14 + cells, the percentage of cells expressing MerTk was reduced by LPS (2.077 ± 0.87%) but restored by incubation with ADM 100nM (3.852 ± 1.063).

Conclusion: ADM is increased and AMBP - 1 reduced according to SOFA - defined disease severity in ALF/ACLF. ADM promotes monocyte pro-restorative, anti - inflammatory phenotypes. Intervention on this molecular pathway is indicated to restore vascular resistance and monocyte function in liver failure syndromes.

FRI-160

Targeting cGAS/STING pathway and ferroptosis for protection against hepatic ischemia-reperfusion injury

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Background and aims: Hepatic ischemia-reperfusion injury (HIRI) is a critical complication in liver transplantation and surgery, often resulting in liver dysfunction or failure and exacerbating the scarcity of donor organs. Characterized by tissue hypoxia during ischemia and excessive inflammation and oxidative stress upon reperfusion, HIRI leads to regulated cell death through mechanisms such as pyroptosis and ferroptosis. Therapies targeting these pathways, including octreotide (OCT), a somatostatin analogue, and deferoxamine (DFO), an iron chelator that prevents ferroptosis, have shown promise. This study sought to investigate whether combining OCT and DFO can protect against HIRI, providing mechanistic insights into the likely implication of ferroptosis and cGAS/STING pathway.

Method: Male Sprague Dawley rats (12–15 weeks old, 180–220 g) were housed under standard conditions and subjected to 70% partial hepatic ischemia by clamping the left lateral and median lobes, followed by 30 minutes of ischemia and 4 hours of reperfusion. Rats were randomized into five groups: Sham, HIRI, HIRI+OCT (75 μg/kg), HIRI+DFO (200 mg/kg), and HIRI+OCT+DFO. Histopathological examination of liver tissues was performed, alongside immunohistochemical analysis of COX-2 expression. GPX4 levels were assessed using colorimetric analysis, while TLR4 was quantified by ELISA. Gene expression of cGAS and STING was analyzed using qRT-PCR.

Results: Histopathological alterations were notably mitigated in the OCT+DFO+HIRI group. cGAS fold change was significantly reduced in the combination group, whereas STING expression remained unchanged. Additionally, HIRI+OCT+DFO group demonstrated a decrease in COX-2 immunohistochemical expression that parallelled an increase in GPX4 levels indicating a potential modulatory effect on ferroptosis.

Conclusion: The protective effect of the OCT and DFO combination against HIRI is likely driven by a modulation of ferroptosis and a possible interference with the cGAS/STING pathway.

FRI-161

Single-cell RNA sequencing reveals a fundamental role of LCN2+ neutrophils in the innate immune response in drug-induced acute-on-chronic liver failure

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Background and aims: Drug-induced liver injury (DILI) accounts for over 50% of acute liver failure cases in the US and Europe, and often requires liver transplantation. In China, most drug-induced acute liver failure cases occur in patients with chronic liver diseases, such as hepatitis B and metabolic dysfunction-associated steatotic liver disease, due to their high prevalence. Although the pathogenesis of DILI is not fully understood, both innate and adaptive immune responses are believed to play central roles. This study aimed to explore the functions of neutrophils in drug-induced acute-on-chronic liver failure (DI-ACLF) using single-cell RNA sequencing (scRNAseq).

Method: Three patients with DI-ACLF (two with hepatitis B and one with cirrhosis), one patient with liver failure due to hepatitis B, and two liver disease-free healthy controls, were prospectively recruited from the liver surgery department. Single-cell suspensions were prepared from liver tissue and peripheral blood and analyzed using scRNAseq. Additionally, patients from China DILI Registry (DILI-P) were included, with serum samples tested via ELISA for validation. Statistical differences between groups were determined using ANOVA and Tukey's multiple comparisons test.

Results: The causative agents of DILI were chemotherapeutic agents, paracetamol, and herbal medicines in three patients, respectively. ScRNAseq analysis yielded 101,644 cells from liver tissue and 250,106 cells from peripheral blood. Unsupervised clustering revealed an increased proportion of liver neutrophils in the DI-ACLF group compared to other groups. Subclustering of neutrophils highlighted a high abundance of lipocalin-2 positive ($LCN2^+$) neutrophils particularly in the DI-ACLF group, both in liver tissue and peripheral blood. Integrated analysis indicated that liver $LCN2^+$ neutrophils were highly likely to migrate from the peripheral blood. Further pseudotime trajectory analysis suggested that $LCN2^+$ neutrophils were the origin of differentiation and maturation of liver neutrophils. Gene ontology enrichment analysis of differentially expressed genes, particularly those involved in cell-cell interactions, showed significant enrichment in neutrophil activation, leukocyte adhesion, and neutrophil chemotaxis. ELISA assays further demonstrated that serum LCN2 levels (pg/mL) were significantly higher in moderate/severe DILI (n = 8) compared to mild DILI (n = 8; 95% CI: 1210–9714, $p = 0.008$), non-DILI liver injury (n = 7; 95% CI: 3278–12081, $p < 0.001$), and healthy controls (n = 7; 95% CI: 1794–10597, $p = 0.004$).

Conclusion: $LCN2^+$ neutrophils appear to play a fundamental role in the intrahepatic and peripheral innate immune responses in DI-ACLF, highlighting their potential as a therapeutic target to mitigate excessive inflammation. Additionally, elevated expression of serum LCN2 may serve as a valuable biomarker for the early detection of severe DILI.

FRI-162

Brown adipose tissue-derived extracellular vesicles administration alleviates liver injury in mice

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Background and aims: Brown adipose tissue (BAT) not only improves the liver microenvironment through metabolic regulation but also mediates inter-organ signaling via extracellular vesicles (EVs), thereby modulating liver immune response and promoting liver repairment. Previous studies have reported that BAT-derived EVs (BAT-EV) reduce liver fat accumulation and exhibit therapeutic effects in metabolic-associated liver diseases. However, research on the innovative therapeutic role of BAT-EVs in acute liver injury remains limited. This study aimed to explore the therapeutic potential of BAT-EV for acute liver injury.
Method: We conducted experiments using three animal models of liver injury which were induced by concanavalin A (Con A), acetaminophen (APAP) or carbon tetrachloride (CCl_4). First, we validated the BAT-liver axis in vivo through BAT resection and BAT activation. Then we isolated BAT-EVs and cultured primary brown adipocyte in vitro. BAT-EVs or primary brown adipocyte was administrated into Con A, APAP, and CCl_4 mice, with liver function and histology assessed. Inflammatory levels were also analyzed using qPCR and ELISA. Further in vitro experiments were performed to explore the underlying mechanisms.
Results: Our results showed that after BAT removal, liver injury in Con A mice deteriorated, with elevated ALT, AST, and increased hepatic inflammatory cell infiltration. However, activating BAT with the selective β_3-adrenergic receptor agonist CL 316243 reduced CCl_4-induced hepatocyte death. Additionally, both BAT-EVs and primary brown adipocyte administration significantly lowered peripheral ALT and AST levels, reduced liver necrosis area and apoptotic hepatocyte count, decreased inflammatory cell infiltration, and lowered inflammatory cytokine levels, such as interleukin-6 and tumor necrosis factor-alpha. Further in vitro results revealed that brown adipocyte-derived EVs suppressed inflammatory cytokines production in macrophage, potentially by modulating macrophage mitochondrial metabolism through mitochondrial protein transfer.
Conclusion: There is BAT-liver protective axis in vivo. BAT-EVs and brown adipocyte significantly alleviate Con A, APAP, and CCl_4-induced acute liver injury in mice, suggesting a novel therapeutic strategy. Modulating macrophage mitochondrial metabolism may represent a potential therapeutic target. However, the possible mechanism is still under exploration.

Acute liver failure and drug induced liver injury – Clinical

TOP-250

Polyreactive immunoglobulin G is elevated in autoimmune hepatitis and acute liver failure

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Background and aims: Polyreactivity describes the ability of an antibody to bind multiple molecular structures, thereby increasing flexibility, affinity, and neutralizing potential. Polyreactive immunoglobulin G (pIgG) can be found in every individual, regardless of disease, and play an important role in primary immune defense and the removal of aging or apoptotic cells. Studies on viral influenza show that the majority of monoclonal antibodies are polyreactive after influenza. Recently pIgG was identified as a novel marker for the diagnosis of autoimmune hepatitis (AIH) in multicenter studies in children and adults. However, these studies included only a few AIH cases with acute liver failure (ALF). This retrospective multicenter study aims to evaluate the diagnostic capacity of pIgG to predict AIH in comparison to non-AIH-ALF, sepsis and influenza in an intensive care unit setting in adult patients.
Method: Quantification of human pIgG was done using a "home-made" solid phase ELISA coated with human huntingtin-interacting protein 1-related protein in bovine serum albumin (HIP1R/BSA). Biomaterial was retrieved from local biorepositories.
Results: 165 adult patients (ALF = 42, AIH = 81, influenza = 17, sepsis = 25) were compared from five centers across Europe. All patients in the control groups with viral (influenza) and bacterial infection (sepsis) related hyperinflammation were treated at intensive care units. Every patient in the influenza-group needed artificial respiration. Median age was significantly different between the groups ($p < 0.001$) with the highest age in the influenza group (59 years) and the lowest age in the ALF-group (42 years). Female rate was highest in the AIH group (79%) and significantly lower in the influenza- (12%) and sepsis-group (24%). IgG elevation rate was 60% in the AIH- and 17% in the ALF-group, whereas no elevation could be seen in influenza- and sepsis-groups ($p < 0.001$). 30-days death rate was significantly higher in sepsis (64%) and influenza (47%) compared to ALF (14%) and AIH (0%, $p < 0.001$). 34% in the ALF- and 2% in the AIH-group underwent liver transplantation. ALF due to AIH was 7.1% in the ALF-group (3 cases). 53% in influenza- and 25% in sepsis-group had immunosuppressive medication at sampling (0% in AIH, 2% in ALF). The median pIgG-level was highest in the ALF-group (2.08 normalized arbitrary units, nAU) followed by AIH (1.87 nAU, $p = 0.786$). In the influenza-group, the median pIgG-level (1.01 nAU) was significantly lower compared to ALF and AIH (both $p < 0.001$). The median pIgG-level was 1.39 nAU in the sepsis-group ($p = 0.092$ vs. AIH; $p = 0.070$ vs. ALF). The background of non-AIH liver diseases in previous studies was 1.01 nAU.
Conclusion: Prevalence and concentration of pIgG are similar in AIH (with and without ALF) and ALF suggesting that pIgG are not suited to distinguish between autoimmune and non-autoimmune origin of ALF. However, hyperinflammatory infectious diseases are associated with lower pIgG concentrations than AIH and ALF.

THURSDAY 08 MAY

THU-193-YI

Therapeutic plasma exchange improves outcomes in Amanita phalloides induced acute liver failure – results from an interim analysis of the Amanita-PEX study

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Background and aims: Amatoxin-related acute liver failure (AT-ALF) is associated with a high mortality rate in the absence of liver transplantation (LTX). The use of therapeutic plasma exchange (PEX) has been demonstrated to improve LTX-free-survival in patients with acute liver failure (ALF) of other etiologies. Nevertheless, it remains unclear whether PEX may also enhance survival in AT-ALF. Additionally, there is considerable variation in the clinical practice of utilizing PEX in AT-ALF across different centers. Given the rarity of this ALF entity, the feasibility of conducting a randomized controlled trial to investigate the use of PEX in AT-ALF remains uncertain. The aim of this study therefore was to record and compare the LTX-free and overall survival within the first 28 days following the fulfillment of ALF criteria (hepatic encephalopathy (HE) and INR >1.5) between patients who received PEX and those who received no PEX.
Method: This is an interim analysis of a multicenter, international, retrospective cohort study (Amanita-PEX study, NCT06187220). The period of inclusion spanned from 2013 to 2024. This report presents the findings for the adult cohort.
Results: A total of 89 adult patients were recruited from 21 centers across eight countries. The median age of the cohort was 58 years (range 18–87 years), and 39 patients (44%) were female, 85 patients (96%) received therapy with silibinin and 83 patients (93%) received additional therapy with N-acetyl cysteine. Twenty-six patients received additional PEX (29%), while 63 received no PEX (71%). Overall, 25 patients (28%) died within the first 28 days, and 26 (29%) required LTX. A multivariate survival analysis was conducted, demonstrating a benefit of LTX-free survival associated with PEX (HR 0.44, CI 0.20–0.94, p = 0.04) when adjusted for age, sex, initial Sequential Organ Failure Assessment (SOFA) score on the first day and HE grade ≥2. The survival curve demonstrated a benefit in LTX-free 28-day survival for PEX when divided into patients with HE = 1 (PEX: 100%; no-PEX: 78%) and HE ≥2 (PEX: 42%; no-PEX: 19%) in comparison with no-PEX with the same grade of HE (log-rank test, p < 0.01). Likewise, there was a benefit in overall survival when divided the patients with HE = 1 (PEX: 100%; no PEX: 87%), and HE ≥2 (PEX: 68%, no-PEX: 52%) in comparison with no-PEX with the same grade of HE (log-rank test, p = 0.01).
Conclusion: In this interim analysis of a multicenter retrospective study, PEX was associated with improved LTX-free survival in patients with AT-ALF.

THU-194

Therapeutic and clinical outcomes of continuous renal replacement therapy and plasma exchange in acute liver failure patients

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Background and aims: Continuous renal replacement therapy (CRRT) and plasma exchange (PLEX) improve outcomes in Acute liver failure (ALF) as a bridge to liver transplant (LT). Both CRRT and PLEX have been shown to improve outcomes in these sick patients. However, seldom studies have compared these two in the real world scenario, which we aimed to compare.
Method: Single-centre retrospective observational study with 50 patients (≥ 18 years of age) presenting with ALF between 2022 and 2024 were included. We compared the improvement in hepatic encephalopathy grade and organ function, the duration of hospital stay and overall survival rate in patients who underwent CRRT, PLEX and Standard medical therapy (SMT), respectively.

Results: Overall, 50 patients (31.0 ± 13.2 years, 62% females, MELD score (31.4 ± 6.9), 30% satisfying Kings College Criteria), with Hepatitis A virus as the most common (34%), met selection criteria. At admission, infection was present in 50%, 30% had shock and 40% had acute kidney injury. 18 (36%) received CRRT (MELD. 32.3 ± 7.2) or PLEX (MELD, 34.0 ± 5.4), while 14 (28%) were on SMT (MELD, 25.5 ± 4.7). Compared to SMT, using CRRT (p = 0.014) was associated with better improvements in HE grades than PLEX (p = 0.29). CRRT significantly reduced ammonia levels (172 ± 43.6 to 136.44 ± 59.37, p = 0.01) compared to SMT (85.62 ± 24.96 to 74.63 ± 25.76) but PLEX did not (132.27 ± 46.56 to 105.47 ± 39.86, p = 0.31). Similarly, compared to SMT, using CRRT (p = 0.007) significantly improved organ function, and PLEX did not show significant organ improvement (p = 0.32). Overall, 28 day transplant-free survival was 40%. Among those receiving CRRT 6(33%), 11(61.1%) of those on PLEX survived. Only 3 (21.4%) of those on SMT survived. On comparing PLEX with CRRT, there was a trend of better survival with PLEX (p = 0.09).
Conclusion: PLEX and CRRT are associated with better outcomes in ALF than SMT. Future randomized trials comparing PLEX and CRRT for outcomes in ALF are mandated.

THU-195
Haemophagocytic lymphohistiocytosis – a rare but deadly cause of acute liver failure

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Background and aims: Acute Liver Failure (ALF) is a rare life-threatening clinical syndrome characterized by liver-related coagulopathy and hepatic encephalopathy (HE) with no pre-existing hepatic pathology. Amongst the rare causes of ALF is haemophagocytic lymphohistiocytosis (HLH), a pathology characterised by life-threatening dysregulated immune activity causing pathological inflammation and multi-organ failure. Acute liver injury (ALI), coagulopathy in absence of HE, is recognised as a common bystander of HLH, however ALF secondary to HLH is a rare phenomenon. Treatment is 3-fold; supportive management for ALF, treatment of the underlying trigger and treatment of HLH guided by the HLH-2004 protocol. Super-urgent transplantation is not advised by EASL, with literature describing recurrence of HLH involving the graft and high mortality. The aim of this case series is to review our admissions of patients with ALF secondary to HLH and describe clinical parameters, management and outcomes for this rare group.
Method: This case series describes patients from a quaternary liver transplant unit, all of whom were managed in the intensive care unit. Patients were identified through retrospective review of the hepatology handover archive between January 2010 and October 2024. Electronic and paper hospital records were reviewed to confirm if ALF criteria were met and to collect numerical and descriptive data. 4 cases of ALF secondary to HLH were identified as well as 3 further cases of ALI.
Results: Of the patients with ALF, all 4 were female with a mean age of 35 years (range 17–66). Two of the patients had history of solid organ transplantation (Renal = 1, Liver = 1). Triggers were identified in 3 patients (Herpes Simplex virus 2 (HSV-2) N = 2, Epstein Barr virus (EBV) N = 1). Management of all included corticosteroids. One patient died prior to any further escalation of HLH management. One patient also received etoposide with the addition of anakinra for refractory HLH. One additionally received anakinra and a course of plasmapheresis followed by intravenous immunoglobulin. The final patient also received rituximab. Despite aggressive HLH treatment and multi-organ support, all resulted in critical illness and death. Issues encountered in all patients included balancing the risk of introduction of corticosteroids when viraemia had not been excluded yet and dosing of chemotherapy regimens with liver dysfunction.
Conclusion: This case series explores the varying presentations and management of a rare cause of ALF with high mortality in a large liver transplant center. This rare condition requires a high index of suspicion to allow prompt recognition and treatment to improve outcomes. Further research and guidance for this subsection of ALF is required with focus on the adjustments needed to HLH management with this degree of hepatic dysfunction.

THU-196
Effects of universal early antimicrobial treatment in acute liver failure patients at a large volume transplant centre in the United Kingdom

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Background and aims: We set out to assess clinical consequences of universal early antimicrobial treatment in critically ill acute liver failure (ALF) patients admitted to a tertiary /quaternary liver intensive care unit (ICU).
Method: A retrospective observational study was performed for patients admitted to ICU with ALF between May 2022–April 2024. Electronic patient records were reviewed for microbiologic, radiologic and blood biomarker evidence of infection and resistance. Systemic inflammatory response syndrome (SIRS), non-neurologic sequential organ failure (SOFA) scores and antimicrobial prescriptions were reviewed. Antimicrobial duration as a proportion of ICU length of stay (LoS) was calculated. Data are expressed as median (interquartile range).
Results: There were 37 critically ill ALF admissions with an ICU LoS of 9 (6–16) days, for review. In line with local Liver unit guidelines, all patients received antimicrobials on admission and patients were prescribed fluconazole (100%) alongside either Pipericiliin/Tazobactam (35/37; 94.6%) or meropenem (2/37; 5.4%). On admission, 10/37 (27%) patients already had some evidence of infection (9 radiologic and 1urine culture) – however, pre-ICU LoS was not significantly different between infected and non-infected groups. SOFA scores were significantly higher in infected patients (12 (8.5–14) vs 8 (7–10)) but C-reactive protein (11 (6–25) vs 11 (3–14)), white cell count (14.5 (9.5–19.5) vs 11.5 (7.5–15)) and SIRS scores (2 (1–2) vs 1 (1–2)) were not. Admission blood cultures were negative in all but were only taken in 20% (2/10) infected patients and 30% (8/27) non-infected. Despite universal antimicrobial treatment from the outset, 18/37 (49%) patients required further antimicrobial escalation/extension for presumed infection during their stay and median ICU antibiotic-free days indexed to ICU LoS was 0% (0–26.5). 3 resistant organisms were found in 2/37 (5%) patients (multi-drug resistant (MDR) Pseudomonas, MDR Staphylococcus Haemolyticus and Carbapenemase producing enterococci). Mortality and (6/37 (16%)) transplantation rate (19/37 (51%)) didn't differ according to presence/absence of admission infections, but 2 patients meeting Kings College Criteria with no contra-indications to transplantation succumbed to uncontrolled sepsis at days 4 and 5.
Conclusion: Admission infections were found in nearly 3 in every 10 ALF admissions. SOFA scores were higher in patients with admission infections, but overlap was high and the poor discrimination of traditional infection markers such as CRP, WCC and SIRS scores demonstrates the difficulty of identifying sepsis in this group. Sepsis remains a driver of avoidable ALF deaths, though the association of universal antimicrobial treatment with few antibiotic-free days, antimicrobial escalation in over half of admissions, and the development of resistant organisms highlights the potential harms of over-treatment. Research into better biomarkers of infection in ALF are warranted.

THU-197

Essential: Efficacy and safety of non-transplant therapies for acute liver failure syndromes due to infective etiologies

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Background and aims: Acute liver failure (ALF) in India primarily stems from infective causes, contrasting with drug-induced etiologies prevalent in the West. We investigate non-transplant therapies like plasma exchange (PLEX) and continuous veno-venous hemofiltration (CVVH) as rescue strategies for ALF, addressing high mortality and limited liver transplantation access in resource-constrained settings.
Method: A retrospective analysis of 76 ALF patients from April 2021 to July 2024 at a single center, approved by the Institutional Review Board. Patients were categorized into three management groups: A: CVVH only, B: PLEX [B1: without CVVH, B2: with CVVH], C: standard medical treatment (SMT). Primary outcome was transplant-free survival at discharge or day 21, defined as 'improvement' versus 'worsening' (death, clinical deterioration, or referral for orthotopic liver transplantation [OLT]). Severity indices - Model for End-Stage Liver Disease (MELD), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE), Assessment of Liver Failure (ALFA) Score, and Acute Liver Failure Study Group (ALFSG) index - were evaluated to create a probability score model for individualized treatment prediction.
Results: Groups showed no significant demographic differences except for creatinine levels (group A: 3.1 vs. groups B/C: 1.4, $p = 0.001$). ALFSG Score was highest in groups A and B2, lowest in B1 and C. Group C demonstrated significantly lower bilirubin, ammonia, International Normalized Ratio (INR), and lactate compared to groups A and B. Seven-day improvements were highest in group B (B2 > B1) > A > C ($p < 0.05$). Survival rates were 78.9% vs. 87.8% vs. 85.7%. Clinical improvement: 45% vs. 71% (81% vs. 56%) vs. 86% ($p = 0.031$). Multivariate analysis revealed significant outcomes using ALFA score, ALFSG index, and SOFA score. Regression analysis developed a worsening probability score: 3.2475 + (−1.3688 × ALFSG Index) + (0.0169 × SOFA), with 90.9% accuracy. Multinomial logistic regression probability scores:.

- Group A: −1.3337 + (0.4471 × ALFSG Index) + (0.0507 × SOFA).
- Group B: 1.3571 + (−0.0504 × ALFSG Index) + (−0.0937 × SOFA).
- Group C: −0.0234 + (−0.3967 × ALFSG Index) + (0.0429 × SOFA).

Models showed 90% sensitivity and 72% accuracy when validated at an independent center. Patients with high creatinine (>1.5) and unstable SOFA/ALFSG index benefited most from CVVH, while high ammonia levels responded best to PLEX.
Conclusion: PLEX proves optimal for unstable infective ALF patients, with CVVH as a valuable intervention for acute kidney injury. The predictive models, validated across two centers, demonstrate high accuracy in guiding individualized treatment strategies, offering a promising approach in resource-limited settings.

THU-198-YI

Combination therapy with plasma exchange and continuous renal replacement therapy improves transplant free outcomes in acute liver failure: a tertiary care center experience

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Background and aims: Acute liver failure (ALF) is associated with overall mortality of 30% and mortality without LT being almost 50%. Plasma exchange(PLEX) helps in improved coagulation, and decreases cytokine storm, while continuous renal replacement therapy(CRRT) improves ammonia level and removes various mediators in the formation of cerebral edema. Hence we hypothesized that the combination therapy is associated with better outcomes in ALF patients. Till date, only one retrospective study and one case series available in assessing outcomes of combination therapy in paediatric ALF and no data in adult patients. Our aim was to assess the 28 day transplant free survival in ALF patients undergoing combination therapy (CRRT + PLEX).
Method: It was a retrospective data analysis done at a tertiary care center from October 2022–September 2024 in patients with ALF. All patients underwent standard volume PLEX (arm A) before April 2023 and standard volume PLEX+ CRRT (arm B) thereafter. CRRT was initiated within 24 hours of admission for hyperammonemia (>90 mmol/L) and cerebral edema.
Results: 54 ALF patients (mean age 30.33 ± 12.33 years, females 55.5%, mean MELD 32.1 ± 4.32) were analyzed. Most common etiology was hepatitis A followed by yellow phosphorus poisoning (31.4% {17/54} vs 29.6% {16/54}). All patients received standard medical care, including N-acetyl cysteine and nutritional support. 29 patients underwent only PLEX and 25 underwent combination therapy. 42 (77.7%) patients were in grade 3 or 4 hepatic encephalopathy at presentation. Median sessions of PLEX (2) were similar between the groups. Incidence of sepsis (13.7% {4/29} vs 12%{3/25; $p = 0.85$), pneumonia (6.8% {2/29} vs 4%{1/25}; $p = 0.65$), acute kidney injury (10.3%{3/29} vs 16%{4/25}; $p = 0.53$), seizures (31%{9/29} vs 40% {10/25}; $p = 0.49$) was noted in arm A and B respectively and was comparable between the arms. Day 5 mean MELD scores were 23.22 ± 8.25 vs 19.23 ± 6.3; $p = 0.05$, arterial ammonia was 94.12 ± 34.34 vs 75.32 ± 32.46, $p = 0.04$ in arm A and B respectively. Mean length of ICU stay was 12.92 ± 4.1 vs 13.02 ± 4.58; $p = 0.93$ and mean hospital stay was 18.58 ± 4.24 vs 18.54 ± 4.08; $p = 0.97$ in arm A and B respectively and was similar. 7-day (44.8% {13/29} vs 68% {17/25}; $p = 0.09$) and 30-day (37.9% {11/29} vs 64% {16/25}; $p = 0.058$) transplant free survival in arm A and B respectively and showed a higher transplant free survival at 30 days in the combination arm.
Conclusion: Our study showed that combination therapy with PLEX and CRRT shows promising outcomes and a trend towards improved 30-day transplant free survival compared to PLEX.

THU-199

Evaluation of different large language models' performance in answering common questions from drug-induced liver injury patients

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Background and aims: Large language models (LLMs) are gaining increasing attention due to their information retrieval capability and ability to generate human-like responses. Drug-induced liver injury (DILI) is a common yet often overlooked disease closely linked to individual medication habits, underscoring the importance of patient education and knowledge support. Therefore, LLMs have the potential to serve as an effective tool for addressing common questions from DILI patients. We evaluated the performance of six major LLMs (LLaMA-3.1, GPT-o1, Claude-3.5, GPT-4.0, Gemini-1.5, GPT-3.5) in delivering accurate responses to common DILI-related queries.
Method: In this study, we collected twenty-eight DILI-related questions frequently asked by patients, which can be categorized into six domains: pathogenesis, risk factors, clinical presentation, diagnosis, treatment and prevention, and prognosis. LLMs were used to generate responses to these questions, which were subsequently evaluated by three consultant-level hepatologists in accuracy,

comprehensiveness, helpfulness and safety. To minimize potential bias, we concealed identifiable features specific to individual LLM-chatbots, randomly shuffled and masked responses before evaluation. Accuracy was graded on a three-point scale (poor, borderline, good), and comprehensiveness, helpfulness and safety were graded on five-point Likert scale. Flesch-Kincaid Grade Level was employed to evaluate the readability.
Results: LLaMA-3.1 demonstrated superior accuracy, with 70.2% of responses graded as 'good', compared to 52.4% in GPT-o1, 31.0% in GPT-4.0, 28.6% in Claude-3.5, 25.0% in Gemini-1.5 and 7.1% in GPT 3.5. (adjusted chi-square, all $p < 0.01$). LLaMA also outperformed others in comprehensiveness (mean score: LLaMA-3.1: 3.86; GPT-o1: 3.49; Claude-3.5: 3.00; GPT-4.0: 2.98; Gemini-1.5: 2.66; GPT-3.5: 2.04, out of a maximum score of 5) and helpfulness (mean score: LLaMA-3.1: 3.92; GPT-o1: 3.71; Claude-3.5: 3.25; GPT-4.0: 3.03; Gemini-1.5: 2.95; GPT-3.5: 2.26, out of a maximum score of 5). All LLMs performed well in safety except for GPT-3.5 (mean score: LLaMA-3.1: 4.02; GPT-o1: 3.80; Claude-3.5: 3.54; GPT-4.0: 3.45; Gemini-1.5: 3.49; GPT-3.5: 2.93, out of a maximum score of 5). As for readability, Gemini-1.5 performed best (mean score: GPT-3.5: 14.16; GPT-o1: 13.91; GPT-4.0: 13.72; LLaMA-3.1: 13.4; Claude 3.5: 12.94; Gemini-1.5: 12.49).
Conclusion: Our study highlights the potential of LLM-chatbots, especially LLaMA-3.1, in delivering accurate, comprehensive, helpful and safe responses to common DILI-related queries. LLMs can serve as effective and safe tools for medical consultation and patient education in DILI.

THU-200
Checkpoint inhibitor-induced liver injury in patients with advanced skin cancer: a single center experience
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Background and aims: Today, immune checkpoint inhibitors (ICIs) are first-line therapy for advanced melanoma and non-melanoma skin cancers. Checkpoint inhibitor-induced liver injury (ChILI) is one of the most common adverse effects (AE) widely reported, with an estimated prevalence of around 10% of patients. In patients who develop ChILI it is currently still unclear whether it is needed to discontinue the drug definitely or whether it is possible to safely re-start the same drug after temporary suspension.
Method: By a retrospective study, we enrolled all consecutive patients admitted to the Dermatology Unit at our center, who underwent ICI therapy for advanced melanoma or non-melanoma skin cancer from June 2016 to April 2024. Diagnosis and severity of ChILI were assessed according to CTCAE v5.0, type of liver injury was defined according to international guidelines. Liver function tests (LFTs) at baseline, after three cycles of therapy, and at ChILI suspicion were retrieved. ChILI management and outcome were retrieved.
Results: We enrolled 111 patients (32.4% female, median age 75 years), 70 (63.1%) patients bearing advanced melanoma, and 41 (36.9%) with locally advanced or metastatic skin squamous cell carcinoma. 3 (2.7%) underwent first-line therapy with anti-CTLA4, 106 (95.5%) with anti-PD1, and 2 (1.8%) with a combination of them. Median therapy duration was 10 months (IQR 5–21). 8 (7.2%) patients developed ChILI after a median of 14 infusions (IQR 7–20). 1 presented grade 2, 3 grade 3, and 4 grade 4. Among patients who developed ChILI, 3 showed anti-nuclear antibody positivity (ANA), 1 showed positive extractable nuclear antigen (ENA) test, and in 2 patients an autoimmune disorder was already known at the beginning of ICI's therapy. All patients stopped ICI, in 5 of them we assisted to a spontaneous and complete LFTs normalization, while in 3 of them steroid therapy was added. No patients underwent drug rechallenge. 2 patients started a different class of ICI without evidence of early or late toxic recurrence. Among the more common extrahepatic AE, ChILI patients showed diarrhea and dermatological papular or bullous rash (37.5% and 50% respectively), with a prevalence significantly higher when compared with no-CHILI patients (7.8% and 15.4% respectively, $p < 0.05$). Comparing patients who developed ChILI with patients who did not, baseline and 3rd infusion LFTs were not significantly different ($p > 0.05$).
Conclusion: The median time of ChILI onset, after multiple cycles of treatment, seems to confirm an indirect mechanism of liver damage rather than toxic direct action. Interestingly, we observed that patients who developed ChILI were those at higher risk of dermatological and/or gastrointestinal AE. Although this observation was conducted on a small sample of patients, it may represent a useful tool for clinicians to prevent the possible onset of ChILI, avoid severe clinical scenarios, and provide early treatment.

THU-205
Increased risk of hepatic steatosis in young adults treated for first-episode psychosis; a retrospective study
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Background and aims: Psychotic disorders in young adults are associated with an increased risk of cardiometabolic complications, to which exposure to antipsychotics contributes. However, little is known about the evolution of liver health in these young adults. We aim to describe the risk of hepatic steatosis over time in young adults followed in a first-episode psychosis program (FEPP).
Method: This retrospective study included 70 young adults followed in a FEPP. Clinical parameters [weight, height, waist circumference, body mass index (BMI)] and biochemical parameters (lipid profile, blood glucose, hemoglobin A1c, renal and liver function markers, etc.) were measured on admission to the FEPP and during follow-up. Based on the estimated results of the Fatty Liver Index (FLI)–a validated predictive score for hepatic steatosis–young adults were individually classified over time as being at low (<30), moderate (30–59) or high (>60) risk of hepatic steatosis.
Results: On admission, the cohort (36% female, mean age 26 ± 5 years) had a BMI of 26.8 ± 7.4 kg/m^2 and a mean FLI of 44.8 ± 32.2. On average, at 14 months follow-up, the FLI score increased to 61.2 ± 33.0. This deterioration was not detectable nnnby liver enzyme monitoring but was associated with an increase in anthropometric parameters (weight, waist circumference and BMI). Exposition to olanzapine, aripiprazole or quetiapine is associated with a higher FLI and cardiometabolic risk.
Conclusion: These results describe an increase over time in the risk of hepatic steatosis in young people experiencing a first psychotic episode, possibly related to the cardiometabolic deterioration following the introduction of psychiatric pharmacotherapy. Better understanding of the hepatic risks associated with psychotropic medication and of the psychotic disorder itself is essential to minimize possible hepatic complications in young people experiencing a first episode of psychosis.

THU-206
Plasma exchange to treat severe acute liver injury: opportunity to improve native liver survival
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Background and aims: Plasma exchange (PLEX) improves survival in patients with phosphorus rodenticidal hepatotoxicity (RH) and paracetamol overdose. In a prior report, no patient with RH who met 'Kochi' criteria (Model for End Stage Liver Disease score ≥36 or baseline International Normalized Ratio ≥6 with hepatic encephalopathy) for urgent liver transplantation survived with medical management alone (PMID: 26310868). Survival benefit with PLEX, reported in a randomized controlled trial from Europe (PMID: 26325537), was not seen in a recent UK study comprising mostly patients with cardio-respiratory failure (PMID: 39362282). In this study, we aim to define an effective window for the utility of PLEX as a stand-alone treatment in patients with RH-induced severe acute liver injury/ failure (sALI/ ALF). We also aim to assess dynamic parameters which can help listing for rescue liver transplant.
Method: Patients with RH from 2014 to 2024 managed in our department were included in this study. We analyzed outcomes in patients (sALI and ALF) who met 'Kochi' criteria, were not on cardio-respiratory support, and were treated with low-volume PLEX earlier in the course of the illness. We also assessed the progression from sALI to ALF. ΔMELD (PMID: 39001974) was calculated as a percentage change from baseline values after the third PLEX session (or last session if < 3 sessions were done). Post–PLEX samples were collected ≥12 hours after completion of each session.
Results: Of 216 consecutive patients with rodenticidal hepatotoxicity managed in our department between January 2014 and August 2024, 130 patients (75 sALI, 55 ALF prior to PLEX) were treated with low-volume PLEX. No patient had liver transplantation. Thirty–three RH patients (age: 21, 7–70 years; F: 64%; sALI: ALF: 19:14; King's College criteria:11/14 ALF patients; 78.6%), who met 'Kochi' criteria and were not on cardio-respiratory support, underwent 3 (2–8) PLEX sessions with 1100 (750–2000) ml volume exchanged per session. In these PLEX–treated patients, 1-month transplant-free survival was 27/ 33 (82%). Patients with ΔMELD decline ≥20% after PLEX had better survival (24/25 v/s 3/8; p-value: 37.5%) and had lesser progression to ALF (2/14 v/s 4/5; p-value: 0.006) vis-à-vis patients who fail to achieve this threshold.
Conclusion: PLEX improves survival in patients with severe RH requiring transplant listing but with preserved cardio-respiratory function. Post-PLEX (day 3) ΔMELD decline < 20% predicts non-response/ worse outcome and can be used to prognosticate/ consider rescue liver transplant.

Alcohol-related liver disease and MetALD – Basic

TOP-474

Bio-molecular characterization of albumin identifies predictors of disease severity and early mortality in severe alcohol associated hepatitis

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Background and aims: Albumin modifications are critically linked with the pathophysiology of severe alcohol associated hepatitis (SAH). Bio-molecular and functional characterization of albumin could help in identification of signatures which can predict early mortality in SAH patients.
Method: Purified plasma albumin from SAH patients (n = 351), alcohol associated cirrhosis (AC, n = 11) and healthy controls (n = 20) was analysed for modifications, functionality, and bound multi-omics signatures (proteins, metabolites, lipids and bacterial peptides). Results of training cohort (n = 131; SAH non-survivors, n = 25; SAH survivors, n = 75; AC, n = 11; healthy controls, n = 20) were tested in the validation cohort (n = 251; 147 SAH-Survivors and 104 Non-Survivors) using High Resolution Mass Spectrometry (HRMS) and machine learning (ML) approach.
Results: Bio-molecular signatures of SAH were distinct with high albumin oxidative state and human non mercapto-albumin 2 levels (HNA2, $P < 0.05$). Albumin bound Multiomics signatures of SAH were distinct as compared to other groups. In SAH non-survivors, albumin was linked to hyper-inflammatory proteins and fatty acid beta-oxidation metabolites. Non-survivors had specific increase in bacterial taxa (Nitrospirota, Mycoplasmatota, and others) correlated with lipids (Cer(d17:1/6:0), TG (11:0/10:0/18:0), and others) and metabolites (C04284, C16525,and others, $R^2 > 0.7$). Albumin bound multi-omics signature-based probability of detection (POD) for non-survival was >90% and correlated with functional and clinical parameters ($R^2 > 0.85$). Top albumin-bound metabolome pannel: Eicosanoic acid, Docosahexaenoic acid, Neuraminic acid, Icosadienoic acid and 2-Heptyl-4-hydroxyquinoline-N-oxide had diagnostic accuracy of 98% and segregated SAH patients predisposed to early mortality (log-rank<0.05). On validation (HRMS, 5-ML algorithm) we affirm that SAH patients with greater change in albuminome, specifically with higher binding of metabolome panel had higher probability of early mortality (w > 90% accuracy/sensitivity/p-value).
Conclusion: In SAH, albumin is severely hyper-oxidized and dysfunctional. Our findings show that significant changes in albumin, indicated by elevated metabolome panel interactions, was able to segregate SAH patients predisposed to early mortality.

THURSDAY 08 MAY

THU-479-YI

Plasma exosome antigens as prognostic biomarkers in alcohol-associated hepatitis

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Background and aims: Plasma exosomes represent an intercellular communication in which the donor cell defines the composition of

the surface antigen. Alcohol-associated hepatitis (AAH) is one of the most severe clinical stages of alcohol-associated liver disease. The characterization of exosome surface antigens may reflect the main immune mechanisms involved in the pathogenesis of AAH. The aim of this study is to characterize the profile of exosomes through the expression of surface antigens in a cohort of patients with AAH and to correlate these values with soluble plasma molecules and clinical events.

Method: Patients with a diagnosis of severe AAH (MELD score > 20) who were admitted to Hospital Santa Creu i Sant Pau, between 2020–2024, were consecutively and prospectively included. Blood samples were collected prior to the initiation of corticosteroid treatment to characterize plasma exosomes. Characterization of surface antigens was performed using conventional flow cytometry with the MACSPlex kit, and soluble plasma molecules were analyzed using ELISA.

Results: A total of 46 patients with AAH were included. Quantification of exosomes was performed by Nanoparticle Tracking Analysis (NTA). The quantity of exosomes by NTA was significantly higher in patients with AAH compared to a control group of 15 healthy donors (HDs). The surface antigen profile expressed by plasmatic exosomes of AAH patients also differed from that of HDs. Patients with AAH exhibited 14 surface antigens with lower expression and 8 with higher expression compared to HDs ($p < 0.05$), and the correlation between these antigens was different between AAH versus HDs. The mean fluorescence intensity (MFI) of CD3 and CD56 was significantly higher in those with AUDIT scores >15 ($p < 0.05$), and the MFI of CD105 was positively correlated with years of alcohol use disorder (r: 0.39, $p = 0.026$). Regarding clinical complications associated to AAH, the MFI of CD20 and CD2 differed between AAH patients with infections and those without an infection. Similarly, the MFI of CD40 and CD146 was correlated with creatinine levels and distinguished between patients who developed acute kidney injury and those who did not. The MFI of CD14, CD25, and CD41b was correlated with systemic inflammatory molecules including interleukin-6 and C-Reactive Protein ($p < 0.05$). The combination of higher levels of CD49e and Ssea4 significantly predicts response to corticosteroid with an AUC 0.847 (CI 0.706–0.988, $p < 0.001$). Combination of CD19 + CD105 + Mcsp significantly predicts mortality in AAH patients with an AUC 0.834 (CI 0.667–1, $p < 0.001$).

Conclusion: Plasma exosomal surface antigens, likely derived from endothelial, monocyte, and platelet activation, are non-invasive markers that could be used to identify those patients with AAH at higher risk of clinical complications, poor response to corticosteroids, and lower survival during follow-up.

THU-481

Gut microbiota derived immunological signature in metabolic alcohol associated liver disease

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Background and aims: Liver has been known as an immune organ rich in innate immune cells and exposed to nutrients and endotoxins derived from the gut microbiome. Mucosal-associated invariant T (MAIT) cells are activated and initiate immune responses when their T cell receptor recognizes the riboflavin metabolite (5-OP-RU) derived from bacteria, presented by MR1, under co-stimulatory signals from specific cytokines or toll-like receptors. Although MAIT cells play a central role in various diseases, studies on the gut microbiome related to the function of MAIT cells are still lacking in metabolic alcohol associated liver disease (MetALD). We aimed to demonstrate the role of *Phocaeicola dorei* (with high riboflavin secretion) and *Bifidobacterium breve* (with low riboflavin secretion) in the MetALD model.

Method: A total of 98 human blood samples [healthy control: n = 8, metabolic dysfunction-associated steatotic liver disease (MASLD): n = 19 and MetALD (hepatitis: n = 16 and cirrhosis: n = 55)] were collected for flow cytometry analysis. Six-week-old male C57BL/6J mice were divided into four groups [n = 9 /normal control, n = 12 /group; Western diet (WD)+EtOH, WD+EtOH+*P. dorei*, WD+EtOH+*B. breve* (10^9 CFU/ 100ul by oral gavage 3 times a week for 20 weeks)].

Results: The expression of CD69 and CD25, activation markers of MAIT cells, was significantly increased in MASLD and MetALD patients compared to healthy controls (CD69: 33.3% vs. 30.1% vs. 1.6%, CD25: 5.7% vs. 7% vs. 1.5%). Importantly, the expression was significantly lower in cirrhosis compared to hepatitis (CD69: 24.6% vs. 49.1%, CD25: 6% vs. 10%). In patients with MetALD, serum albumin levels, which decrease with liver damage, showed a positive correlation with the frequency of CD69+ MAIT cells ($r = 0.3683$, $p = 0.0016$). In the MetALD mouse model, *P. dorei* supplementation significantly decreased the frequency of MAIT cells (3.54% vs. 1.95%) and significantly increased the frequency of CD69+ MAIT cells (24.6% vs. 49.6%) compared to the WD+EtOH group. In contrast, *B. breve* supplementation significantly decreased the frequency of CD69+ MAIT cells compared to *P. dorei* (21.1% vs. 49.6%). Furthermore, *P. dorei* or *B. breve* supplementation significantly decreased the expression of CCL5 and CXCR3, which play an important role in immune cell migration and inflammatory response, compared to the WD+EtOH group. The expression of CXCR3, IL-17, and PD-1 was also decreased in CD69+ MAIT cells isolated from mouse liver tissue.

Conclusion: P.dorei suppresses inflammatory responses, alleviates liver damage, and contributes to regulating immune balance in the liver through activation of MAIT cells.

THU-482

Outcomes in a real-world patient group started on Acamprosate for alcohol use disorder (AUD) with co-existent advanced fibrosis: adherence, efficacy and clinical impact over 24 months

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Background and aims: In England, rates of alcohol-associated mortality have been generally increasing in men and women for decades. Despite this, there are no internationally agreed upon guidelines for the conduct of clinical trials in Alcohol Use Disorder (AUD) and the majority of trials for pharmacotherapy in AUD have relatively low patient numbers. We aimed to retrospectively review patients reported to have been started on Acamprosate to report on real-world outcomes at a 2-year time-frame to further develop our understanding of pharmacotherapy use for this complex patient group specifically looking at adherence, efficacy and clinical outcomes including delta change in liver stiffness, GGT and ED attendances. Here we report on a sub-group of patients who were shown to have advanced fibrosis around the time of Acamprosate initiation.

Method: A search tool was used to identify Acamprosate initiation from clinic letters written by the Alcohol Care Team (ACT) at large hospital in England. Electronic patient records were subsequently cross-referenced for serial biomarkers, FibroScan© results and manual review by a clinician and a pharmacist of clinic letters additional systems allowed capture of alcohol status at 3,6,12 and 24 months following the initiation. Additional captured data included; duration of Acamprosate prescription, reason for cessation and additional/alternative pharmacotherapy prescription.

Results: 122/1634 patients had an FibroScan >11.0 kPa. 67 of these FibroScans were performed within 90 days of the initiation of Acamprosate and therefore have been included in this report.

46/67 were male. 40/67 were compliant with pharmacotherapy at 3 months. 32/67 (48%) were abstinent at 3 months, 29 (92%) were adherent to acamprosate. 10/67 had reduced their alcohol consumption, 8 (80%) were adherent to acamprosate, 13/67 reported no reduction in alcohol use but only 4 (30%) were adherent. 12 patients (17%) had already been lost from service by the 3 month mark. Clinical parameters all showed positive delta change over the subsequent 2-year period with acamprosate/alternative pharmacotherapy compliance. Only 9 of the initial 40 patients adherent to acamprosate, and 19/67 (28%) patients in this group reported ongoing abstinence/reduction in alcohol use at 24months.

Conclusion: There is a clear improvement in biochemical markers and liver stiffness if adherent to pharmacotherapy as expected and a reduction in ED attendances. Acamprosate appears to be as well tolerated in advanced liver stiffness as in other groups. Short-term efficacy and safety of acamprosate appears good however reduces over time. The key problems this data presents therefore is 1) how to maximise engagement from the outset and 2) how to maintain patient engagement over time. It is possible this large and chaotic patient group likely demand a higher amount of clinical support than they are currently receiving.

THU-483

Potential therapeutic target for the treatment of alcohol-related liver disease through magnesium homeostasis

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Background and aims: Excessive alcohol consumption represents one of the main causes of chronic liver disease and liver-related mortality in Western countries. It has been reported that prolonged alcohol exposure leads to an impair in Magnesium (Mg^{2+}) homeostasis, decreasing Mg^{2+} serum levels and increasing Mg^{2+} excretion into the urine. This disorder is known as hypomagnesemia and aggravates disease progression. In this study, we investigate the role of Mg^{2+} in alcohol-derived liver disease (ALD), to find a potential therapeutic target.

Method: We have confirmed that ALD patients as well as preclinical mouse model of Chronic and binge ethanol feeding (the NIAAA model) possess a decrease in Mg^{2+} serum levels. Moreover, we have identified that the Mg^{2+} transporter Cyclin M4 (CNNM4) is upregulated under ethanol stimuli in ALD patients and in preclinical NIAAA model, acting as a Mg^{2+} extruder in the liver. For the preclinical studies, WT mice were treated with the NIAAA model for 11 days. At 3rd day, EtOH-fed mice were divided into two groups. One group was injected subcutaneously with GalNAc *Cnnm4* siRNA technology, which silenced *Cnnm4* specifically in the liver. At day 11, EtOH-fed mice and pair-fed mice were gavaged in the early morning with a single dose of EtOH or isocaloric maltose dextrin respectively. Mice were euthanized 9 hours after gavage.

Results: We proposed a new therapeutic target to treat the damage caused by ethanol consumption by specifically modulating the expression of CNNM4 in the liver through GalNAc siRNA technology. The effect of *Cnnm4* silencing was evaluated in primary hepatocytes and in the preclinical mouse NIAAA model. GalNAc si*Cnnm4* restored Mg^{2+} levels to baseline, improving mitochondrial dysfunction and reducing endoplasmic reticulum stress associated with this pathology. On the other hand, silencing *Cnnm4* restored the expression levels of the methyltransferase enzyme Protein L-Isoaspartate O-Methyltransferase (PCMT1), whose main role is the repair of alcohol-induced protein damage. To corroborate this finding, we silenced *Pcmt1 in vitro* and in the NIAAA model in the presence of GalNAc si*Cnnm4*, and we observed that si*Pcmt1* inhibited the therapeutic effect of GalNAc si*Cnnm*4.

Conclusion: Magnesium homeostasis disruption worsens the prognosis of ALD, and the restoration of hepatic Mg^{2+} levels through GalNAc si*Cnnm4* reverses alcohol-induced damage. Furthermore, GalNAc si*Cnnm4* therapy enhances the repair of alcohol-damaged proteins by increasing PCMT1 activity, offering a new therapeutic approach for the treatment of this disease.

THU-484

Digital pathology biomarkers describe fibrosis severity and disease activity in the FAT-MASH murine model and response to preventative treatment with mannose

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Background and aims: Current histological staging methods used to quantify fibrosis severity and disease activity in metabolic dysfunction-associated steatohepatitis (MASH) are semi-quantitative and subject to poor intra and inter observer variability. We report on use of multiple analogous continuous quantitative digital pathology biomarkers to describe the effects of mannose supplementation on fibrosis and MASH activity.

Method: We used the FAT-MASH model (doi:10.1016/j.jhep.2018.03.011). 43 mouse liver samples were histologically prepared for PSR and H&E and scanned at 40X. Study groups: normal diet (n = 4), MASH diet (high fat, fructose, cholesterol, and low-dose carbon tetrachloride) for 6 weeks (n = 5) or 12 weeks (n = 9); MASH diet for 12 weeks with mannose supplement at 5% (n = 8) or 20% (n = 9) starting at week 0 (prevention arm) or at 5% (n = 4) or 20% (n = 4) starting at week 6 (therapy arm). Development of the Digital Pathology and AI biomarker for fibrosis severity (Ph-FCS), steatosis burden (A%, macro-steatosis area ratio%), hepatocytes with steatosis (SHD, count/mm²), Inflammatory Cells Density (ICD, count/mm²), and Inflammatory Cells Ratio (IC%, % total cells) is described in doi:10.3390/ijms24108494 and doi:10.1101/2024.01.17.576067. The

PT-prefix normalizes biomarkers to the steatosis-free parenchymal tissue area.
Results: During the induction of the 12-week disease stage, the 6-week timepoint was characterized with different relative change (R-Change, 12w change accounting for 100%) showcasing the initial activation of inflammation (PT-ICD, 65.9% R-Change, IC% 79.0% R-Change,) and initial steatotic burden (A%, 59.8%) along with hepatocytes steatotic involvement (SHD, 75.0% R-Change). Fibrosis progression was secondary to these events with a 6-week relative change of 18.2% of Ph-FCS. These different phases were described with other biomarkers in DOI: 10.1016/j.jhep.2018.03.011. The prevention reduced steatosis burden (A%, −43.4% less than the 12-week regimen with 5% and −69.5% for 20% mannose) and for hepatocytes with steatotic involvement (SHD, −20.3% and −64.8% respectively). Inflammatory biomarkers demonstrated opposite behaviors at 5% and 20% mannose (PT-ICD, −36.7 and +11.9%, IC%, −26.7% and +15.2%) showing that mannose supplementation at 20% exacerbated inflammation while significantly reducing steatosis. The 5% mannose supplementation arm was more protected for fibrosis progression than the 20% Arm (PT-FCS, −8.0% and −0.7%).
Conclusion: Digital pathology biomarkers calculated from H&E and PSR digital images provide a holistic quantification of the MASH disease severity and activity and related treatment effects, showcasing only low doses of mannose (5%) dampen inflammation, steatosis and fibrosis severity in a rodent model.

THU-485
Prevalence, genetic risks, and cardiovascular outcomes of Met-ALD in a longitudinal multiethnic U.S. cohort

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Background and aims: Met-ALD is a newly described entity where steatotic liver disease (SLD) occurs in individuals with both metabolic risk factors and moderate alcohol consumption. Its prevalence, genetic architecture, and outcomes are yet to be fully understood. We compared the prevalence, genetic background, and cardiovascular outcomes of Met-ALD to MASLD in a large multiethnic longitudinal cohort in adults in the United States.
Method: We examined the prevalence of MASLD and Met-ALD in the Multiethnic Study of Atherosclerosis (MESA) cohort at baseline (N = 5182, non-Hispanic White (NHW): 2284. non-Hispanic Black (NHB): 1530, Hispanic: 1368). Hepatic steatosis was defined as liver attenuation < 51 HU and/or liver to spleen < 1 on CT imaging. MASLD and Met-ALD were defined using modified AASLD criteria. We examined the association between 5 selected SLD and cirrhosis polygenic risk scores (PRS) were derived based on recent publications by Chen et al., Emdin et al., Whitfield et al., Schwantes-An et al., and Vujkovic et al. and MASLD and Met-ALD. We also examined the association between MASLD and Met-ALD and prevalent subclinical atherosclerosis measured by coronary artery calcium (CAC) presence and incident cardiovascular events (CVD). We used logistic regression models for the cross-sectional analyses, and cox-proportional hazard models for the longitudinal analyses, controlling for age, gender, and race/ethnicity.
Results: The prevalence of MASLD and Met-ALD WAS 15.1% and 1.3%, respectively. The prevalence of MASLD in NHW, NHB, and Hispanic participants was 11.78%, 11.18%, and 24.8%, whereas the prevalence of Met-ALD among NHW, NHB, and Hispanic participants was respectively. All 5 PRS were significantly associated with MASLD but PRS-Chen (estimate 0.45, p = 7.44E-31) and PRS-Whitfield (estimate 0.39, p = 1.91E-23) had higher estimates than others. Similarly, all 5 PRS were associated with Met-ALD but PRS-Chen (estimate 0.49, p = 3.30E-05) and PRS-Schwantes-An (estimate 0.42, p = 5.28E-04) had higher estimates than others. Both MASLD (OR: 1.58, 95% CI 1.32–1.88, p = 3.55E-07) and Met-ALD (OR: 2.19, 95% CI 1.24–3.84, p = 0.006) were associated with prevalent CAC. MASLD was significantly associated with incident CVD (HR: 1.29, 95% CI: 1.08–1.55, P = 0.0048) whereas Met-ALD had borderline association with incident CVD (HR: 1.56, 95% CI: 0.95–2.57, P = 0.077).
Conclusion: Prevalence of Met-ALT was low in MESA participants, but it appeared to exhibit genetic risks and cardiovascular risks comparable to MASLD.

THU-486
The anticoagulant Edoxaban improves portal hypertension and liver injury in progressive liver disease

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Background and aims: A novel treatment approach in the field of liver disease is the inhibition of protease-activated receptors (PARs). The PAR agonists thrombin and Factor Xa (FXa) can cause liver sinusoidal microthrombosis, activation of hepatic stellate cells, and increased inflammatory cell recruitment. In this study we investigated the effect of the direct oral anticoagulant Edoxaban, which inhibits FXa, in mouse models of progressive and regressive liver disease.
Method: Liver fibrosis was induced in male wildtype C57BL/6 mice by oral gavage of carbon tetrachloride (CCl4, 2 ml/kg, 3x/week) for 12 weeks (Peak). Healthy control animals received olive oil gavage (Ctrl). In the first treatment group, animals were treated with Edoxaban (10 mg/kg) twice daily during the last 2 weeks of CCl4 disease induction (i.e., during disease progression). The second treatment group received Edoxaban for 2 weeks following CCl4 cessation in regressive liver disease. We measured portal pressure (PP), collagen proportionate area (CPA) for fibrosis, and AST/ALT for liver injury severity. Furthermore, bulkRNA-Sequencing of liver tissue was performed and analysed using DESeq2 and GSEA.
Results: Compared to Ctrl, animals at peak disease severity showed significantly higher levels of fibrosis (CPA: 9.36 ± 2.72 vs. 1.54 ± 0.23%), portal hypertension (PP: 9.06 ± 0.89 vs. 5.67 ± 0.89 mmHg) and liver injury (median AST: 1341 vs 17 U/L; median ALT: 1882 vs 12 U/L) (all p < 0.05 vs Ctrl). Administering Edoxaban in disease progression significantly ameliorated portal pressure (7.22 ± 1.23 mmHg) and liver injury (median AST: 343 U/L; median ALT: 637 U/L) when compared to Peak (all p < 0.05 vs. Peak), while CPA remained unaffected. In disease regression, Edoxaban treatment did not induce significant improvements in portal pressure, liver injury or CPA. Differential gene expression analysis confirmed an upregulation of epithelial to mesenchymal transition (EMT) and inflammatory

pathways, including TNFa signaling via NFkB and IL-6/JAK/STAT3 signaling in Peak. Metabolic pathways, such as oxidative phosphorylation, bile- and fatty acid metabolism were downregulated in Peak compared to Ctrl. In animals treated with Edoxaban during disease progression, a downregulation of both EMT and inflammatory signaling could be observed, while metabolic pathways were upregulated compared to Peak.
Conclusion: Edoxaban treatment in progressive liver disease resulted in significantly ameliorated portal hypertension and liver injury. BulkRNA-Seq confirmed the role of Edoxaban in reducing inflammatory and EMT signaling and improving liver function, as indicated by the upregulation of metabolic pathways.

THU-487

Liver-targeted mRNA therapeutics through fibroblast growth factor 21 and apolipoprotein A1 delivery in experimental acute pancreatitis

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Background and aims: Acute pancreatitis (AP) presents significant clinical challenges with limited treatment options. Clinical studies suggest that elevated fibroblast growth factor 21 (FGF21) during AP may act as a defense mechanism. Liver-targeted lipid nanoparticles (LNP) delivering mRNA therapy harness the liver's natural protein production capacity. Our study investigates FGF21 and APOA1 mRNA-based therapies, alone and combined, using liver-targeted LNPs to enhance therapeutic efficacy in experimental AP models. Targeting the liver, the main source of circulating APOA1 and nascent HDLs, could restore FGF21 and HDL functionality, often impaired in metabolic and inflammatory conditions, offering a novel therapeutic avenue.
Method: We developed LNP-mRNA formulations encoding FGF21, APOA1, and a chimeric APOA1-FGF21. Protein expression and bioavailability *in vitro* and in high-fat diet-fed mice were assessed. Efficacy was evaluated in the caerulein-induced AP (Cer-AP) model, and the ethanol feeding and binge NIAAA model plus palmitoleic acid administration (EtOH/POA-AP). Serum levels of pancreatic lipase (LIPC), amylase (AMYL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), along with histopathological analyses, were conducted to assess treatment effects. IL-1β serum levels were determined 12 h post-AP induction by ELISA. Liver *Ho1* and *Ppara* expression were analyzed via qPCR in the EtOH/POA-AP.
Results: In vitro studies demonstrated the translation and secretion of APOA1, FGF21, and APOA1-FGF21 proteins encoded by the LNP-mRNAs. In vivo, LNP-mRNA administration increased serum levels of the respective proteins in metabolically impaired (i.e., high-fat diet-fed) mice. In the Cer-AP model, LIPC and AMYL serum markers of pancreatic injury were similarly reduced when mice were treated with APOA1, FGF21, and APOA1-FGF21 LNP-mRNA; this effect was also observed in the histopathological analyses. In the more aggressive EtOH/POA-AP model, FGF21 and APOA1-FGF21 LNP-mRNAs were protective, as evidenced by lower LIPC and AMYL serum levels, while APOA1 LNP-mRNA had minimal impact. However, histological improvements were more evident in mice receiving APOA1 LNP-mRNA. FGF21 and APOA1-FGF21 LNP-mRNAs reduced serum AST and ALT levels, indicating hepatoprotective activity. In the Cer-AP model, serum IL-1β decreased 12 h post-induction in mice treated with APOA1, FGF21, and APOA1-FGF21 LNP-mRNAs. Finally, EtOH/POA-AP model, FGF21 and APOA1-FGF21 LNP-mRNAs reduced liver Ho1 expression, while APOA1-FGF21 LNP-mRNA increased liver Ppara expression, suggesting enhanced hepatoprotection.
Conclusion: This proof-of-concept study shows the potential of mRNA-based therapies delivering FGF21 and APOA1 in experimental AP. Liver-targeted LNP-mRNA delivery of FGF21 and APOA1 improved experimental AP, underscoring their potential as innovative treatment options for AP.

THU-488

A new translational dietary rat model allows studying MetALD natural history and assesing the efficacy of various therapeutic interventions

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Background and aims: Metabolic and alcohol-related liver disease (MetALD) was recently proposed as a distinct entity. However, the natural history and optimal therapy for MetALD are still largely unknown. During the last decade, glucagon-like peptide-1 receptor agonists (GLP-1) have been under evaluation for metabolically-induced liver injury, and recently trials have started in ALD. Our primary aim was to test various interventions in a new rat model of MetALD. Secondary objectives included defining the features of MetALD and comparing them to those of MASLD.
Method: To carry out this study, male Sprague Dawley rats were subjected to 20 weeks of dietary intervention consisting of a high-fat diet supplemented with 2% cholesterol and 0.1% cholate, along with a glucose-fructose beverage (HFD/GF) and/or alcohol (HFD/GF+OH). Three different groups were defined: Control group (Chow diet; n = 12), MASLD group (HFD/GF; n = 12) and MetALD group (HFD/GF+OH; n = 96). After 16 weeks, the MetALD group was divided into four subgroups to undergo different interventions for the last 4 weeks consisting on: (1) no intervention (MetALD group; n = 24), (2) dietary intervention (DI; n = 24), (3) alcohol removal (AR; n = 24), (4) combination of both (DI+AR; n = 24). Furthermore, half of the individuals in each of these subgroups (n = 12) underwent

pharmacological treatment with Semaglutide (GLP-1 receptor agonist). The control and MASLD group did not undergo any intervention. By the end of the model, liver hemodynamics, histological staining, metabolic and biochemical evaluation and gene expression analyses were performed.
Results: Compared to controls, individuals in the MetALD group had significantly higher rates of obesity, dyslipidemia, intrahepatic insulin resistance, fibrosis and portal hypertension (PHT). Rates of advanced fibrosis were higher in the MetALD group compared to MASLD (75% vs. 58.3%) but the difference was not statistically significant, nor was it for PHT. Semaglutide (GLP-1) treatment was associated with significant weight loss in all groups. Dietary intervention (DI) and alcohol removal (AR), alone or combined, led to significant fibrosis regression, but no significant improvement of PHT. All interventions except those without DI led to significant improvements of steatohepatitis. Combining DI + AR was not significantly more efficacious that either both alone in improving liver fibrosis. GLP-1 alone did not lead to significantly improve neither fibrosis nor PHT. DI+GLP-1 led to significant reductions in fibrosis and PHT. The most effective treatment was the combination of DI+AR+GLP-1, for fibrosis and PHT.
Conclusion: Our new model of MetALD comprehensively recapitulates both metabolically and alcohol-induced liver injury, leading to advanced fibrosis and PHT. A combined strategy encompassing DI, AR and GLP-1 appears as the most efficacious to treat MetALD. Further investigations are warranted to elucidate whether GLP-1 has weight loss-independent effects on outcomes.

THU-489

Disruption of receptor-interacting protein kinase 1 post-translational modifications in alcohol-associated liver disease

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Background and aims: Alcohol-associated liver disease (ALD) is the leading cause of advanced liver disease, with limited therapeutic options currently available. Inflammation and cell death pathways are pivotal to ALD pathogenesis. Receptor-interacting protein kinase 1 (RIP1), a component of the necroptotic pathway of cell death, plays a critical role in determining cellular fate in response to death receptor activation. RIP1 function is tightly regulated by post-translational modifications, especially ubiquitination and phosphorylation; these post-translational modifications regulate the balance between pro-inflammatory, pro-survival, and/or cell death signaling in a cell-specific manner. Notably, RIP1 signaling to activate NFκB in hepatocytes is hepatoprotective, whereas in innate immune cells, it drives pro-inflammatory responses. Given this complexity, we aim to investigate the mechanisms and cell-specific roles of RIP1 post-translational modifications in ALD.
Method: Tandem Ubiquitin Binding Entity (TUBE) pull down assays and western blotting were conducted in livers from murine models of ALD, as well as human livers from patients with alcohol-associated hepatitis (AH) and healthy controls (HC), to assess the ubiquitination and phosphorylation status of RIP1. Bulk RNA-seq and single-cell RNA-seq datasets were analyzed for expression profiles of mRNA for proteins involved in ubiquitination and de-ubiquitination of RIP1 in liver and peripheral blood mononuclear cells (PBMCs) from HC and AH patients challenged with lipopolysaccharide (LPS). THP-1 monocytic cells were challenged with LPS alone or in combination with ethanol.
Results: Ubiquitination of hepatic RIP1 was decreased and phosphorylation of RIP1 increased in patients with AH compared to HC. Similarly, RIP1 ubiquitination was decreased in livers of mice exposed to both acute-on-chronic or chronic ethanol. Bulk RNA-seq meta-analysis revealed significant perturbations in expression of mRNA for proteins involved in ubiquitination/de-ubiquitination of RIP1 in livers of patients with AH. Furthermore, single-cell RNA-seq analysis revealed widespread dysregulation in expression of ubiquitination/de-ubiquitination mRNAs in $CD14^+$ and $CD16^+$ monocytes from AH patients compared to HC both at baseline and in response to LPS. Similar alterations were observed in THP-1 monocytes challenged with either LPS alone or combined with ethanol.
Conclusion: Taken together, these data suggest that ethanol disrupts the post-translational modification of RIP1 in the liver and immune cells. Such disruptions may contribute to dysregulation of the downstream signaling pathways contributing to inflammation and cell death in the pathogenesis of ALD.

THU-490-YI

Cytokine release assay QuantiFERON Monitor predicts 90-day mortality in patients with severe alcohol-related hepatitis

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Background and aims: Alcohol-related hepatitis (AH), a severe complication of long-term harmful alcohol use, has a 30% 90-day mortality. More accurate predictors of mortality and infection are needed to help guide patient management. QuantiFERON Monitor (QFM) is a commercially available interferon (IFN)-γ release assay that measure global immune function using whole blood stimulation with innate and adaptive immune ligands. A preliminary single-centre study demonstrated that QFM accurately predicted 90-day mortality and incident infection in patients with AH. This study aimed to validate these findings in a multicentre study.
Method: Consecutive patients with AH (bilirubin >50 µmol/L, coagulopathy, and harmful alcohol use [40 g/60 g ethanol/day in females/males]) recruited to the Multicentre Cohort of AH (MICAH) study at Imperial College Healthcare and University Hospitals Plymouth NHS Trusts, took part in this validation study. Outcomes of survival and development of infection were collected up to day 90. Infection was defined according to NACSELD criteria. A sample of blood was obtained at study baseline and QFM was performed according to manufacturer's instructions. Serum Interferon (IFN)-γ concentration was determined by ELISA.
Results: 46 participants were recruited; 61% male, baseline MELD 20.8. IFN-γ release measured by QFM was significantly higher in survivors compared to non-survivors at day 90 (74.1 vs 4.7 IU/mL; $p < 0.0001$). Area under receiver operating characteristic (AUROC) for QFM was 0.85. Positive predictive value of QFM to predict mortality within 90 days was 77% with a threshold of 15.5 IU/mL. Baseline MELD was significantly lower in survivors compared to non-survivors at day 90 (15.2 vs 24.1; $p = 0.0002$; AUROC 0.81). Using a threshold of 30, the positive predictive value of MELD to predict mortality within 90 days was only 50%. Neither QFM nor MELD was able to differentiate patients with incident infection from those without infection.
Conclusion: Assessment of global immune function measured by QFM accurately predicts 90-day mortality in patients with severe AH. It is superior to MELD in predicting patients at high risk of 90-day mortality. However, it is unable to reliably predict incident infection. This study confirms that QFM could be integrated into clinical

management pathways for AH as a decision tool to guide treatment options.

THU-491

Metabolomic and transcriptomic insights into gender-specific PFAS effects on liver disease

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Background and aims: Per- and polyfluoroalkyl substances (PFAS) are emerging environmental pollutants linked to metabolic disorders, including metabolic dysfunction-associated steatotic liver disease (MASLD). This study investigates the associations between PFAS exposure and MASLD progression, focusing on lipidomic, metabolomic, and transcriptomic biomarkers, functional pathways, and gender-specific responses.
Method: Metabolomic and lipidomic analyses were performed to examine changes in metabolite and lipid composition across steatosis grades (0–3) and between MASH-positive and MASH-negative samples. Transcriptomic data were analyzed using weighted gene co-expression network analysis (WGCNA), with KEGG pathway enrichment for functional insights. Mediation analysis explored whether specific metabolites mediated the association between PFAS exposure and steatosis.
Results: Lipidomic analysis revealed significant shifts in lipid composition with steatosis severity, including increased TG-SFA and TG-MUFA levels in MASH-positive samples and decreased phosphatidylinositol and phosphatidylcholine levels. Gender-specific transcriptomic analysis using WGCNA identified significant modules in both females and males. These modules were significantly negatively correlated with pathways, including arginine biosynthesis, amino acid metabolism, and other related processes in both genders. Metabolomics analysis supported these findings, identifying metabolites negatively correlated with MASLD progression enriched in similar pathways, implicating a disruption in amino acid metabolism with disease progression. Positively correlated transcriptomic modules in females were linked to cell cycle, steroid biosynthesis, and fatty acid metabolism. Furthermore, significant positive correlations were observed between PFAS compounds (e.g., PFUnDA, PFDoDA) and lipids such as phosphatidylinositol, while acylcarnitines showed negative correlations. Mediation analysis showed that specific metabolites partially mediated the relationship between PFAS exposure and steatosis. Phosphatidylinositol mediated the effect of PFHxA ($p = 0.002$), TG-SFA mediated PFHpA's effect ($p = 0.028$), and lactosylceramide (Laccer) mediated PFHpA's effect ($p = 0.004$).
Conclusion: This study provides insights into the molecular mechanisms linking PFAS exposure to MASLD progression, highlighting disrupted amino acid and lipid metabolism and gender-specific responses. Identifying specific metabolites as mediators highlights new targets for addressing PFAS-related liver diseases.

THU-492-YI

Altered high density lipoprotein 3 and associated proteins signatures contribute to immune dysfunction in alcohol associated liver cirrhosis

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Background and aims: Alcohol-associated liver cirrhosis (AALC) is associated with high mortality and involves toxins, gut microbiota imbalance, and immune dysfunction. Enteric high-density lipoprotein subtype 3 (HDL3) is known for its immune-protective role, but its impact on AALC remains unclear. This study explores HDL subclasses and associated protein signatures linked to immune dysfunction and disease progression in AALC.
Method: We included 89 cirrhosis patients (Model for End Stage Liver Disease (MELD) 16 ± 8), including AALC (n = 67, age 45 ± 10 years, all male), non alcoholic steatohepatitis (NASH, n = 15, age 52 ± 9 years, 6 females), and hepatitis B/C virus (HBV/HCV, n = 6, age 47 ± 7 years, 1 female). These patients were monitored for three months post TIPS (trans juglar shunt) for infections, bleeding, and mortality. HDL3 and HDL2 levels (mg/dl) in peripheral (PV), portal (POV), and hepatic (HV) venous blood were measured using enzyme linked immunosorbent assay (ELISA) and compared with healthy controls. HDL3 was fractionated for protein analysis via ultracentrifugation and liquid chromatography mass spectrometry (LC-MS). Immune cell functions were evaluated with flow cytometry and validated by quantitative reverse transcription polymerase chain reaction (qRT PCR).
Results: HDL3 levels were significantly lower in the PV of AALC patients compared to healthy controls ($p < 0.001$), but no difference was observed in NASH or viral hepatitis. HDL2 levels did not differ significantly. HDL3 levels in PV (11.3 ± 5), POV (7.6 ± 3), and HV (8.0 ± 3.8) showed strong intraclass correlation (Lin ' s concordance: 86%). The 3 month mortality post TIPS was 28%, with low HDL3 (< 6.6 mg/dl) predicting poor outcomes (AUC: 0.94, specificity 88.6%, sensitivity 88.4%, $p = 0.001$). Proteomics analysis identified 542 associated proteins, including immunoglobulins, apolipoproteins, and complement proteins. Alcoholic HDL3 had reduced levels of paraoxonase 1 (PON1), apolipoprotein A1 (ApoA1), lipopolysaccharide binding protein (LBP), and sphingosine 1 phosphate (S1P) lyases ($p < 0.001$) but increased apolipoprotein C1 (ApoC1), alpha 1 antitrypsin (AAT), and serum amyloid A (SAA). In vitro studies showed that healthy HDL3 with LBP downregulated inflammatory markers (TLR4, TNFalpha, IL1beta) ($p < 0.05$) and increased IL10 production, whereas alcoholic HDL3 had no such effect. Additionally, alcoholic HDL3 activated T cells (CD3 + CD4 + CD38 +; $p = 0.04$), increased dendritic cells (CD11c + CD80 + CD86 +; $p = 0.03$), and upregulated IL-17A. qRT PCR confirmed increased mRNA levels of IL1beta, TNF alpha, and caspase 3, ($p < 0.05$) while decreased SOD2 and eNOS levels were observed after treatment with alcoholic HDL3.
Conclusion: AALC patients show low HDL3 levels and altered protein profiles, indicating HDL3 dysfunction. Alcoholic HDL3 activates T cells and promotes inflammation. These findings suggest that targeting HDL3 could be a therapeutic strategy to address immune complications and improve outcomes in AALC.

THU-493

Single-cell RNA sequencing and lipidomics identify synergistic effects of alcohol and PNPLA3 I148M on hepatic pathology

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Background and aims: Previous work in the DIAMOND mouse model demonstrated that overexpression of PNPLA3 variant I148M accelerates steatohepatitis through metabolic reprogramming, lipidomic alterations, and inflammation. While its role in diet-induced liver disease has been partly characterized, the interplay between I148M and alcohol exposure remains poorly understood. This study utilized single-cell transcriptomics and lipidomics to investigate the interaction of alcohol with I148M in a mouse model.

Method: MASH was induced in DIAMOND mice via a high-fat diet with ad libitum sugar water (WD). The WD groups were divided into those receiving liver-targeted delivery of luciferase (AAV-luc), AAV-I148M, AAV-luc and alcohol, or AAV-I148M and alcohol. Single-cell RNA sequencing and lipidomic profiling were performed on liver tissues to assess cell type composition, cell type-specific gene expression, and lipid composition. Interaction effects between alcohol and PNPLA3 I148M were identified through differential expression and pathway enrichment analyses. CellPhoneDB was used to assess changes in cell-cell signaling networks.
Results: Alcohol exposure and I148M had synergistic effects on processes linked to cell stress/death, inflammation, steatosis, and fibrosis. These effects were observed as changes in cell type composition, pathway-level gene regulation, lipid profiles, and cell-cell signaling. Together, the two treatments led to a synergistic increase in the Kupffer cell-to-hepatocyte ratio, indicating an increased inflammatory response. Hepatocytes exhibited increased transcriptional regulation of apoptosis and glycogen metabolism pathways, suggesting increased cellular stress. Fibrosis-related cell-cell signaling pathways were also impacted. For instance, collagen-integrin interactions were enhanced between hepatocytes and stellate cells, as well as between cholangiocytes and stellate cells. Lipidomic analysis revealed several lipid species altered by the interaction between alcohol and I148M, including many glycerophospholipids. Notably, an increase in the lipogenic index (the palmitate: linoleate ratio) suggests enhanced de novo lipogenesis.
Conclusion: These findings reveal a critical interaction between alcohol and PNPLA3 I148M, advancing our understanding of the mechanisms driving liver inflammation, metabolic reprogramming, and fibrosis.

THU-494

PNPLA3 risk variant and shortened telomere are independent risk factors for alcohol related liver disease: an indian cohort study

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Background and aims: Alcohol related liver disease (ALD) is primary cause of cirrhosis and contributes to 5.3% of global deaths. However, only 30% of heavy drinkers develop steatohepatitis, suggesting influence of genetic factors in ALD. Chronic alcohol consumption accelerates cellular function decline, which is a hallmark of aging. This study explores the association of PNPLA3(patatin-like phospholipase domain-containing protein 3) I148M (rs738409) genetic variant and leukocyte telomere length in heavy drinkers, with and without liver disease.
Method: ALD (N = 131) and AUD (Alcohol usage disorder, without any underlying liver disease, N = 54) were enrolled. The PNPLA3 genotype was analysed using PCR-RFLP, with validation by Sanger sequencing. Leukocyte telomere length (TL) was quantified through qPCR, expressed as a T/S ratio relative to a standard reference DNA.
Results: The quantity (140.2 ± 79.12 gm vs. 117.7 ± 42.34 gm, p = 0.595) and duration (13.27 ± 6.99 years vs. 15 ± 9.64 years, p = 0.571) of alcohol consumption were comparable between the ALD and AUD groups. PNPLA3 rs738409 CC, CG, and GG genotypes in ALD patients were 35.88%, 47.33%, and 16.79%, with $\chi^2 = 0.0408$, while in AUD it was 59.26%, 38.89%, and 1.85% with $\chi^2 = 0.4046$. PNPLA3 I148M variants (CG and GG) were significantly more frequent in ALD (q = 0.4046) than AUD (q = 0.213) p < 0.01. Univariate regression showed, genotype CG has OR: 2.013 [95%CI: 1.066–4.151], $p = 0.032$ and genotype GG has OR: 13.422 [95%CI:1.709–105.44], $p = 0.014$. Additionally, the telomere length was significantly shorter in ALD compared to AUD subjects (8.53 ± 1.14 vs. 8.97 ± 1.06, p = 0.031). Further, ROC curve analysis for telomere length between ALD and AUD group with an AUC of 0.60 (p = 0.029) suggests that telomere length decreased with age in AUD (r = -0.3, p = 0.029) but not in ALD (r = -0.01, p = .951). A cut-off value of 8.8 for telomere length was obtained by ROC analysis. Based on this cut-off ALD and AUD patients were divided into two groups, Group 1: RTL ≤8 .8 and Group 2: RTL>8.8. A predictive model was created using age and RTL which shows decrease in RTL with age in both the groups ALD = 0.001*Age +8.533 AUD = -0.025*Age+9.987, also using univariate analysis RTL group 1 has (OR: 2.012 [95%CI: 1.029–3.933], $p = 0.041$).
Conclusion: There are 2-fold odds of disease in CG genotype and it increases to 13-fold with GG Genotype. Also, 2 -fold odds of disease with relative telomere length shorter than 8.8. This shows that PNPLA3 rs738409 risk variant and shorter telomere length are associated with alcohol related liver disease.

THU-495-YI

The role of aryl hydrocarbon receptor across different cellular targets in pectin's improvement of alcohol-associated liver disease

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Background and aims: Alcohol-associated liver disease (ALD) is the leading cause of cirrhosis worldwide, with few therapeutic options other than alcohol withdrawal. Intestinal microbiota (IM) plays a causal role in the severity of the disease both in mice and humans. Among metabolites produced by IM, bile acids and tryptophan metabolites are mainly modified in ALD. We previously demonstrated that pectin, a soluble fiber, improves liver and gut injuries in ALD through bile acid metabolism and indoles production acting through the aryl hydrocarbon receptor (AhR) signaling. However, which cellular AhR targets are involved in improving ALD by pectin supplement remains unknown. In this study, we aimed to decipher the role of AhR, specifically in the liver, the intestinal epithelium, myeloid cells, and innate lymphoid cells (ILC).
Method: We established conditional knockout mice models for AhR in hepatocytes ($AhR^{KO\text{-}Alb}$), enterocytes ($AhR^{KO\text{-}villin}$), dendritic cells (DCs), and CD11c expressing macrophages ($AhR^{KO\text{-}CD11c}$), or ILC3 ($AhR^{KO\text{-}Rorgt}$), followed by implementing preventative treatments with pectin in the context of ALD. Then we analyzed liver tissue, ileal and colon tissue, blood, colon, and caecum content samples. Based on metagenomic and metabolomic analyses, we focused on changes in IM, bile acids, and microbiota tryptophan metabolites which are ligands of AhR.
Results: We found that AhR deficiency in hepatocytes or enterocytes worsen the liver injury by increasing the level of alanine transaminase (ALT) and the expressions of inflammation genes, including IL1β, TNFα, CCL2, and CCL3. What's more, pectin reduced liver ALT levels independent of AhR genotypes, but its improvement in hepatic inflammation gene expression was abrogated in mice with $AhR^{KO\text{-}villin}$. Colon flow cytometry showed that pectin reduced cDC2b levels, which was not observed in $AhR^{KO\text{-}villin}$ mice. In $AhR^{KO\text{-}CD11c}$ or $AhR^{KO\text{-}Rorgt}$ mice, they were no worsening of the liver injury in alcohol-treated group, and pectin consistently maintained its protective effect on the liver compared to wild-type littermates. Furthermore, alcohol and pectin supplementation altered the compositions of IM and metabolism independent of genotype.

Conclusion: Our results suggest that AhR expression in enterocytes and hepatocytes plays a protective role in alcohol-induced liver inflammation, conversely to AhR expression in DCs and ILC3. Pectin improves alcohol-induced liver injury in ALD partly through the AhR expression in enterocytes, but the improvement in hepatic steatosis may be also associated with changes in IM and metabolism. These findings unveil the role of AhR in different cellular targets in the improvement of ALD by pectin, that needs to be further explored to propose the AhR pathways activation as an alternative therapeutic approach of pectin. But also raise that other mechanisms are involved.

Alcohol-related liver disease and MetALD – Clinical

TOP-459
MetALD has a higher rate of extrahepatic cancer and cardiovascular events compared to other subtypes of steatotic liver disease

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Background and aims: Steatotic liver disease (SLD) is the most common chronic liver disease worldwide. Research to date suggests that people with metabolic dysfunction associated steatotic liver disease (MASLD) or alcohol-related liver disease (ALD) have a high risk of developing cardiovascular (CV) events or extrahepatic cancers, but little is known about MASLD with increased alcohol intake (MetALD) group. We aimed to investigate the incidence of CV events and extrahepatic cancers in SLD subgroups.
Method: Patients with histologically confirmed SLD at a single tertiary centre were included. During follow up new CV events (heart failure (HF), ischaemic heart disease (IHD), cerebrovascular disease (CVD), peripheral vascular disease (PVD)) and extrahepatic cancers was collected from the electronic patient record. Cumulative incidence (CI) and sub-distribution hazards for CV and extrahepatic events were calculated over a five-year period with mortality or transplantation as competing events. All analyses were done in R.
Results: 726 patients were included**:** 516 (71%) had MASLD, 85 (12%) had MetALD and 125 (17%) – ALD. Median age was 53 (IQR 43–61) and 63% were males. F3 fibrosis was observed in 184 (25%) patients and F4–99 (14%) patients. During a median follow up period of 60.5 (IQR 29–84.5) months 64 (8.8%) patients died (including eight extrahepatic cancer deaths and four CV event deaths), 44 (6.1%) had a decompensating event, 3 (0.4%) had liver transplant and 10 (1.4%) had hepatocellular carcinoma. We observed fifty CV events where IHD (48%) was the most common event. The five-year CI for CV events was 4.9% (3.0%, 7.6%) in MASLD, 8.8% (3.5%, 17.0%) in MetALD and 2.5% (0.68%, 6.7%) in ALD. In total 39 patients were diagnosed with extrahepatic cancers during follow up; the most common sites were skin (18%), prostate (13%) and colorectal cancer (13%). The five-year cumulative incidence of extrahepatic cancers was 3.6% (2.0%, 6.0%) in MASLD, 5.9% (1.9%, 13%) in MetALD and 4.7% (1.7%, 10%) in ALD. Competing risk regression analysis at five years controlling for age, BMI and smoking showed that ALD and MetALD cohorts were associated with higher risk of extrahepatic cancers compared to MASLD: sHR 2.40 (1.20–4.79, p = 0.013) and sHR 2.73 (1.09–6.81, p = 0.031), respectively. However, ALD and MetALD subgroups did not have a significantly higher risk of CV events compared to MASLD.
Conclusion: Patients with MetALD have a higher five-year incidence of CV events and extrahepatic cancers compared to MASLD and ALD groups. This is likely due to synergetic effect of alcohol intake and metabolic risk factors that drives these events and high rates of liver-related events in patients with ALD as a competing risk.

TOP-460
Urinary proteomics identifies complement as potential biomarkers in severe alcohol-associated hepatitis patients

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Background and aims: Alcohol-associated hepatitis (AH) is characterized by sudden onset of uncontrolled liver inflammation. Urine samples can be collected easily and in a non-invasive manner, which makes it a preferred body fluid for biomarker discovery. Complement, a component of the innate immune system, is implicated in the pathogenesis of alcohol-induced liver injury in murine models and complement proteins in plasma are diagnostic and prognostic biomarkers in patients with AH. However, no data is available to the utility of urinary complement signatures as biomarkers in AH. We hypothesize that complement may provide important biomarkers in AH and that urine may be a suitable body fluid for new biomarker discovery.
Method: Baseline urine samples from the AlcHepNet Observational study (27 healthy controls (HC), 25 heavy drinkers (HD) and 27 severe AH (sAH)) were used for global quantitative proteomics using a label free quantitation. Samples were analyzed using a Data Independent Acquisition (DIA) method and searched against an in-house spectral library and SwissProt database.
Results: A total of 2716 proteins were identified in the urine samples. PCA analysis showed a clear segregation of patients with sAH and HC and segregation of sAH and HD, with some overlap of proteins. In the enrichment analysis using gene ontology between sAH and HC, complement activation was upregulated in the biological process sub-ontology. In the molecular function sub-ontology, complement binding was also enriched. These pathways were not enriched in the sAH/HD or HC/HD comparisons. Based on these findings, we then evaluated individual complement components. Multiple complement components were perturbed in sAH compared to HD and HC. C1qb was the most up-regulated protein in sAH and HD compared to HC and Uromodulin and MASP1 the most down-regulated protein found in the urine of sAH compared to HC and HD, respectively. AUC for Uromodulin between HC and sAH was 0.9890 and C1qb was 0.90. The AUC between HD and sAH for C1qb was 0.8948 and for MASP2 was 0.9022.
Conclusion: Urine collection is easy and non-invasive, making it a suitable sample for biomarker discovery. Here we show that urinary proteomics analysis discovered 2716 proteins in the urine of sAH patients and that complement is dysregulated in the urine of those patients. Uromodulin, C1qb and MASP2 are good candidates as biomarkers of AH. More studies are needed to further characterize urinary complement as potential diagnostic and prognostic biomarkers of AH.

TOP-473
Histological features predict response to corticosteroids and short-term survival in severe alcohol-associated hepatitis

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Background and aims: Liver biopsy is useful to confirm alcohol-related steatohepatitis (ASH) in patients with alcohol-associated liver disease (ALD) and clinically suspected alcohol-associated hepatitis (AH). Current clinical practice guidelines recommend prednisolone

for the treatment of severe AH with Maddreýs discriminant function (MDF) ≥ 32 or model for end-stage liver disease (MELD) > 20. However, steroid treatment may lead to severe side effects like sepsis. Therefore, treatment response is assessed at day 7 using the Lille model and steroids are discontinued in non-responders to limit the risk of unnecessary steroid exposure. The aim of our study was to investigate the utility of histologic features of ALD for prediction of response to corticosteroids by Lille score in patients with histologically confirmed ASH.

Method: We analyzed data of a multinational cohort of patients with severe AH and MELD > 20. All patients underwent liver biopsy for confirmation of ASH and were treated with prednisolone. Morphological features of ALD including steatosis, activity (contributed by hepatocellular ballooning and lobular neutrophils), canalicular and ductular cholestasis as well as fibrosis stage were assessed using the ALD-specific SALVE grading and staging system. Logistic regression was performed to evaluate the effects of histological variables on response to steroids by Lille score and on 90-day survival.

Results: A total of 142 patients with MELD > 20 at baseline were enrolled at 5 centers. Out of these, histological ASH was retrospectively confirmed in 114 patients (80%). Response to prednisolone by Lille score < 0.45 was observed in 61 /114 patients (54%). Logistic regression analysis of histologic variables adjusted for age, sex, and center revealed absence of ductular cholestasis as predictor of Lille response (OR 0.38, 95% CI 0.14–0.98, p = 0.046) and presence of SALVE fibrosis stage 4c (severe cirrhosis) as predictor of 90-day mortality (OR 3.93, 95% CI 1.39–11.83, p = 0.010).

Conclusion: Liver biopsy plays an important role to confirm histological ASH in patients with clinically suspected severe AH and was found useful to aid prediction of steroid efficacy and short-term mortality.

SATURDAY 10 MAY

SAT-463

A prospective study on hepatic fibrosis evaluation in an alcohol withdrawal unit of an university hospital: role of FIB-4 and elastometry. FIBRADDICT study

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Background and aims: Excessive alcohol consumption is the major cause of liver-related death and the leading cause of liver transplantation in France. Many patients are seen too late, at a decompensated stage. Early diagnosis of cirrhosis would allow early diagnosis for esophageal varices, screening for hepatocellular carcinoma and reinforcement of addictive behaviour care.

Method: 299 excessive alcohol consumers, defined by the AUDIT-C score, benefited from measurement of liver stiffness (LS) with Fibroscan (Echosesns, France) equipped with two probes M and XL upon entering in the unit (LS1, first measure). LS1>25 kPa ruled in advanced fibrosis (F3F4) and a LS1<10 kPa ruled out advanced fibrosis (F0F1F2) (Legros et al. CGEH 2022). If LS1 was found between 10 and 25 kPa, the status was determined by the second LS (LS2) realised at least two weeks after LS1. If LS2 was >10 kPa, the patient was considered to have advanced fibrosis. A first cohort of 187 patients was included and the second cohort of 112 patients was considered as the internal validation cohort. We have analysed the diagnostic performance of FIB-4, Prothrombin time (PT) and ASAT/ALAT>1. We will present only the results of the FIB-4 as its performance was superior to PT and ASAT/ALAT > 1. The performance of the two cohorts were not significantly different, we will present the results of the whole cohort.

Results: Mean age of the patients was 49 years, sex ratio 2.8, median consumption of alcohol 192 g/day, 11% were obese, 46% had ASAT > ULN, 46% PT < 85% and 13% platelets < 150 G/L. 34 out of 299 patients had severe fibrosis (11%). CAP>248 dB/m was found in 100/299 (33%). The diagnosis performance of the FIB-4 was excellent with an AUC = 0.895. To get a sensitivity higher than 90%, the threshold was 1.45. We used as suggested by the international guidelines, the threshold of 1.3. This threshold had a sensitivity of 91% and a specificity of 67% and could allow to reduce the number of LS measurement in 182 out of 299 patients (60%). In patients with ASAT > 100 IU/L and platelets < 150 G/L, the AUC were respectively 0.73 and 0.62. The sensitivity of the FIB-4 was > 90% in these two subgroups. According to Papatheodoridi et al. (J Hepatol 2021), at least 42 patients were considered to have severe fibrosis (FS1 > 12 kPa).

Conclusion: 1) Eleven percent (34/299) of patients admitted to an addictology unit had an advanced fibrosis, 2) a FIB-4 higher than 1.3 has a sensitivity higher than 90% to rule in severe fibrosis and allow to avoid 60% of Fibroscans, 3) the combination of FIB-4, ELF or Fibrotest and LS should be studied on a larger number of patients to validate this algorithm, 4) the algorithm of Legros should be compared to the Papatheodoridi algorithm (J Hepatol 2021), 5) finally this study suggests that screening for advanced fibrosis should be performed in all hospital units for alcohol withdrawal.

SAT-464

Prospective evaluation of undiagnosed MetALD prevalence in MASLD patients using the ani score

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Background and aims: The recent EASL-EASD-EASO guidelines differentiate MASLD from MetALD, the latter linked to higher alcohol intake and worse prognosis. However, there is a lack of validated, user-friendly scores or biomarkers for differentiation between both entities. The Alcoholic Liver Disease/Non-Alcoholic Steatohepatitis Index (ANI) score is simple and effective in identifying patients at risk for alcoholic liver disease. Our aim is to assess MetALD presence using the ANI score in MASLD patients and examine their characteristics.

Method: This single-center, prospective study involved MASLD patients attending Digestive Pathology consultations from September to November 2024. MASLD was defined by hepatic steatosis, alcohol intake < 20/30 g/day (women/men), ≥ 1 cardiovascular risk factor, and no other discernible cause, excluding suspected advanced liver disease. MetALD was considered if ANI > 0 (probability of alcoholic liver disease > 50%). Sociodemographic and analytical variables, self-reported alcohol consumption, liver fibrosis, and Controlled Attenuation Parameter (CAP) were assessed using Fibroscan®. Variables were compared between ANI > 0 and ANI < 0 groups, with significance set at p < 0.05.

Results: We included 100 patients, mean age 61.1 ± 9.9 years, 64% men. Fifty-one percent reported no alcohol consumption (0 g/week), and 26% consumed 10–20/30 g/day (women/men). ANI > 0 occurred in 23% (23/100), with 52.2% of them (12/23) having > 90% probability of MetALD/ALD. The ANI > 0 group was exclusively male (100% vs 53.2%, p < 0.001), with lower BMI (29.0 ± 4.4 vs 31.5 ± 4.7, p = 0.03) and CAP (269.7 ± 46.3 vs 305.0 ± 40.8, p = 0.03). Alcohol intake of 10–20/30 g/day was more common in the ANI > 0 group (56.5% vs 16.9%, p < 0.001), as was 30–70 g/week (21.7% vs 5.2%, p < 0.001). No alcohol consumption predominated in the ANI < 0 group (62.3% vs 13%, p < 0.001). The ANI > 0 group showed higher fibrosis (8.1 ± 2.6 vs 5.2 ± 2.1 Kpa, p < 0.001), higher GGT levels (150.5 ± 186.4 vs 67.4 ± 75.4 U/L, p = 0.04), and, although not significant, higher AST levels (43.9 ± 31.2 vs 31.8 ± 14.4 U/L, p = 0.057).

Conclusion: Although the ANI score is not validated to distinguish MASLD from MetALD, our study shows a significant prevalence of potential MetALD in MASLD patients. These findings highlight the need for developing and implementing clinical scores and biomarkers to accurately differentiate alcoholic-associated liver disease, crucial for minimizing the risk of misclassifying MetALD as MASLD.

SAT-465

Performance of MELD 3.0 in predicting 90- and 180-day mortality in alcoholic hepatitis

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Background and aims: Alcohol-associated hepatitis (AH) is a severe condition with high short-term mortality. The MELD (Model for End-Stage Liver Disease) score is commonly used to identify patients with severe AH, aiding in risk stratification and therapeutic decisions. The updated MELD 3.0 score has been proposed to improve prognostic accuracy. This study aims to evaluate the performance of MELD 3.0 compared to MELD, MDF, MELD-Na, ABIC, and GAHS.
Method: We conducted a retrospective analysis of 156 consecutive patients admitted with AH meeting the NIAAA criteria between January 2016 and May 2024. We calculated the area under the curve (AUC) for MELD 3.0, MELD, MDF, MELD-Na, ABIC, and GAHS. DeLong tests were performed to compare AUCs between models. The Reclassification Index (NRI) was calculated to evaluate the improvement in classification provided by MELD 3.0 over MELD. Additionally, we determined the sensitivities (S) and specificities (E) for MELD at the threshold of 21 and compared to MELD 3.0.
Results: The global mortality rates at 90 and 180 days were 16.67% and 19.75%, respectively. MELD 3.0 demonstrated superior AUCs for both time points: 0.879 (90 days) and 0.871 (180 days). These values were higher compared to MELD (0.857 and 0.863), MELD-Na (0.870 and 0.855), MDF (0.821 and 0.816), ABIC (0.747 and 0.729), and GAHS (0.796 and 0.775). The DeLong test showed that MELD 3.0 significantly outperformed ABIC and GAHS ($p < 0.05$), while differences between MELD-Na and MELD were not statistically significant. The optimal threshold for MELD 3.0 was 26 for both 90- and 180-day mortality. At 90 days, MELD 3.0 achieved a S of 84.6% and a E of 80.6%. In comparison, MELD at threshold 21 showed a S of 92.9% but a reduced E of 63.2%. Al 180 days, MELD 3.0 achieved a S of 80.6% and E of 82.3%, compared to MELD, which demonstrated a S of 86.7% but a E of 62.2%. The NRI for MELD 3.0 compared to MELD was 0.124 at 90 days and 0.097 at 180 days, reflecting modest improvements in reclassification.
Conclusion: MELD 3.0 showed comparable predictive performance to MELD for 90- and 180-day mortality but demonstrated greater E and modest reclassification improvements. These findings suggest MELD 3.0 may be a potentially valuable tool for more accurate risk stratification in alcoholic hepatitis. Further studies with larger cohorts are needed to validate these findings.

SAT-466

Plasma exchange as a rescue therapy for patients with severe alcohol-associated hepatitis

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Background and aims: Patients with severe alcohol-associated hepatitis (SAH) and advanced liver failure have limited treatment options. Plasma exchange (PLEX) is a bridging modality for such patients with liver failure; the use of which is common in centers with limited access to early liver transplantation. We aimed to assess the outcomes of PLEX in patients with SAH.
Method: In this multicenter retrospective study, we included patients with SAH who underwent PLEX from India and Slovakia. The primary objective was to determine the transplant-free survival (TFS) at 90 days, and the secondary was to assess the change in serum bilirubin levels and model for end-stage liver disease (MELD) score after the last session of PLEX and adverse events related to PLEX. We also compared the outcomes of patients who underwent high volume (HV) and standard volume (SV) PLEX.
Results: We included 128 patients with a mean age of 41 ± 10.3 years. Ninety-three percent of patients were men. The mean MELD score was 32 ± 6, and all these patients met the acute-on-chronic liver failure (ACLF) criteria of APASL. Twenty one percent (27/128) had renal failure and/or underwent renal replacement therapy. TFS was 28.1% (26/128; 95%CI, 20.5–36.7) at day 90. The cumulative change in serum bilirubin levels and MELD score was −10.9 ± 7.4 mg/dl and −6.8 ± 5.8, respectively, after a median PLEX session of 2 (1–5). Seven patients developed adverse events (hypotension-3; fever and rigors-2; hypocalcemia-1 and volume overload-1). Sixty-eight patients underwent HV PLEX, and 60 underwent SV PLEX. The mean change in serum bilirubin (HV: −13.1 ± 8 mg/dl vs. SV: −8.6 ± 5.5 mg/dl; $P < 0.001$) and MELD score (HV: −8.2 ± 6.5 vs. SV: −5.2 ± 4.4; $P = 0.004$) was higher in HV group than SV group. TFS at day 90 was 28% (19/68) in HV PLEX and 28.3% (17/60) in SV group ($P = 1$). On adjusting for age and MELD score, the hazard ratio for survival with HV PLEX was similar to SV PLEX (HR, 0.69 [95%CI, 0.43–1.11]) at day 90.
Conclusion: PLEX provides decent transplant-free survival in patients with advanced liver failure due to SAH. Standard-volume and high-volume PLEX are similar in effectiveness.

SAT-467

Fibroblast activation assessed by PRO-C3 and PRO-C6 is associated to accumulation of key bile acids - A hallmark of fibrosis initiation and mortality in alcohol-related liver disease

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Background and aims: Alcohol-related liver disease (ALD) results from persistent liver damage due to excessive alcohol consumption, often progressing to fibrosis, cirrhosis, and end-stage liver failure. Disrupted bile acid homeostasis is considered a key feature in liver fibrosis development in ALD. Studies in MASH and PSC patients have shown that potent antifibrotic therapy reduces bile acid levels and the fibroblast activity biomarker PRO-C3, hinting at a link between bile acid accumulation and fibrosis induction. However, the role of bile acids as drivers of fibrosis remains unclear. The current study investigates the potential role of bile acids driving fibrogenesis in ALD by exploring associations between fibroblast activity biomarkers, bile acids, and clinical outcomes.
Method: Serum levels of nordicPRO-C3 (N-terminal pro-peptide of type III collagen) and nordicPRO-C6 (endotrophin; type VI collagen formation) obtained by ELISA; and plasma concentrations of bile acids (CA, TCA, GCA, LCA, DCA, TUDCA, GUDCA) obtained by mass-spectrometry were assessed in a cross-sectional cohort of 450 patients with biopsy-proven ALD. Associations between circulating bile acid concentrations and the fibroblast activity biomarkers were

analyzed using Spearman correlation (coefficient r). A Wilcoxon test was applied to compare PRO-C3 and PRO-C6 levels in ALD patients stratified by low and high risk of outcomes over a median follow-up period of five years using Kaplan-Meier survival analysis to obtain survival curves and hazard ratios for mortality and decompensation.
Results: Fibroblast activity markers PRO-C3 and PRO-C6 correlated to glycine conjugated bile acids GCA (r = 0.67 for PRO-C3 and r = 0.45 for PRO-C6) and GUDCA (r = 0.53 for PRO-C3 and r = 0.34 for PRO-C6); taurine conjugated bile acid TCA (r = 0.64 for PRO-C3 and r = 0.46 for PRO-C6) at baseline. The bile acids GCA, GUDCA and TCA were elevated in at-risk ALD patients that developed adverse outcomes such as all-cause mortality and decompensation (GCA, cutoff high/low of 684 ng/mL, $p < 0.001$, $HR_{mortality} = 3.5$ and $HR_{decompensation} = 7.6$; GUDCA, high/low cutoff of 575 ng/mL, $p < 0.001$, $HR_{mortality} = 2.8$ and $HR_{decompensation} = 4.1$; TCA, high/low cutoff of 720 ng/mL, $p < 0.001$, $HR_{mortality} = 2.6$ and $HR_{decompensation} = 3.7$). Baseline levels of the fibroblast activity markers were found to be significantly increased in the high-risk groups stratified according to baseline bile acid concentrations of GCA (PRO-C3, $p = 1.15\ 10^{-28}$; PRO-C6, $p = 8.9\ 10^{-14}$) GUDCA (PRO-C3, $p = 2.67\ 10^{-12}$; PRO-C6, $p = 1.93\ 10^{-5}$) and TCA (PRO-C3, $p = 2.87\ 10^{-20}$; PRO-C6, $p = 5.57\ 10^{-11}$).
Conclusion: Increased circulating levels of toxic hydrophobic bile acids relate to activation of fibroblasts and to poor prognosis in ALD patients, suggesting that bile acids are linked to activation of fibrogenesis, and therefore are key to the induction and development of liver fibrosis in ALD.

SAT-468
Hot & cold fibrosis: fibro-inflammatory biomarkers as prognostic tools in alcohol-related liver disease

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Background and aims: Alcohol-related liver disease (ALD) encompasses a spectrum of liver conditions that begin with inflammation (steatohepatitis) and progress to fibrosis, cirrhosis, and associated complications. In ALD, various fibrotic and inflammatory processes drive disease progression and influence clinical outcomes. The concept of "hot and cold fibrosis" — referring to the presence (hot) or absence (cold) of immune cells in fibrotic tissue — has emerged to help understanding the role of inflammation in liver fibrosis and its impact on ALD progression. This study aims to investigate whether immune cell activity biomarkers can enhance the prognostic performance of established fibrogenesis biomarkers for risk stratification in ALD.
Method: Levels of the fibrogenesis marker nordicPRO-C3 (N-terminal pro-peptide of type III collagen), fibrosis resolution marker nordicCTX-III (MMP degraded fragment of cross-linked type III collagen), neutrophil activity marker nordicCPa9-HNE (calprotectin fragment degraded by neutrophil elastase) and T-cell activity marker C4G (type IV collagen fragment degraded by granzyme-B) were measured in serum from 450 patients with biopsy-proven ALD and 147 matched healthy controls. The prognostic performance of individual and combined biomarkers for the risk of all-cause mortality and decompensation over a median of 6 years was investigated by Kaplan-Meier survival analysis using a time-dependent cox model to obtain survival curves and hazard ratios (HR).
Results: Kaplan-Meier curves stratified by biomarker quartiles were used to determine cut-off values for CTX-III, C4G and CPa9-HNE that better stratify patients into groups with lower or higher risk of events. ALD patients with PRO-C3 levels above 12.6 ng/mL (literature cut-off) exhibited a 4-fold increased risk of mortality ($p < 0.001$; HR = 4.1; 75 events/450 patients) and 10-fold increased risk of decompensation ($p < 0.001$; HR = 10.6; 65 events/450 patients). When combining the PRO-C3 cutoff of 12.6 ng/mL with markers of fibrosis resolution and immune cell activity, the prognostic value of PRO-C3 improved by further stratifying patients by CTX-III levels above or below 15.6 ng/mL ($p < 0.001$; HR = 9.9 and HR = 25.4 in the groups with higher risk of mortality and decompensation, respectively), C4G levels above or below 33 ng/mL ($p < 0.001$; HR = 7.32 and HR = 31.7 in the groups with higher risk of mortality and decompensation, respectively) or by CPa9-HNE levels above or below 60 ng/mL ($p < 0.001$; HR = 12.8 in the group with higher risk of decompensation).
Conclusion: ALD patients at higher risk of adverse clinical outcomes demonstrated a distinct profile of heightened fibrogenesis and inflammation. Integrating biomarkers representing diverse biological processes significantly enhanced the predictive accuracy for clinical outcomes compared to individual biomarkers alone.

SAT-469
Maintaining a low to moderate alcohol consumption over time in MASLD patients increases the risk of fibrosis progression over moderate drinkers and MetALD patients

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Background and aims: Metabolic and Alcohol-Related Liver Disease (MetALD) is characterized by the coexistence of metabolic dysfunction and alcohol consumption of 20–50 g/day for women and 30–60 g/day for men. New evidence shows that low to moderate alcohol consumption in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) significantly increases the risk of liver fibrosis. This study aims to assess the prevalence of MetALD in a cohort of outpatients and to investigate the influence of alcohol consumption and abstinence at the end of follow-up on fibrosis progression and cardiovascular events (CVE).
Method: A retrospective cohort study was conducted using a prospectively collected cohort of MASLD outpatients. Participants were categorized into four groups based on alcohol consumption: very low-risk drinkers (VLD) (0–40 g/week), low-risk drinkers (LD) (41–90 g/week), moderate drinkers (MD) (91–140 g/week women, 91–210 g/week men), and further reclassified as MetALD or Alcohol Related Liver Disease (ArLD). Liver fibrosis was evaluated using non-invasive markers, and data on alcohol abstinence and CVE were recorded throughout the follow-up period.
Results: 482 patients were included for analysis. 77% VLD, 6.75% LD, 7.81% MD, 8.02% MetALD, and 0.42% ArLD. The median follow-up period was 66 months. 52.28% patients were women with a mean age of 59 years. Significant sex differences were observed between groups ($p < 0.0001$), with statistically differences between MetALD vs MD ($p = 0.03$) and VLD groups ($p = 0.01$). No significant age differences were noted ($p = 0.1$). No differences were found at baseline ($p = 0.661$) or at the end of the study in the number of cardiovascular risk factors (CVRF) ($p = 0.7$). At baseline significant differences in liver stiffness (LSF) were only observed within MD vs LD ($p = 0.005$) and MD vs VLD groups ($p = 0.005$). At the end of follow-up, MD group had the highest mean LSF (47.3 KPa), significantly higher than VLD group ($p = 0.008$). This finding may be explained by the difference in alcohol abstinence at the end of the study ($p < 0.0001$) between VLD vs MD and LD groups. No significant differences in overall survival were observed,

including stratified analyses for liver-related complications or CVE. CVE risk during follow-up showed no significant group differences (p = 0.2), though the MD group had the highest risk (HR = 2.3, 95% CI [1.1, 5.1]). For the incidence of the novo CVRF, no significant differences were observed between groups (p = 0.87). The highest risks were seen in the LD (HR = 1.2, 95% CI 0.85–1.8), MD (HR = 1, 95% CI [0.7, 1.4]) and MetALD (HR = 1, 95% CI [0.7, 1.5]) groups.
Conclusion: The prevalence of MetALD in our cohort aligns closely with findings from other recently published studies. Low to moderate alcohol consumption in MASLD patients significantly increases the risk of liver fibrosis, with MD group showing the highest LSF levels during follow up, highlighting the critical role of alcohol abstinence in disease progression.

SAT-470

Impact of diabetes mellitus on mortality in alcohol-related acute-on-chronic liver failure: a study from the AARC database

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Background and aims: Acute-on-Chronic Liver Failure (ACLF) is a life-threatening condition characterized by acute decompensation in patients with chronic liver disease, often resulting in multi-organ failure and high mortality rates. Alcohol is the predominant cause of ACLF worldwide. Although diabetes mellitus is a recognized risk factor for adverse outcomes in chronic liver disease, its role in influencing mortality in alcohol-related ACLF is not well understood. This study evaluates the effect of diabetes mellitus on 90-day mortality in patients with alcohol-related ACLF.
Method: Data were obtained from the APASL ACLF Research Consortium (AARC) registry, including patients diagnosed with alcohol-related ACLF where alcohol was identified as both the cause of chronic liver disease (CLD) and the acute precipitant. Patients with additional etiologies of CLD or alternative precipitants (e.g., HBV, HCV, HEV, DILI) were excluded. Participants were categorized into diabetic and non-diabetic groups. The primary outcome was 90-day mortality, analyzed using baseline clinical and laboratory parameters as well as severity scores.
Results: A total of 2150 patients with alcohol-related ACLF were included: 121 diabetics (median age 45 years; 91.7% male) and 2029 non-diabetics (median age 42 years; 90.9% male). The median MELD-Na score was 31.1 (IQR 27.0–36.0), and the median CTP score was 12.0 (IQR 11.0–12.0) for both groups. Overall, 986 patients (46%) died within 90 days, while 110 (5%) underwent liver transplantation (LT), of whom 12 died post-transplantation. The 90-day mortality rate was significantly higher in diabetics compared to non-diabetics (68.1% vs. 45.4%, $p < 0.05$). Survival analysis revealed a significantly poorer prognosis for diabetic patients, both in overall survival ($p < 0.01$) and transplant-free survival ($p < 0.01$).
Conclusion: Diabetes mellitus significantly exacerbates mortality risk in alcohol-related ACLF. These findings highlight the urgent need for targeted research to unravel the mechanisms behind this association and to develop effective interventions to improve outcomes for diabetic patients with alcohol-related ACLF.

SAT-471-YI

Bacterial infections in patients with severe alcoholic hepatitis: drivers of organ failure and mortality

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Background and aims: Severe alcoholic hepatitis (sAH) is a critical condition and treatment remains challenging. Corticosteroids have been associated with an improved short-term survival and therefore play a major role in sAH therapy. However, their safety is still questionable as a linkage with elevated incidences of infections has been suggested by previous studies. We aimed to investigate the impact of steroid use on infections and to analyze the relevance of infections for the clinical outcome of sAH patients.
Method: We performed a post-hoc analysis of the prospective, multicentric VTI-308 trial including 151 consecutive patients with sAH. Competing risk models were used to evaluate the influence of corticosteroids on infection development up to one year of follow-up. To investigate the impact of infections on the risk for multi-organ failure (MOF) and overall mortality, cox proportional hazard regression analyses with time-dependent covariate were performed.
Results: The studied patients had a median baseline MELD of 25, median Maddrey Discriminant Function of 63 and a median age of 40 years. Overall, a number of 35 (23.2%) patients fulfilled the criteria for MOF during one year of follow-up, 4 (2.6%) underwent liver transplantation and 42 (27.8%) patients died. Any bacterial infection was acquired by 90 (59.6%) subjects. Among these, urinary tract infections (n = 31; 34.4%), bloodstream infections (n = 27; 30.0%), and pneumonia (n = 15; 16.7%) were most frequent. In 40 patients, the infection causing pathogen was isolated, with Enterococcus sp. being most common (n = 14; 35.0%). Fungal infections were observed in 19 (12.6%) patients during follow-up. Of note, corticosteroid therapy was neither linked to an increased risk for bacterial (HR = 0.48; p = 0.05) nor to a higher likelihood of fungal infections (HR = 1.74; p = 0.42) within one year. This observation was confirmed in the multivariable competing risk model, adjusted for MELD and previous infections (bacterial infections: HR = 0.48; p = 0.06; fungal infections: HR = 1.77; p = 0.42). Bacterial infections were significant predictors of MOF in the univariate (HR = 2.07; p = 0.04) as well as in the multivariable model, including the components of the Glasgow Alcoholic Hepatitis Score as covariables (HR = 2.54; p = 0.01). In line with this, bacterial infections were strongly linked to mortality, with hazard ratios between 3.54 and 5.14, indicating a four- to five-fold increased mortality. This remained statistically significant in the multivariable model (univariate: HR = 3.54; p < 0.001; multivariable: HR = 5.14; p < 0.001).
Conclusion: Bacterial infections are frequent complications in sAH patients and relevant contributors to MOF, finally leading to a dramatic increase of mortality. However, the use of corticosteroids

was not associated with an aggravated risk for infectious complications, which might ameliorate previous safety concerns.

SAT-472

Misclassification of alcohol use disorder in MASLD and MetALD: prevalence, clinical characteristics, and outcomes

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Background and aims: Within MetALD, there exists a continuum where the condition can conceptually shift between being metabolic dysfunction associated steatosis disease (MASLD) or alcoholic liver disease (ALD). However, alcohol use disorder (AUD) is often included in these diagnoses. This study aimed to investigate the prevalence and clinical characteristics of misclassified AUD among patients with MASLD and MetALD.
Method: The study included a total of 3,362,552 participants from the National Health Screening Program. Steatosis was defined as a Hepatic Steatosis Index score of 36 or higher. Significant alcohol intake was calculated based on a self-reported questionnaire. AUD was defined as having received medical care for an alcohol-related condition at least once during the study period. The average follow-up period for participants was 9.8 years.
Results: Among the 3,362,552 participants analyzed, the prevalence of MASLD and MetALD was 23.8% and 1.9%, respectively. Of those classified as MASLD and MetALD, 1.1% (8,481 individuals) and 4.7% (2,989 individuals) had a history of AUD in the index year. MASLD and MetALD with medical records of AUD (AUD misclassified as MASLD or MetALD) in the index year showed higher all-cause mortality compared to MASLD and MetALD without AUD. Liver-related mortality was also significantly elevated in the AUD misclassified as MASLD or MetALD. Adjusted hazard ratios (HRs) of 6.53 for AUD misclassified as MASLD and 6.98 for AUD misclassified as MetALD compare to non-AUD group, respectively. aHR for extrahepatic cancer mortality was 1.33 in the AUD misclassified as MASLD, and 1.44 in AUD misclassified as MetALD groups.
Conclusion: A considerable number of 'AUD' cases were misclassified as MASLD and MetALD in cross-sectional investigations of alcohol consumption. The misclassified AUD as MASLD or MetALD had higher liver-related mortality than the pure MASLD and MetALD groups.

SAT-475

Unemployment and social isolation predict relapse in patients with alcohol related cirrhosis

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Background and aims: Abstinence from alcohol is critical for patients with alcohol related cirrhosis (AC). We sought to understand the clinical and psychosocial factors which predict abstinence in patients with AC following admission to hospital.
Method: This was a retrospective single centre study. We reviewed data on all patients admitted to a large tertiary centre in the UK with a diagnosis of AC and/or alcohol-associated hepatitis between Sept 2014 and March 2023. Where there were multiple admissions the first admission on or after the diagnosis of AC was used. We collected a granular dataset which included clinical and psychosocial factors felt to be relevant in predicting abstinence. A hepatologist reviewed all case notes individually. The outcome of interest was abstinence at one year. We used Mann-Whitney U test to compare continuous variables and chi-square test to compare categorical variables. Those variables that were statistically significant ($p \leq 0.05$) on univariate analysis were entered into a backward stepwise elimination variable selection procedure (multivariate logistic regression).
Results: We identified 646 patients who met the inclusion criteria. Median age was 58 (IQR 50–67) and 37% were female. Reasons for admission were: decompensated liver disease 57%; other alcohol related reasons 20%; and other 23%. Median length of stay was 6 days (IQR 3–13). Median MELD score was 14 (IQR 8–21). Median alcohol consumption in units/week was 70 (IQR 14–140). The abstinence rate at one year was 56% and mortality was 29%. Patients who were abstinent at one year were more likely to have been admitted with decompensated liver disease (64% vs 43%, $p < 0.001$); had a higher MELD score at admission (median 14 vs 10 $p = 0.001$); had lower levels of alcohol use at admission (median 50 vs 100 units/week, $p < 0.001$); were more likely to have a partner (64% vs 42% $p < 0.001$); more likely to be in employment (33% vs 22% $p = 0.002$); and were less likely to have a co-morbid psychiatric diagnosis (15% vs 26% $p = 0.01$). After backwards stepwise elimination, co-morbid psychiatric diagnosis was removed from the model. The following categorical variables remained statistically significant on multiple logistic regression: lack of partner (OR 0.55 p 0.03); Unemployment (OR 0.52 p 0.04) and admission with decompensated liver disease (OR 3.65 $p < 0.001$). In addition, for every 10 units additional alcohol consumption/week, likelihood of abstinence decreased by 4% (OR 0.96 p0.002). For each one unit increase in MELD, likelihood of abstinence increased by 6% (OR 1.06 p 0.004).
Conclusion: These predictors highlight potential populations of patients with AC who could be targeted for relapse prevention strategies after a hospital admission. Specific interventions could be designed to target those with the highest levels of alcohol intake, without social support and who have not yet developed decompensated liver disease in order to improve outcomes in this patient group.

SAT-476-YI

Liver death trajectories differ in patients with alcohol consumption and/or metabolic syndrome: a 13-year nationwide study

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Background and aims: Alcohol-related liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) are 2 main causes of chronic liver disease. Alcohol drinkers are also exposed to metabolic syndrome (MS), requiring investigating trajectories of liver death in those with underlying cirrhosis and/or HCC by comparing ALD with MS (ALD+MS+) to ALD without MS (ALD +MS-) or MASLD alone.
Method: Data of ALD+MS-, ALD+MS+ and MASLD patients hospitalized between 2011 and 2023 with ≥1 ICD-10 code of cirrhosis and/or HCC were extracted from the French national medicalized information system program. Overall and liver-related deaths (HCC or liver decompensation (LD)), age-standardized mortality rates (ASMR, per 100 000), age at death and years of life lost (YLL) over the period were assessed by group.
Results: Death occurred in 176,026 of 376,348 patients with either cirrhosis and/or HCC (ALD+MS-: 44.6%; ALD+MS+: 39.6%; MASLD:

15.8%). Among deaths in ALD groups, MS prevalence was high (47.1%) as was that of severe alcohol use disorder (66.6% in ALD+MS-; 67.0% in ALD+MS-). 63.4% of total deaths were liver-related, with a higher proportion of deaths due to LD in ALD groups (65.9%) and due to HCC in MASLD group (57.9%). The proportion of deaths due to HCC increased in ALD+MS+ (36.6%) compared to ALD+MS- (31.3%, $p < 0.01$). Between 2011 and 2023, liver-related ASMR decreased in ALD +MS- (from 7.9 to 5.0, $p < 0.01$) and increased in ALD+MS+ (from 4.5 to 5.1, $p = 0.01$) and MASLD (from 1.8 to 2.5, $p < 0.01$). In 2023, ALD remained the leading cause of liver-related ASMR (80.2%) but MASLD's contribution increased from 12.7% to 19.8% over the period. Age at death increased in all 3 groups but remained younger in ALD+MS- (from 64.0 to 66.5, $p < 0.01$) and ALD+MS+ (from 67.0 to 68.9, $p < 0.01$) than in MASLD (from 73.9 to 75.1, $p < 0.01$). Knowing 2023 mean age at death in the general population was 79.6, YLL per individual are twice as high in ALD+MS- (15.8 years) and 1.6 times higher in ALD+MS- (12.6 years) than in MASLD (7.8 years, $p < 0.01$).

Conclusion: MS is highly prevalent among deaths in ALD cirrhotic and HCC patients. ALD is associated with an increased risk of LD-related death whereas MS increased HCC risk, the leading cause of death in MASLD. Premature death remains frequent in ALD with high YLL per individual. The paradoxical older age at death in ALD+MS+ and MASLD may be linked to either later onset of MS and/or multidisciplinary management of MS, leading to better access to care.

SAT-477-YI

Feasibility and effectiveness of a liver health check clinic in community alcohol services

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Background and aims: Liver cancer affects 6,600 people annually in the UK. As part of an NHS England pilot programme, Liver Health Check Clinics (LHCC) were established within alcohol services across North Central London. Between September 2022 and October 2024, 2,658 liver stiffness measurements (LSM) were conducted to identify individuals at risk of cirrhosis and liver cancer (HCC).

Method: LSM tests were performed by trained clinician assistants during pre-booked and walk-in sessions. Individuals with probable significant fibrosis (LSM 8–11.4 kPa) were offered a repeat scan after 1 year. Those with probable advanced fibrosis/cirrhosis (LSM ≥11.5 kPa) were offered an on-site non-invasive liver screen, referral to hepatology, and a liver ultrasound before their first hepatology appointment. A leaflet with their LSM result and explanation of its significance was provided to all patients.

Results: Of the 2,658 patients, the average age was 46.2 years (±12.1), 64% male; median LSM 5.4 kPa (IQR: 4.3–7.5). Probable significant fibrosis (8–11.4 kPa) in 307 patients (11.5%), probable advanced fibrosis/cirrhosis (LSM >11.5 kPa) in 224 patients (8.4%). 91 of these patients met the Baveno VII criteria for clinically significant portal hypertension with LSM ≥25 kPa. Complete follow up data was available for 101/307 patients. During follow-up, 46 (45%) were diagnosed with cirrhosis, 1 with HCC, 30 (30%) reported abstinence. Complications included 4 admissions with decompensation, 6 alcohol-related admissions, and 4 deaths. There were 5 cases of varices and 11 with portal hypertensive gastropathy. The cumulative non-attendance rate for hepatology clinic appointments was 26%. Retrospective analysis of LSM and FIB-4 scores was conducted for 122 patients who had appropriate blood test results on their electronic patient record to calculate a FIB-4 as well as LSM ≥11.5 kPa. 27 (22.1%) of these patients had FIB-4 scores < 1.3. 109 patients with probable significant fibrosis attended for 1-year follow up scans. 80 LSM values fell below 8 kPa, 17 remained within the significant fibrosis range, and 12 progressed to advanced fibrosis/cirrhosis.

Conclusion: Initial scanning revealed that 20% of patients with a history of alcohol misuse had LSM values indicating at least probable moderate fibrosis, with 8.4% showing probable advanced fibrosis/cirrhosis. This population had not previously undergone liver assessment. The broader impact of LHCCs, including their influence on alcohol use and fibrosis progression, will be further evaluated.

SAT-478

Routine, pre-emptive anti-craving treatment to prevent alcohol relapse after liver transplantation

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Background and aims: Alcohol-associated liver disease (ALD) is the fastest-rising and leading indication for liver transplantation (LT) in the United States, with acute alcohol-related hepatitis (AAH) and acute-on-chronic ALD with inadequately treated substance use disorder—groups with post-LT alcohol relapse risk 25–50%–representing increasingly-accepted indications. We investigated whether routine, pre-emptive pharmacologic ACT in all such high-risk LT recipients would reduce alcohol relapse rates at 12 months compared to a historical, untreated cohort.

Method: From December 2023, all patients who underwent LT under our Center's Pathways for AAH and ALD with inadequately treated substance use disorder (Exceptions) were initiated on daily acamprosate, topiramate, or naltrexone after LT, with intended treatment of >/ = 12 months. Patients received standard LT care including follow up with addiction psychology and psychiatry teams. Relapse was defined as abnormal serum phosphatidylethanol level when tested per-protocol at 3 weeks, 2, 3, 4, 8, and 12 months after LT, or at any ad-hoc timepoint.

Results: Of 17 LT recipients, 10 were transplanted under Exceptions (median pre-LT sobriety 230 days) and 7 under AAH (median pre-LT sobriety 35 days) Pathways. ACT was initiated at mean 13 days after LT, with 14 receiving acamprosate, 3 receiving topiramate, and 2 transitioned to naltrexone during follow-up. Treatment was well-tolerated, with no serious adverse effects warranting discontinuation. The main adverse effect was diarrhea. Renal impairment was the main reason for agent or dose changes. All patients reported compliance with treatment. Relapse occurred in 2/17 (11.7%) during 12 month follow up: one with a one-time relapse at 3 months, and one with two relapses at 3 and 8 months. In comparison, our 2019–2022 historical cohort of 42 LT recipients who did not receive ACT had an alcohol relapse rate of 22%.

Conclusion: ACT was safe, well-tolerated, and associated with a lower alcohol relapse rate, both absolute and in terms of severity, than previously reported at our center. To our knowledge, these data represent the first assessment of routine, pre-emptive ACT use after LT in patients deemed at high risk of relapsing to alcohol use.

SAT-480

Efficacy and safety of fecal microbiota transplantation in patients with severe alcohol-related hepatitis or decompensated liver cirrhosis: a systematic review and meta-analysis

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Background and aims: Severe alcohol-related hepatitis (SAH) and acute on chronic liver failure (ACLF) are serious conditions associated with increased mortality. By modifying the liver-gut axis, fecal microbiota transplantation (FMT) has been proposed as a therapeutic option for SAH/decompensated liver cirrhosis with recurrent hepatic encephalopathy (HE). The aim of our systematic review and meta-analysis is to assess the short and long-term efficacy and safety profile

of FMT versus standard of care (SOC) in patients with these conditions.
Method: A thorough search across electronic databases was conducted from inception till November 2024. Included studies involved adult patients with SAH or decompensated liver cirrhosis who received FMT versus SOC (nutritional support, lactulose and rifaximin, pentoxifylline, or corticosteroids). The primary endpoints were short and long-term survival while secondary endpoints were rates of HE, gastrointestinal bleeding (GIB), ascites, infection, and alcohol relapse. Results were pooled together using Reviewer Manager 5.4 software and odds ratios (ORs) with 95% confidence intervals (CI) were calculated.
Results: 13 studies involving 577 patients with either SAH or decompensated liver cirrhosis were included in our pooled analysis, 3 of which were randomized controlled trials. Our findings demonstrate that patients who received FMT had higher survival rates at 1 month (OR = 2.71, 95% CI [1.48, 4.95]), 3 months (OR = 3.15, 95% CI [1.92, 5.17]), 6 months (OR = 2.59, 95% CI [1.45, 4.64]), and 1–3-years (OR = 3.36, 95% CI [2.00, 5.66]) compared to those who received SOC. The rates of HE, ascites, and infection were significantly lower in the FMT group with OR of 0.21 (95% CI [0.10, 0.44]), 0.22 (95% CI [0.11, 0.43]), and 0.24 (95% CI [0.14, 0.42]), respectively. The rate of GIB was similar between both groups (OR = 0.73, 95% CI [0.37, 1.44]). In patients with alcohol use disorder, relapse rates were similar between both groups as well (OR = 0.39, 95% CI [0.15, 1.03]).
Conclusion: In patients with SAH/decompensated liver cirrhosis, FMT demonstrated short and long-term survival benefit over SOC. FMT use was also associated with lower rates of HE, ascites, and infection. To date, this is the most comprehensive systematic review that pooled efficacy and safety data related in FMT use in patients with SAH/chronic liver disease. Additional data regarding changes in gut microbiota following FMT use will be pooled and added to the final report.

SAT-481-YI
Performance of six biomarkers compared to histological fibrosis stage as surrogate markers of clinical endpoints in drug trials of patients with MetALD and ALD - a dual biopsy study
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Background and aims: There is increasing interest in developing therapies for MetALD and ALD with two recently launched phase II trials and several underway. However, no generally accepted endpoints exist. While several non-invasive tests (NITs) show good diagnostic and prognostic accuracy, it remains unclear if changes in these tests predict liver-related outcomes. We compared the predictive performance of changes in six non-invasive tests compared with paired liver biopsies.
Method: We collected data from two RCTs and two prospective studies of participants with MetALD and ALD who underwent baseline and follow-up liver biopsy with concurrent measurement of NITs. Histological fibrosis stage was scored by one pathologist according to NASH CRN and NITs included transient elastography (TE), ELF, PRO-C3, Agile3+, FIB-4 and LiverPRO. We evaluated changes from baseline to follow-up and correlated delta values with Spearman's coefficient. By manual review of electronic medical records, we classified hepatic decompensation per Baveno VII and registered any deaths. To evaluate the six biomarkers as surrogate markers of clinical endpoints, we performed Cox regression models with the delta values adjusted for the baseline value. Model performance for predicting outcomes was compared with Harrell's C.
Results: We included 164 patients with MetALD and ALD, mean age 59 years (±8.5), BMI 30 kg/m² (±6). Alcohol abstinence 1 week prior to inclusion was reported by 42%, while 57% had significant fibrosis (≥F2) and 19% cirrhosis (F4). The median time from baseline to follow-up biopsy was 1.9 (IQR 1.3) years. Referenced to histologic Kleiner fibrosis stage, changes (delta value) in the respective NITs showed the following Spearman's correlation coefficients: Agile3+ (r = 0.80), ELF (r = 0.43), TE (r = 0.27), LIVERPRO (r = 0.26), PRO-C3 (r = 0.20), and FIB-4 (r = 0.08). After follow-up liver biopsy, we further followed patients for a median duration of 2.1 years (range: 0.4–6.0 years). During this period, 13 decompensated and 17 died. Changes (delta value) in histologic fibrosis stage and the six biomarkers were each included in separate Cox regression models, where all predicted hepatic decompensation and death (p-values < 0.01). The performance for predicting outcomes was compared by calculating Harrell's C-index: ELF (0.77), PRO-C3 (0.77), LiverPRO (0.78), Agile3+ (0.75), Kleiner fibrosis stage (0.73), FIB-4 (0.68), to TE (0.66).
Conclusion: In designing clinical trials for MetALD and ALD, it is important to select biomarkers that accurately reflect changes in the risk of liver-related outcomes. ELF, PRO-C3, and LiverPRO demonstrated best predictive performance, warranting greater emphasis in future trial interpretations compared to widely used diagnostic tools such as FIB-4 and TE.

SAT-482-YI
Prospective study of phosphatidylethanol as a quantitative, objective biomarker to detect under-reported alcohol use in steatotic liver disease
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Background and aims: The current subclassification of steatotic liver disease (SLD) strongly relies on using validated questionnaires, such as Alcohol Use Disorders Identification Test (AUDIT) and Lifetime Drinking History (LDH), which, while useful, are impractical and lack precision for their use in routine clinical practice. Indeed, self-reported alcohol use is frequently associated with inaccurate reporting, potentially leading to misclassification. Phosphatidylethanol (PEth) is an abnormal phospholipid formed only in the presence of ethanol and a quantitative, objective biomarker for alcohol use with high sensitivity and specificity. In this study, we aimed to quantify alcohol use and estimate the prevalence of under-reported alcohol use using PEth in a large, population-based cohort of individuals with overweight or obesity in the United States.
Method: This is a cross-sectional analysis of a prospective study including 556 community-dwelling adults with overweight or obesity residing in Southern California, 391 of whom had SLD as defined by MRI-PDFF ≥ 5%. The clinical research visit included medical history, biochemical and PEth testing, standardized validated questionaries for alcohol assessment, physical examination and advanced liver imaging using MRI-PDFF and MRE. Participants were subclassified as having metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-associated liver disease (MetALD) or alcohol-associated liver disease (ALD) in accordance with the new nomenclature guidance from AASLD–EASL–ALEH. Under-reported alcohol use was defined as individuals

originally classified as MASLD with PEth ≥ 25 ng/mL or individuals originally classified as MetALD with PEth ≥ 200 ng/mL.
Results: In the overall cohort, the mean (SD) age and BMI were 51 (13) years and 32.4 (5.7) kg/m^2, respectively. As PEth levels increased, body mass index, insulin resistance and hemoglobin A1c decreased, while the prevalence of male sex, blood pressure and HDL cholesterol increased (all $p < 0.05$). In the overall SLD population, under-reporting of alcohol use occurred in 16% of individuals, with 16% misclassified as MASLD having PEth ≥ 25 ng/mL and 29% misclassified as MetALD having PEth ≥ 200 ng/mL. In multivariable logistic regression, male sex (OR 1.11, 95%CI 1.03–1.20, p = 0.005), Caucasian ethnicity (OR 1.08, 95%CI 1.00–1.16, p = 0.047) and the absence of type 2 diabetes (OR 1.12, 95%CI 1.04–1.21, p = 0.005) were the strongest independent factors associated with under-reported alcohol use in this population.
Conclusion: PEth is a precise, direct biomarker that can objectively quantify alcohol use and classify SLD subcategories, bypassing the misclassification bias associated with self-reporting strategies.

SAT-483-YI
Younger, sicker, higher mortality; the burden of alcohol related liver disease in Ireland
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Background and aims: The burden of liver disease admissions on acute hospitals in Ireland is not clear. This study aimed to examine alcohol related (ARLD) and non-alcohol related (Non-ARLD) liver disease inpatient hospital admissions over a six year period from 2017–2023.
Method: National quality assurance and improvement system (NQAIS) inpatient admission (≥1 day) data was reviewed from 1/1/2017 to 12/12/2023 for all 26 model 3 and 4 general medical hospitals in Ireland. Demographics, inpatient mortality data, average length of stay (LOS), total bed days and total critical care bed days were calculated.
Results: There were a total of 19,298 inpatient hospital admissions as a result of liver disease across the 26 hospitals in 6 years. 54% of these were related to ARLD. ARLD accounted for 135,567 bed days and 8476 critical care bed days. Non-ARLD admissions comprised 92,556 bed days and 4024 critical care bed days. ARLD was associated with longer average LOS (13 days v 10 days for non-ARLD; $p < 0.0001$). Males accounted for 66% of ARLD and 48% of non-ARLD admissions. The median age was 54 years for ARLD and 64 years for non-ARLD ($p < 0.0001$). Patients with a previous diagnosis of cirrhosis had longer average lengths of stay when admitted with UTI (15 days vs 10 days $p < 0.0001$), pneumonia (23 days vs 12 days $p < 0.0001$), TB (58 days vs 20 days $p < 0.0001$), influenza (15 days vs 8 days $p < 0.0068$) or intestinal infection (14 days vs 17 days $p < 0.0001$), when compared to patients without cirrhosis admitted with these conditions. There were a total of 1733 inpatient liver disease deaths over the 6 year period. 63% of these were related to ARLD (1089). ARLD deaths were more likely to be men (66%) and younger than non-ARLD (56 years vs 72 years < 0.0001). Inter-hospital liver related death rates varied significantly between 6 and 13%, whilst ARLD death rates varied between 6 and 18%. Inpatient liver disease death rates were double those of COPD and acute myocardial infarction respectively. Patients with cirrhosis also had statistically significant higher inpatient death rates when admitted with UTI, Pneumonia, TB, Influenza and intestinal compared to those without cirrhosis.
Conclusion: Liver disease poses a huge burden on the acute hospital infrastructure in Ireland, especially ARLD. ARLD patients are younger, more likely to be male, spend longer in hospital including intensive care and are at increased risk of death compared to non-ARLD. Liver disease mortality is higher than other common chronic conditions and appears to vary across hospitals. More effective public health and clinical measures are urgently required to reduce the morbidity and mortality associated with ARLD and its impact on acute hospitals.

SAT-484
Impact of alcohol binge duration and metabolic features on liver stiffness in steatotic liver disease
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Background and aims: Current screening questions for alcohol related liver disease (ALD) quantify total grams of alcohol intake within a day or week, but the duration of binges is not specified. We sought to understand trends in the impacts of binge drinking during short periods of time and metabolic factors on liver stiffness using transient elastography.
Method: Utilizing the National Health and Nutrition Examination Survey (NHANES) 2017 – March 2020, we included survey respondents with the following inclusion criteria: 1. ages 18 and older, 2. steatotic liver disease, defined as CAP score of at least 285 dB/min, 3. documented liver stiffness measurements (LSM) on transient elastography, 4. responses to alcohol intake questions, 5. presence or absence of metabolic risk factors. Patients not meeting all inclusion criteria were excluded. Using R (version 4.4.1), we applied survey-weighted generalized linear models with a quasibinomial link function to examine the relationship between alcohol intake and significant or advanced fibrosis, adjusting for covariates including gender, age, race, diabetes status, waist circumference, dyslipidemia, hypertension, and obesity.
Results: Of the 15,560 survey responses, 2,902 had steatotic liver disease (SLD). LSM > 8.5 kPa was considered as any fibrosis, and LSM > 13.1 kPa as advanced fibrosis, based on prior studies of SLD. Diabetes, hypertension and obesity remained significant risk factors for advanced fibrosis (OR 1.75, 95% CI 1.05–2.94; OR 2.27, 1.56–3.31, OR 7.36, 2.93–18.4). Non-Hispanic Black race was protective against advanced fibrosis (OR 0.57, 0.33–0.96). Based on documented alcohol intake and gender, 35% of respondents belonged in the MASLD category, 20% met-ALD category, and 11% ALD category. Categorization into either MASLD, Met-ALD, or ALD groups was not associated with fibrosis. To assess the impact of binge drinking, respondents were divided into three categories: excessively (every day to 4 times a week), moderately (twice a week to 2 times a month), rarely (once a month or less). Those with SLD who excessively drank 4–5 drinks within 2 hours had increased risk for both any and advanced fibrosis (OR 15.98, 14.49–17.47; OR 17.26, 15.13–19.38). Those who drank 12 or more alcohol drinks in one day excessively and moderately had increased risk for advanced fibrosis (OR 20.34, 16.96–23.71; OR 19.08, 16.28–21.88).
Conclusion: Our study underscores the impact of both metabolic risk factors and duration of intake periods of large quantities of alcoholic beverages on liver stiffness. Screening for ALD in the future may be enhanced by considering both the duration of alcohol binges and metabolic risk factors to stratify for risk of ALD and fibrosis.

SAT-485
Comorbidities at diagnosis of alcohol-related liver cirrhosis compared to the general population: a population-based case-control study of 11,989 patients
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Background and aims: Alcohol-related liver cirrhosis (ARLC) infrequently gives any symptoms before decompensation, leading to patients being diagnosed at a late stage when prognosis is dismal. Patients with ARLC may have a different comorbidity pattern than the general population, allowing for potential screening of pre-cirrhotic disease or high alcohol consumption in specific patient groups. Here, we compare the prevalence of comorbidities at or prior to the time of diagnosis of ARLC, to the prevalence in the general population.
Method: Using national registers, we identified all patients in Sweden with a first diagnosis of ARLC (ICD-10 code: K70.3) from 2006 to 2020 (n = 11 989) with up to 10 controls (n = 113 657), matched on age, sex, and place of residence at the time of ARLC diagnosis. Comorbidities were identified from 1998 to 2020 using ICD-codes from all in- and outpatient contacts with specialized care in Sweden.
Results: At diagnosis of ARLC we found several diagnoses with a significant difference between cases and controls. The comorbidities with the highest prevalence difference were: diseases of the liver (ICD-10 code: K70-K77, excluding K70.3), 48.3% in cases vs 0.3% in controls, mental and behavioral disorders due to psychoactive substance use (F10-F19), 48.8% in cases vs. 3.9% in controls, symptoms and signs involving the digestive system and abdomen (R10-R19), 43.9% in cases vs. 14.5% in controls and diseases of the esophagus, stomach and duodenum (K20-K31), 33.1% in cases vs 8.8% in controls. All differences were significant (p-value< 0.001).
Conclusion: Several comorbidities differ significantly between ARLC patients and controls at diagnosis. Almost 50% of patients later diagnosed with ARLC have diagnoses related to psychoactive substance abuse, suggesting screening in an alcohol use disorder center may be a potential tool to identify pre-cirrhotic disease. These findings may be of importance for early detection of patients at risk for future development of ARLC.

SAT-486

Fecal microbiota transplantation is associated with improvement in survival compared to standard of care in severe alcoholic hepatitis: systematic review and meta-analysis

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Background and aims: Alcohol-related liver disease (ALRD) affects 4.8% of the global population. Among these patients, 13.4% to 19.6% suffer from alcoholic hepatitis, which carries significant short- and long-term mortality rates. Current therapeutic options are limited, offering only modest short-term survival benefits aside from liver transplantation. Recent studies suggest that microbiota-based therapies may offer a novel therapeutic opportunity for patients with ARLD. In this study, we aim to evaluate and synthesize data from the literature focused on the application of FMT in ARLD.
Method: Databases including Embase, Medline, and CENTRAL were searched up to September 27, 2023. The pre-registered protocol on PROSPERO (CRD42023467455) was followed with no deviations. Studies comparing adult patients with ALRD, treated with fecal microbiota transplantation (FMT) or standard of care (SOC), were included. Investigated outcomes included overall survival, alcoholic recidivism, adverse events, and disease severity scores.
Results: Overall, ten studies were eligible for inclusion, comprising a total of 494 patients, of whom 339 were eligible for synthesis. Nine of ten included publications focused on severe alcoholic hepatitis (SAH). In these patients, FMT was associated with a significantly improved overall survival compared to SOC, with a hazard ratio (HR) of 0.50 (95% CI: 0.35–0.72; p = 0.0002). Survival benefits were most pronounced in patients who were ineligible for corticosteroid therapy. Specifically, when comparing FMT to pentoxifylline, the HR was 0.45 (95% CI: 0.21–0.96; p = 0.0345), and when comparing FMT with nutritional support, the HR was 0.36 (95% CI: 0.19–0.66; p = 0.0001).
Conclusion: FMT is a promising therapeutic option for improving short- and medium-term survival in patients with severe alcoholic hepatitis, particularly for those who are ineligible or unresponsive to corticosteroid therapy.

SAT-487

Disease severity is more important than age and underlying cirrhosis at predicting mortality from alcohol related hepatitis

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Background and aims: Alcohol related hepatitis is associated with a high mortality rate. Currently biochemical data is used to determine prognosis however there is a lack of data on the impact of pre-existing liver cirrhosis and age. We therefore analysed a cohort of patients with Alcohol related Hepatitis who had biopsy data to assess the influence that age and the presence of cirrhosis have on outcomes.
Method: The worldwide alcohol liver disease outcomes (WALDO) study is an international collaboration to create a database of patients with biopsy-proven liver disease and follow up information. Baseline information and clinical outcomes are noted from clinical records. Statistical analysis was performed using GraphPad Prism 10.4.
Results: 193 patients (97 (50.3%) males, mean age 47.4 years) with Alcohol related Hepatitis were included of which 116 (60.1%) patients had biopsy proven liver cirrhosis. 108 (56.0%) patients were under the age of 50. There were no significant differences in gender proportions between patients < 50 years and >50 years old (p = 0.082). Patients under 50 years presented with a higher mean white cell count (13.7 vs 10.9 (p = 0.016; 95% CI 2.81–1.15)) than those >50 years however there were no differences in mean bilirubin (259 vs 247 µmol/L; p = 0.661) or creatinine (88.83 vs 84.07 µmol/L; p = 0.521). Male patients

presented with a significantly higher creatinine (96.8 vs 75.4 (p = 0.003, 95% CI 7.32–35.56)). 128 (66.3%) patients died of which 61 (47.7%) deaths were liver related. In patients with cirrhosis, 41 (35.3%) patients died from liver related causes. 25 (19.5%) patients died within 90 days. Patients with underlying cirrhosis did not have a higher likelihood of overall mortality (OR 1.59, p = 0.155) or death within 90 days of biopsy (OR 1.88, p = 0.217). In patients under 50, the presence of cirrhosis did not increase the likelihood of liver related mortality (OR 0.74, p = 0.461). Male patients had a significantly increased risk of death within 90 days (OR 3.13, p = 0.019, 95% CI 1.20–8.15) and this remained significant when adjusted for the presence of cirrhosis (OR 2.91, p = 0.031, 95% CI 1.10–7.68). Age did not impact on 90-day mortality (OR 1.02) or overall liver related mortality (p = 0.350) however patients with a higher MELD score had a higher likelihood of 90-day mortality (OR 1.14, p = 0.021, 95% CI 1.03–1.29).
Conclusion: Liver related mortality is high in alcohol related hepatitis. Disease severity was predictive of death within 90 days however the presence of cirrhosis, age and gender did not impact on overall liver related mortality rates.

SAT-488-YI
Alcohol as a mediator of genetic and metabolic risk for fibrosis and steatosis in SLD

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Background and aims: The interplay of alcohol consumption and metabolic dysfunction in steatotic liver disease (SLD) progression is increasingly being acknowledged, e.g., by the novel category of "MetALD." Although genetic risk factors have been identified for both metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease, their contribution within distinct disease phenotypes is unclear. Thus, we aimed to explore the relationship between alcohol consumption, genetic risk, and metabolic dysfunction.
Method: A cohort of 1,442 patients with suspected SLD referred to a tertiary care center was retrospectively studied. Inclusion criteria were information on insulin resistance (IR) as quantified by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), self-reported alcohol consumption classified into three categories - abstinence or low (<20/30 g/day), moderate, and high consumption (>50/60 g/day) - as well as genetic testing of risk-modifying single nucleotide variants (PNPLA3 rs738409, TM6SF2 rs58542926, HSD17B13 rs72613567, and SERPINA1 rs28929474), and reliable liver stiffness measurement (LSM) with controlled attenuation parameter (CAP) using vibration-controlled transient elastography. LSM was used as surrogate for hepatic fibrosis, hepatic steatosis was defined as CAP ≥248 dB/m, IR as HOMA-IR ≥2.5.
Results: Mean age was 51.7 (15.5) years, 780 (54.1%) were male. 1138 (79.6%) patients reported no alcohol consumption, 203 (14.1%) reported moderate consumption, and 91 (6.3%) significant consumption. Mean CAP was 276 (63.1) dB/m, median LSM was 5.4 [4.3–7.1] kPa, 294 (20.4%) patients had suspected advanced fibrosis (LSM ≥8 kPa). 560 (38.8%) had IR. Genetic risk allele prevalence was as follows: PNPLA3 C/G in 561 (38.9%) and G/G in 129 (8.9%), SERPINA1 M/Z & S/Z in 92 (6.4%), TM6SF2 C/T in 243 (16.9%) and T/T in 12 (0.8%), and HSD17B13 T/A in 511 (35.4%) and A/A in 98 (6.8%). Moderate alcohol consumption (regression coefficient β = 0.19, p < 0.001), significant alcohol consumption HOMA-IR (β per log = 0.24, p < 0.001), BMI (β per kg/m² = 0.006, p = 0.003) (β = 0.71, p < 0.001), PNPLA3 G allele (β = 0.10, p < 0.001), and TM6SF2 T-allele (β = 0.08, p = 0.020) were independently associated with LSM (log-transformed). However, when considering interactions with alcohol consumption, a significant amplifying interaction between TM6SF2 T-allele (β for interaction = 0.47, p < 0.001) and PNPLA3 G-allele (β = 0.33, p = 0.001) and significant alcohol consumption was evident. Interestingly, the association of HOMA-IR with LSM was significantly enhanced by moderate alcohol consumption (β = 0.21, p = <0.001). Moderate alcohol consumption potentiated the effect of BMI (β = 2.98, p = 0.002) on hepatic steatosis.
Conclusion: Significant alcohol consumption potentiates the association between PNPLA3 and TM6SF2 risk alleles and hepatic fibrosis. Moderate alcohol consumption appears to accelerate fibrosis and steatosis development through its interaction with IR and BMI.

SAT-489
Monitoring hepatic function at 90 days of abstinence predicts recompensation and reduced liver-related mortality in patients with decompensated alcohol-related cirrhosis

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Background and aims: Alcohol abstinence can facilitate improvements in hepatic synthetic function and improve the prognosis in patients with alcohol-related (ALD) cirrhosis. However, the impact of dynamics in laboratory markers of hepatic function following abstinence on subsequent disease course requires further investigation.
Method: This study analyzed patients with decompensated ALD cirrhosis who achieved abstinence and underwent a paired blood-draw at time of abstinence and after 90 days (±30 days; = M3). The primary events of interest were liver-related death and hepatic recompensation (as defined by Baveno VII). Alcohol relapse and liver transplantation were considered competing events.
Results: 87 patients with decompensated ALD cirrhosis (89.7% ascites, 9.2% bleeding, 21.8% encephalopathy, 48.3% jaundice) were included at time of alcohol abstinence (median age: 52.4 years; 74% male) and followed for a median 31.8 (IQR: 10.9–48.9) months. At time of abstinence, median MELD was 20 (IQR: 16–26) and median albumin was 29.0 (IQR: 26.4–32.3) g/dL. At M3 reassessment under sustained abstinence, MELD decreased by a median 23% (p < 0.001), with 48 patients (55.2%) achieving a decrease >20%, and 16 (18.4%) reverting to MELD<10. Albumin increased by 18% (p < 0.001), with 40 patients (46.0%) achieving an increase >20%, and 40 (46.0%) replenishing to Albumin >35 g/dL. Over the course of the study, 21 patients (24.1%) achieved hepatic recompensation, while 14 patients (16.1%) experienced liver-related death. A decrease in MELD was associated with a significantly higher likelihood of recompensation (subdistribution hazard ratio [SHR] per 10% decrease: 1.19, p = 0.033), yet no association was observed for increased albumin (SHR per 10% increase: 1.07, p = 0.300). Improvements in both MELD and albumin were associated with a significantly decreased risk of liver-related death (MELD - SHR per 10% decrease: 0.85, p = 0.013; Albumin - SHR per 10% increase: 0.72, p = 0.008). In contrast, neither baseline MELD nor albumin alone were linked to hepatic recompensation (MELD - SHR: 1.02, p = 0.420; albumin - SHR per mg/dL: 1.00, p = 0.990) or to liver-related death (MELD - SHR: 1.06, p = 0.110; albumin - SHR per mg/dL: 1.02, p = 0.630). While M3 MELD and albumin as standalone values were significantly associated with liver-related death (MELD-SHR: 1.18, p < 0.001; albumin-SHR per mg/dL: 0.86, p = 0.023) both M3 MELD and M3 albumin were not associated with hepatic

recompensation (MELD-SHR: 0.93, p = 0.110; albumin-SHR per mg/dL: 1.07, p = 0.084; date of second blood draw as baseline).
Conclusion: Longitudinal monitoring of MELD and Albumin at M3 of continued abstinence enables the assessment of clinically meaningful improvements in hepatic synthetic function in ALD cirrhosis. While neither baseline nor M3 values alone predicted hepatic recompensation, improvements in MELD and albumin at M3 of abstinence were associated with a significantly higher probability of hepatic recompensation and a reduced risk of liver-related death.

SAT-490-YI
ALD is diagnosed at more advanced stages of fibrosis as compared to MetALD and MASLD in the general population
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Background and aims: Alcohol-associated liver disease (ALD) is more frequently diagnosed at stages of decompensated cirrhosis as compared to other etiologies of liver disease in tertiary care. However, there is no evidence on the stage of diagnosis of ALD in the general population. The aim of our study was to investigate the stage of fibrosis at diagnosis of ALD as compared to other causes of steatotic liver disease (SLD) in the general population.
Method: Cross-sectional analysis of two prospective cohorts included in screening programs for liver disease with transient elastography (TE) in the general population in Spain. SLD was determined by fatty liver index (FLI)≥60, Controlled Attenuation Parameter (CAP)≥263 dB/m or liver stiffness measurement (LSM) by TE≥10 kPa. Patients were categorized into: 1) ALD; 2) Metabolic dysfunction and alcohol associated liver disease (MetALD); 3) Metabolic dysfunction-associated steatotic liver disease (MASLD); 4) Others. Based on LSM by TE patients were classified in stages of no liver fibrosis (<10 kPa), liver fibrosis without portal hypertension (PHT) (10–25 kPa), fibrosis and PHT (>25 kPa).
Results: Out of 4,198 participants included in the study, 1,930 (46%) had SLD: 64 (3%) ALD, 216 (11%) MetALD, 1,639 (85%) MASLD and 11 (1%) others. The proportion of patients with liver fibrosis without PHT and liver fibrosis with PHT was 23% and 6% in patients with ALD, as compared to 7% and 1% in MetALD and 6% and 1% in MASLD ($p < 0.001$). Median LSM of the different SLD subtypes were 7.1 kPa, 5.6 kPa and 5.3 kPa in ALD, MetALD and MASLD ($p < 0.001$). Additionally, FLI values were highest in patients with ALD as compared to patients with MetALD and MASLD (90 vs 83 vs 78 [$p < 0.001$]); there was also a trend towards higher CAP values in patients with ALD and MetALD (296 vs 299 vs 288 dB/m in MASLD [$p = 0.095$]).
Conclusion: In a population-based setting, patients with ALD are identified and diagnosed at more advanced stages of fibrosis as compared to MetALD and MASLD. This study reinforces the need for developing screening programs specifically in patients with high-risk alcohol consumption.

SAT-491
ELIBIO MRI-based Digital liver biopsy correlates with elastography and blood test in patients with chronic liver diseases (CLD)
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Background and aims: Liver chemical shift-encoded MRI (CSE-MRI) is used for simultaneous fat and iron liver content estimation through PDFF and R2* measurements. However, CLD also requires evaluation of fibrosis severity. Although derived from a standard MRI sequence, CSE-MRI is underexploited. The use of phase CSE-MRI information allows the estimation of the magnetic susceptibility (CHI), a surrogate marker of the liver bulk macromolecule accumulation in the extracellular matrix. Previous work has demonstrated its interest in the diagnostic of MASH among MALFD patients (Leporq et al., NMR Biomed. 2017). This study aims to assess relationships between CHI and standard clinical parameters in a heterogeneous cohort of CLDs.
Method: Between February and November 2024, 106 patients who underwent a 1.5 T MRI CSE-MRI acquisition were retrospectively included. Considering a retrospective delay of 6-month between MRI and blood tests, FibroScan or SWE results, 38 patients were deemed eligible. PDFF, R2* and CHI values were automatically computed using EliBio software (SoQut-imaging, France). Correlations with blood tests, FibroScan LSM and SWE measurements were evaluated using Spearman's correlation test. Patients were stratified considering a LSM cut-off of 8.0 Kpa or 12.0 KPa as defined by the new EASL Clinical Practice Guidelines on MASLD management. Comparisons between stratified patients were performed using Man-Whitney test.
Results: Significant correlations ($p < 0.05$) were obtained between CHI and LSM ($r = -0.55$) or SWE stiffness ($r = -0.47$). Significant correlations ($p < 0.05$) were also obtained between CHI and blood tests: FibroTest ($r = -0.40$), Hepascore ($r = -0.67$), Agile 3+ ($r = -0.66$), Agile 4 ($r = -0.56$), Forns ($r = -0.51$) and FAST ($r = -0.48$). PDFF was significantly correlated ($p < 0.01$) with the controlled attenuation parameters ($r = -0.47$) and BMI ($r = 0.56$). CHI was significantly lower (-0.0272 vs -0.0154 ppm, $p < 0.01$) in patients with LSM lower than 8.0 Kpa ($n = 22$) when compared to those above 8.0 Kpa ($n = 16$) or considering a threshold of 12.0 KPa (-0.02 vs -0.0275, $p < 0.01$).
Conclusion: Due to its sensitivity to bulk macromolecules, magnetic susceptibility parameter CHI has a great potential to assess liver fibrosis. CSE-MRI could be an all-in-one alternative to provide a comprehensive liver analysis including fat, iron and fibrosis assessment using a single 20 s breath-holding acquisition. Further studies in larger cohorts are needed to confirm these preliminary results.

SAT-492
Colorectal cancer incidence in steatotic liver disease (MASLD, MetALD, and ALD)
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Background and aims: Obesity and alcohol consumption are established risk factors for colorectal cancer (CRC). Recently, a multi-society consensus group has introduced a new classification for steatotic liver disease (SLD), which encompasses metabolic dysfunction-associated SLD (MASLD), MASLD and increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD). However, the risk of developing CRC in each of these SLD subgroups is unknown. This nationwide cohort study investigated the risk of

CRC in MASLD, MetALD, and ALD patients. The primary endpoint was the occurrence of CRC in each SLD subgroup.
Method: We conducted a nationwide, population-based study that included 1,497,813 patients diagnosed with MASLD, MetALD, or ALD, alongside 4,885,536 individuals serving as normal liver control. The ***primary outcome*** was the incidence of CRC and the risk of CRC was compared between MASLD, MetALD and ALD.
Results: The 5- and 10-year cumulative CRC incidence rates were 0.22% and 0.48% for MASLD, 0.32% and 0.73% for MetALD, and 0.43% and 0.97% for ALD, and 0.15% and 0.31% for the normal liver control, respectively. The cumulative incidence of CRC was highest for ALD and significantly greater than that for MetALD, MASLD, and normal liver control (both $p < 0.001$). Using normal liver control as the reference and adjusting for age, sex, smoking habit, number of colonoscopies, diabetes mellitus, dyslipidemia, hypertension, and medication use, the adjusted hazard ratios (95% confidence interval) for CRC were 1.66 (1.54–1.80) for ALD, 1.31 (1.23–1.40) for MetALD, and 1.25 (1.18–1.31) for MASLD.
Conclusion: The risk of CRC differs significantly among patients with SLD, with the highest incidence observed in those with ALD, followed by MetALD and MASLD.

SAT-493-YI
A call to action - shortfalls and variation in care for inpatients with alcohol related liver disease in the UK: results of the ALERT UK national audit
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Background and aims: Alcohol-related liver disease (ALD) is the leading cause of liver related morbidity and mortality in the United Kingdom (UK). UK professional societies have recently published quality standards and key performance indicators (KPIs) to benchmark care. The Alcohol related LivER disease audit (ALERT- UK) is the first national evaluation of care for patients with ALD. We aimed to assess adherence to quality standards and to explore factors associated with the quality of care.
Method: All UK hospitals treating people with ALD were eligible to participate, with site recruitment facilitated via endorsing national societies, trainee networks and social media. Each site included the first 20 patients admitted with ALD with a discharge date from July 1st 2022–September 30th 2022. Patients were identified from site coding data using the validated Liverpool ALD Algorithm (LAA). Data on patient variables were recorded from the admission episode and at 1 year follow up. Audit compliance was set *a priori* at 90%.
Results: Centre level data were provided by 102 hospitals, with 81 hospitals submitting patient data (specialist centre n = 444, non-specialist centre n = 1078). 1522 individual patients were included (63% male, median age of 54 years (IQR 46,62), median UKELD 57 (IQR 52,62) and median length of stay of 8 days (IQR 4,18)). At admission, 82% of patients were active alcohol users and 27% presented with ALD for the first time. 68% of patients lived in the most deprived areas (index of multiple deprivation 1–5). None of the 7 KPIs met the compliance target. All KPIs were achieved in only 19.8%. Compliance was independently associated with age (0.97 (0.96–0.98, $p < 0.001$)), UKELD (OR 1.05 (1.03–1.07, $p < 0.001$)), region (OR 0.12 (0.01–0.63, $p = 0.044$) and specialist led care (OR 3.23 (2.17–4.95, $p < 0.001$)). Specialty review occurred within 24 hours for 62% of patients, alcohol care team involvement for 52% and dietician review for 44%. Of 149 patients eligible for consideration of liver transplantation, 115 (77%) were referred to a transplant centre. Only 39% of patients discharged had clinic follow up within 6 weeks, 6% received alcohol relapse prevention medications, and 4.8% were enrolled in a research study. Overall, 87% of patients survived to discharge and 62% were alive at 1 year. Survival rates did not differ between specialist and non-specialist centres but varied significantly across regions (admission survival: range: 78.8%–91.7%, p = <0.001); one year survival range: 49.1%–68.4% (p = 0.018)). At 1 year, 50% of surviving patients remained decompensated, 12% were referred to palliative care services and 21% of patients were lost to follow up.
Conclusion: ALERT-UK has revealed suboptimal adherence to quality standards and significant variations in care between centres and regions. Specialist care was associated with better adherence to quality standards. These findings highlight the need to address barriers to care and implement targeted interventions to improve outcomes.

SAT-494
Validating the association between alcohol-related hepatitis and alcohol-related cirrhosis: a population-based study
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Background and aims: Patients with alcohol-related hepatitis (AH) may present with features of decompensated cirrhosis. However, the association between the index date of cirrhosis and first admission of AH has not yet been well described. In this study, we identified all index admissions of AH in Alberta. We then described and validated the diagnosis and temporal association between alcohol-related cirrhosis among patients with AH.
Method: We used the national institute on alcohol abuse and alcoholism (NIAAA) criteria to identify index AH admissions in Alberta between 2012 and 2022 (n = 2,158) using the discharge admission database and provincial laboratory database. Validated algorithms of alcohol-related cirrhosis were used to identify the index diagnosis of cirrhosis among the AH cohort. We then selected a systemic random sample of 200 electronic medical records (EMR) for patients with cirrhosis prior to AH index date (n = 1,303, 60.4%) and 100 EMR for patients with cirrhosis after AH index date (n = 587, 27.2%) for validation. We also validated all EMR for patients with a cirrhosis diagnosis on the same AH admission date (n = 211) or no evidence of cirrhosis during the study time (n = 57). Data on ascites and portal hypertensive gastropathy (PHG) or variceal bleeding were obtained.
Results: During the study period, a cirrhosis diagnosis was identified in 97.4% of the whole cohort. The temporal relationship between index AH admission and cirrhosis was 60.4% with cirrhosis diagnosis prior to AH admission, 27.2% with cirrhosis after AH admission, and 9.8% with cirrhosis diagnosed at the same time of AH admission. In our study, 96.3% had validated AH diagnosis. The positive predictive value (PPV) of a cirrhosis diagnosis was 82.6% (422/511). PPV of having cirrhosis did not differ according to sex (male: 253/309 [81.9%] vs female: 169/202 [83.7%], p = 0.87). There was no difference in sex according to timing of cirrhosis (female sex: 41.5% cirrhosis prior to AH, 41.0% cirrhosis after AH and 37.0% cirrhosis at time of AH, p = 0.62). Comparably, age was similar among the groups (median age: 49 years among cirrhosis prior to AH, 45 years among cirrhosis after AH, and 48 years among cirrhosis at time of AH, p = 0.07). Features of decompensated cirrhosis were prevalent in our cohort (ascites 67.2%, variceal bleeding 14.8%, and PHG bleeding 19.4%).
Conclusion: Alcohol-related cirrhosis is more common than previously reported among patients with AH where 60% had cirrhosis

prior to their index presentation of AH. Early diagnosis and preventative measures are warranted among patients with high-risk alcohol consumption.

SAT-495

Stratification of liver fibrosis in individuals at-risk of metabolic dysfunction and alcohol-associated liver disease (MetALD)

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Background and aims: Metabolic dysfunction and alcohol-associated liver disease (MetALD) may increase liver fibrosis progression, but data on the optimal screening strategies are limited. We aimed to assess the performance of non-invasive tests (NITs) for detecting significant fibrosis in individuals at risk of MetALD.
Method: Cross-sectional study of prospectively enrolled adults identified as overweight or obese. We included adults at risk of MetALD defined by ≥1 of 5 cardiometabolic risk factors and self-reported alcohol use within MetALD ranges or lower self-reported alcohol use but with phosphatidylethanol (PEth) levels ≥25 ng/mL. Clinical assessment included contemporaneous magnetic resonance elastography (MRE) and vibration-controlled transient elastography (VCTE). Significant fibrosis was defined as MRE ≥3.14 kPa (or VCTE ≥7.6 kPa if MRE was missing). Analyses included area under the receiver-operating curves (AUROCs).
Results: Among 617 individuals screened, we identified 97 (15.7%) at risk of MetALD. The mean age was 50.6 ± 12.8 years, 67% were men, mean body mass index was 31.4 ± 6.5 kg/m2, and 12.4% had diabetes. Eight percent of individuals had significant fibrosis. Fibrosis-4 (FIB-4) ≥1.3 demonstrated good performance for significant fibrosis (AUROC 0.78, 95%CI:0.58–0.98, sensitivity 80%, specificity 76%, positive predictive value [PPV] 17%, and negative predictive value [NPV] 98%). VCTE ≥8 kPa also had good performance (AUROC 0.85, 95% CI:0.66–1.00, sensitivity 80%, specificity 91%, PPV 36%, and NPV 99%). A stepwise approach using FIB-4 followed by VCTE yielded a low false negative rate (2% with significant fibrosis misclassified as low-risk).
Conclusion: A clinical care algorithm utilizing a stepwise approach with FIB-4 and VCTE shows adequate performance in detecting significant fibrosis in individuals with suspected MetALD.

SAT-496

Steatosis independent of fibrosis predict hepatic decompensation and mortality in patients with MetALD and ALD

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Background and aims: Hepatic steatosis define SLD, but steatosis is considered benign in MASLD and is not linked to liver-related outcomes. Alcohol disrupts hepatic lipid metabolism why steatosis may increase the risk of liver-related outcomes in MetALD and ALD. This study investigated the role of steatosis as a predictor of liver-related outcomes in MetALD and ALD.
Method: This prospective cohort recruited individuals aged 18–75 with a current or previous alcohol overuse (>24 g/day for women, >36 g/day for men) > 1 year, and with no history of hepatic decompensation. Participants were categorized based on the grade of steatosis in their biopsy, according to the NAFLD Activity Score and fibrosis stage according to the NASH CRN classification. Patient follow-up was conducted through manual reading of electronic medical records, with hepatic decompensation events defined according to the Baveno VII criteria. We performed Cox regression models for hazard ratio.
Results: We biopsied 341 patients with excessive alcohol intake, with a mean age of 55 years (± 11 years), 256 (75%) were male, with a mean BMI of 28 (± 5) kg/m². At inclusion, 158 patients (47%) reported abstinence the week before inclusion. Histological steatosis was present in 192 (56%) patients. Among patients with histological steatosis, 26% had advanced fibrosis (>F3) while 28% had >F3 in the non-steatosis group. The distribution of steatosis ranged from mild steatosis (S1) in 82 patients (43%), moderate steatosis (S2) in 71 (37%), and severe steatosis (S3) in 39 (20%). During a mean follow-up period of 75 months (IQR 38), 56 patients experienced hepatic decompensation. We recorded 35 (18%) decompensating events in the steatosis group and 21 (14%) events in the non-steatosis group. A total of 84 patients died, hereof 49 patients (26%) with steatosis and 35 (24%) without steatosis. Patients with steatosis had a significantly higher risk of hepatic decompensation and overall mortality than those with non-steatosis, independent of age, sex, histological fibrosis stage and current alcohol intake. With non-steatosis as the reference, the risk of decompensation increased in a stepwise manner from S1 (HR = 0.98, 95% CI: 0.48–1.97) to S2 (HR = 1.62, 95% CI: 0.78–3.36) and S3 (HR = 2.48, 95% CI: 1.07–5.73). Similarly, overall mortality increased from S1 (HR = 1.22, 95% CI: 0.60–2.49) to S2 (HR = 1.63, 95% CI: 0.79–3.39) and S3 (HR = 3.68, 95% CI: 1.55–8.75).
Conclusion: The grade of steatosis is associated with the risk of hepatic decompensation and mortality in patients with MetALD and ALD. This suggests that lipid metabolism is central in MetALD and ALD and disrupted lipid metabolism may be linked to a higher risk of liver-related outcomes.

SAT-497

Predictors of alcohol relapse in patients with alcohol-associated liver disease after liver transplant evaluation

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Background and aims: Alcohol-related liver disease (ALD) is a foremost cause of liver transplantation (LT) in the United States, yet alcohol relapse remains a significant concern. Real-world evaluations of relapse prediction scores are limited and focus on relapse post-transplant. To optimize liver transplant outcomes, early identification of individuals at risk for alcohol relapse is crucial. This study primarily aimed to identify risk factors for alcohol relapse after liver transplant evaluation.
Method: Retrospective cohort including patients with ALD and/or alcoholic hepatitis (AH) referred for evaluation for LT from October 2021 to August 2023 at Baylor College of Medicine. ALD was defined as cirrhosis in patients consuming > 3 drinks (40 g) a day for women and > 4 drinks (60 g) for men in the absence of concomitant liver disease. AH was defined according to the NIAAA diagnostic criteria.

Retrospective chart review and collection of data were performed. Patients were divided into two groups: listed or not listed. Patients were categorized into 2 groups: those who relapsed after evaluation and those who did not. Alcohol Relapse was defined as a positive Peth test after evaluation following a period of sobriety.
Results: A total of 158 patients were included in our study (age 52.6 ± 10.8 years, BMI 28.6 ± 6.1 kg/m2, Female 43.7%). Demographics and clinical characteristics were similar between the relapse and non-relapse groups (all $p > 0.05$). When comparing patients who relapsed after liver transplant evaluation to those who did not, the following parameters were associated with a higher risk of relapse on univariable analysis: positive Peth test during the evaluation (OR 5.14; $p < 0.001$), lower age of alcohol consumption start (OR 0.82; $p = 0.015$), previous alcohol-related legal issues (OR 3.67; $p = 0.006$), more than 10 drinks/day during peak of alcohol consumption (OR 3.34; $p = 0.008$), history of bipolar disorder (OR 7.15; $p = 0.014$), and history of anxiety disorders (OR 3.14;$p = 0.019$). Active illicit substance abuse ($p = 0.068$) and shorter time from last drink to the evaluation date ($p = 0.066$) were close to significance. On multivariable analysis, positive Peth test on evaluation (OR 10.20; $p = 0.010$), previous alcohol-related legal issues (OR 14.65; $p = 0.008$), and history of bipolar disorder (OR 49.68; $p = 0.038$) were significantly associated with alcohol relapse after liver transplant evaluation.
Conclusion: Positive Peth test during the evaluation, alcohol legal issues, and a history of bipolar disease are the predictors of alcohol relapse after liver transplant evaluation.

SAT-498-YI
Cause-specific mortality across the spectrum of steatotic liver disease: a nationwide cohort study
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Background and aims: Steatotic liver disease (SLD) includes a heterogeneous group of phenotypes, with metabolic dysfunction and harmful alcohol use increasing the risk of liver and non-liver-related death. However, cause-specific death across SLD subtypes remain not well characterized in population-based cohorts, particularly for metabolic and alcohol-associated liver disease (MetALD). This study aimed to determine the risk of cause-specific death across the spectrum of SLD.
Method: We conducted a retrospective cohort study of adult patients with hepatic steatosis identified via natural language processing receiving regular outpatient care between 2010 and 2021 using data from the Veterans Health Administration linked to the National Death Index. The primary exposure was SLD subtype (metabolic dysfunction-associated steatotic liver disease [MASLD], alcohol-related liver disease [ALD], and MetALD) determined using a combination of cardiometabolic risk factors, alcohol use disorder diagnosis, and alcohol use disorders identification test-consumption (AUDIT-C) scores. The primary outcome was cause-specific death. The index date was defined as the first imaging study identifying hepatic steatosis. Follow up started from the index date to the occurrence of the primary outcome, lost to follow-up, or study end date (December 31, 2021). We first estimated incidence rates per 100 person-years and 10-year cumulative incidence within a competing risk framework. We then obtained hazard ratios (HR) using multivariable cause-specific Cox regression models with death from any other cause as the competing risk. Analyses were stratified by baseline cirrhosis status.
Results: Among 387,996 patients with SLD (MASLD 77.1%, MetALD 18.1%, ALD 4.8%), the mean age was 60.4 years, 7.5% were female, 66.8% were non-Hispanic White, and 1.9% had cirrhosis. Over a median follow-up of 5.5 years (IQR, 3.1–8.5), cardiovascular disease (CVD) and extrahepatic cancer were the leading causes of death in non-cirrhotic MASLD (10-year cumulative incidence 8.4% and 7.6%), MetALD (8.0% and 7.6%), and ALD (8.5% and 7.7%). Among those with cirrhosis, liver and CVD death dominated, with 10-year incidences of 9.3% and 10.6% in MASLD, 17.8% and 11.6% in MetALD, and 24.6% and 9.6% in ALD. The risk of HCC-related death was significantly higher in MetALD without cirrhosis (hazard ratio [HR], 1.19; 95% CI, 1.04–1.35) compared to MASLD. The risk of liver-related death was significantly higher in MetALD (HR, 3.38; 95% CI, 3.06–3.72) and ALD (HR, 6.88; 95% CI, 6.10–7.75) compared to MASLD without cirrhosis. Similar results were seen among those with cirrhosis.
Conclusion: CVD and extrahepatic cancer were leading causes of death in MetALD without cirrhosis, whereas liver-related deaths predominated in those with cirrhosis. MetALD showed a significant higher risk of HCC and liver-related death compared to MASLD.

SAT-499
Will individuals with alcohol use disorder participate in screening for chronic liver disease?
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Background and aims: Screening for chronic liver disease with a blood test or transient elastography is recommended in high-risk populations such as individuals with alcohol use disorders (AUD), but less is known about the user's perspective. This study aims to explore attendance and perceptions of screening for chronic liver disease with transient elastography vs. blood test in individuals with AUD.
Method: We used data from an ongoing randomized controlled trial (RCT) of screening for chronic liver disease in individuals attending treatment for AUD, allocating participants 2:1 to a transient elastography or a blood test with FIB-4 measurement, both performed in the nearby hospital clinic. Participants allocated to the blood test were responsible for calling to book their appointment, whereas those allocated to transient elastography were contacted directly by the investigator to plan their screening. We conducted a mixed-methods study. First, we used the exact binomial test to examine whether participation rates depended on screening modality. Then, we conducted semi structured individual interviews with participants of the RCT. Data from the interviews were analyzed using thematic analysis and informants were recruited until data saturation was reached.
Results: Individuals allocated to a transient elastography were much more likely to attend for the screening [115/121 (95%) attended the transient elastography] than were individuals allocated to a blood test [35/59 (59%) attended the blood test], p for a difference in the proportion < 0.00001. Based on interviews with 15 individuals attending the transient elastography, key motivators for attending the transient elastography included contributing to research, receiving a health check not offered by their general practitioner, and feeling privileged to get a free screening. For informants who expected a poor result, a good result brought relief, while some learned about liver health and alcohol's effects. For those with poor results, it was experienced as motivating to reduce alcohol use. Based on interviews with 10 individuals not attending the blood test, the main barriers were personal challenges and the time commitment required. Participants reported that they were not concerned about liver disease but might have been more likely to participate if the blood test could have been performed at the alcohol treatment center.

Conclusion: Attendance in screening for chronic liver disease was much higher for screening with transient elastography than blood test in individuals with AUD. If the blood test is taken at the AUD treatment center, it may increase the attendance for screening by blood test, however, this study revealed that some individuals with AUD might benefit from the conversation they have while having performed a transient elastography.

SAT-500-YI

Augmenter of liver regeneration as a novel biomarker in alcohol-related liver disease: insights into disease progression and prognosis

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Background and aims: Augmenter of Liver Regeneration (ALR) is critically linked to apoptosis and hepatic regeneration. However, its role in alcohol-related liver disease (ALD) remains unexplored. This study investigates the expression of ALR across the spectrum of ALD, its clinical course, and its prognostic significance.
Method: We enrolled 354 patients with ALD, categorized into acute-on-chronic liver failure (ACLF, n = 143), acute decompensation (AD, n = 57), non-acute decompensation (NAD, n = 100), compensated cirrhosis (CC, n = 23), alcohol-use disorder with fatty liver (AUD-FL, n = 20), and healthy controls (n = 10). Plasma levels of ALR and cytokines (IL-6, TNF-α, MCP-1, IL-10) were measured using ELISA. Associations between ALR, clinical parameters, and mortality were analyzed.
Results: Among 354 patients (median age: 45 years; IQR: 14; 97.5% male), ALR levels progressively increased from healthy controls to AUD-FL and CC but significantly declined from NAD to AD and ACLF ($p < 0.001$). ALR further decreased with advancing grades of ACLF ($p < 0.001$). In decompensated ALD (DeALD: NAD, AD, ACLF), ALR levels were lowest in patients with MELD >25 compared to MELD ≤ 25 ($p < 0.001$). ALR was negatively correlated with bilirubin, INR, creatinine, AST, and MELD ($p < 0.001$ each) and positively associated with albumin ($p < 0.001$), while these correlations were absent in non-decompensated ALD (NDALD: AUD-FL, CC). In AD and ACLF patients, higher baseline ALR levels predicted a resolving disease course ($p < 0.001$) and were associated with survival at 30 days, 90 days, and one year ($p < 0.001$ each). Each unit increase in ALR reduced the risk of mortality by 38% at 30 days (HR: 0.62, $p < 0.001$), 35% at 90 days (HR: 0.65, $p < 0.001$), and 32% at one year (HR: 0.68, $p < 0.001$). In DeALD, ALR was negatively associated with pro-inflammatory cytokines IL-6, TNF-α, and MCP-1 ($p < 0.05$ each), while a positive trend between IL-6 and ALR was observed in NDALD ($p = 0.051$), suggesting early regenerative activity.
Conclusion: This study identifies ALR as a novel biomarker reflecting hepatic regeneration, disease severity, and prognosis in ALD. ALR levels increase from fatty liver to CC but decline in decompensated stages, highlighting preserved regeneration in early stages and impaired regeneration in advanced disease. These findings position ALR as a potential therapeutic target to restore hepatic regeneration in advanced ALD.

SAT-501

Steatosis predicts poor abstinence rates in patients with alcohol use disorder

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Background and aims: Recent studies have shown that alcohol-induced steatosis is associated with increased long-term liver-related mortality. It remains unclear whether this is related to sustained alcohol use during follow-up. This study aimed to evaluate hepatic steatosis, measured by the Controlled Attenuation Parameter (CAP), as a predictor of abstinence in individuals with hazardous alcohol use.
Method: We conducted an analysis of a prospective liver disease screening cohort in patients with alcohol use disorder (AUD) treated at the Addiction Unit of a tertiary hospital between November 2019 and March 2024. Each patient underwent detailed medical history including AUDIT test, laboratory tests, and CAP measurement using transient elastography (TE). All patients were followed in the Addiction Unit for AUD for at least 6 months. Steatosis was defined as CAP ≥ 250 dB/m, and abstinence as no alcohol consumption for at least three consecutive months leading up to the six-month follow-up visit. Predictors of abstinence were evaluated using univariate and multivariate logistic regression.
Results: A total of 400 patients were included, of whom 168 (42%) had steatosis. Patients with steatosis were older, had higher rates of diabetes and dyslipidemia, and had increased body mass index. At six months, 42% of the cohort had achieved alcohol abstinence. Among patients with steatosis, 35% were abstinent, compared with 47% in those without steatosis ($p = 0.018$). Steatosis was independently associated with abstinence (OR 0.49 [95% CI 0.30–0.78]) along with age (OR 1.03 [1.01–1.05]), AUD medication (OR 1.85 [1.09–3.14]) and cholesterol levels (OR 0.99 [0.98–0.99]). Neither the amount or the duration of alcohol consumption, nor the severity of AUD (assessed by AUDIT), were associated with abstinence. In the subgroup analyses, CAP (OR 0.39 [0.21–0.72]) and comorbid substance use disorder (OR 0.53 [0.29–0.99]) were the only factors associated with abstinence in non-obese patients. There was no association between CAP and alcohol abstinence in obese patients.
Conclusion: These findings demonstrate for the first time that the presence of steatosis is linked to lower alcohol abstinence in patients with hazardous alcohol consumption. The difficulty in achieving abstinence during follow-up likely contributes to the poorer prognosis of patients with alcohol-related steatosis.

SAT-502

Prevalence and predictors of early re-hospitalization or death among a national cohort of veterans hospitalized for alcohol-associated hepatitis in the United States

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Background and aims: Pandemic-related surges in unhealthy alcohol use led to increasing incidence of acute hospitalizations due to alcohol-associated hepatitis (AH). High-risk alcohol use is particularly prevalent among U.S. Veterans, further fueling rates of AH in this population. We aim to evaluate prevalence and predictors

of early re-hospitalization or death among a national cohort of U.S. Veterans hospitalized for AH.
Method: Adults without cirrhosis hospitalized for AH from 1/1/2010–6/30/2024 were evaluated using the national Veterans Affairs (VA) database, which captures data for all Veterans utilizing VA healthcare facilities in the U.S. AH was identified using established criteria that incorporate both ICD-9/10 diagnosis codes and supporting laboratory data. The primary outcome was early re-hospitalization or death (reH/D) within 28-days, and the secondary outcome was reH/D within 90-days. Comparisons of reH/D within 28-days or 90-days was compared between groups using chi-square tests. Adjusted multivariable Cox proportional hazards models (adjusted for age, sex, race/ethnicity, ascites, hepatic encephalopathy, number of organ failures, MELD score, steroids or N-acetylcysteine treatment) evaluated for predictors of reH/D within 28-days or 90-days.
Results: Among 1,825 unique patients hospitalized for AH (91.5% men, mean age 51.6 ± 11.3y, 68.1% non-Hispanic white (NHW), 15.9% African American (AA), 8.2% Hispanic, 59.7% MELD > 20), 16.8% had reH/D within 28-days and 27.0% within 90-days. While no sex-specific differences in reH/D were observed, increasing age was associated with higher rates of early reH/D within 28-days (23.3% in age >60 y vs. 10.5% in age 18–39 y; aHR 0.58, 95% CI 0.39–0.86, $p < 0.01$) and 90-days (35.5% in age >60 y vs. 16.7% in age 18–39 y; aHR 2.69, 95% CI 1.90–3.81, $p < 0.01$). When stratified by race/ethnicity, Hispanics (21.2%) had the highest early reH/D and AA (11.0%) had the lowest. Compared to NHW, AA patients had lower risk of early or delayed reH/D (28-day: HR 0.58, 95% CI 0.39–0.86; 90-day: HR 0.72, 95% CI 0.54–0.96). Compared to patients with MELD<20, those with MELD>20 had greater risk of early reH/D (23.3% vs. 8.1%, aHR 2.56, 95% CI 1.83–3.57$p < 0.01$) and within 90-days (37.1% vs. 14.2%; aHR 2.42, 95% CI 1.88–3.11, $p < 0.01$).
Conclusion: Among a national cohort of U.S. Veterans hospitalized for AH, one in six experienced early reH/D, with older age and higher MELD as strong predictors. Timely identification of high-risk alcohol use and linkage to addiction treatment among Veterans is critical, but equally important is close follow-up and referral to alcohol abstinence support and treatment following AH hospitalization.

SAT-503-YI
Cardiac performance is impaired in patients with proven alcohol related hepatitis and and predicts 3-month mortality in this patient population
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Background and aims: Cardiac and systemic hemodynamic changes associated with alcohol-related hepatitis (AH) are unknown. This study aimed to assess cardiac and systemic hemodynamic changes in patients with a clinical suspicion of AH, as well as their prognostic value.
Method: We conducted a retrospective analysis of prospectively collected data. All patients referred for transjugular liver biopsy for a clinical suspicion of AH between January 2013 and December 2023 were included and separated into proven and unproven AH based on histology. A group of patients with alcohol-related cirrhosis assessed for liver transplant (LT) and abstinent from alcohol was also included, as a reference group. Serum bilirubin was > 50 µmol/L in all patients. All patients underwent right heart and liver catheterization. Cardiac performance was assessed using the left ventricular stroke work index (LVSWI). Comparisons between groups were unadjusted (Mann-Whitney) and adjusted on MELD and on either leukocyte count or CRP (multivariable logistic regression).
Results: 749 patients were included: 463 with histologically proven AH (median MELD 23), 188 with histologically unproven AH (median MELD 22), and 98 with alcohol-related cirrhosis (median MELD 20). HVPG was not different between the 3 groups. Compared to patients with alcohol-related cirrhosis assessed for LT, those with proven AH had lower LVSWI ($p = 0.001$), cardiac index ($p < 0.001$), and higher diastolic blood pressure ($p = 0.01$) and systemic vascular resistance ($p = 0.001$), when adjusted on MELD and leukocyte count (similar for CRP). Compared to patients with a suspicion of AH ruled out by liver biopsy, those with proven AH had lower LVSWI [median 56.6 g/m2/beat (IQR 47.6–68.9) vs. 50.9 g/m2/beat (IQR 42.9–59.9), respectively; $p < 0.001$], and higher heart rate [median 79 bpm (IQR 68–90) vs. 87 (IQR 75–97), respectively; $p < 0.001$]. Difference of LVSWI remained significant when adjusting on MELD and leukocyte count or CRP ($p < 0.001$). Lower LVSWI was still associated with proven AH, when focusing on patients with or without beta-blockers, analyzed separately. In patients with proven AH, the only hemodynamic values associated with 3-month survival was LVSWI ($p < 0.001$). LVSWI remained associated with survival when adjusting on clinical variables associated with outcome at univariate analysis, i.e. age, sex, hepatic encephalopathy, prothrombin index, leukocyte count, serum bilirubin, creatinine, CRP and AST. Cumulative incidence of death at 90 days was higher (41%) in patients with proven AH with LVSWI < 44.7 g/m2/beat (i.e. the Youden index value), than in patients with proven AH with LVSWI above that threshold (23%) and than in patients with unproven AH with low (29%) or high LVSWI (23%) ($p < 0.001$).
Conclusion: This study showed that proven AH is strongly associated with compromised cardiac performance, a feature associated with impaired 3-month survival.

SAT-504
Rising proportion of young adults and women on the U.S. liver transplant waitlist for end-stage liver disease attributed to rising alcohol-associated liver disease following the COVID-19 pandemic
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Background and aims: Significant increases in high-risk alcohol use among U.S. adults were observed following the onset of the COVID-19 pandemic. This led to a spike in alcohol-associated liver disease (ALD) hospitalizations and liver transplants (LT). We aim to evaluate how LT trends have evolved 4 years following onset of the COVID-19 pandemic in the U.S., with a focus on understanding differences in LT indication by race/ethnicity and other sociodemographic factors.
Method: Adults (≥18 years old) with ESLD without HCC who were listed for LT from 2018 to 2024 were evaluated using data from the United Network for Organ Sharing registry using three time periods corresponding to the period before, during, and following the COVID-19 pandemic: Era 1 (3/1/2018–2/29/2020), Era 2 (3/1/2020–2/28/2022), and Era 3 (3/1/2022–2/29/2024). Trends in new LT waitlist registrants were evaluated by liver disease etiology and patient demographics. Comparisons of trends across aforementioned time periods were evaluated using the z-statistic and trends test.
Results: We identified 49,949 adults with ESLD awaiting LT from 2018–2024 [median age [IQR] 57 years [48–64], 62.6% men, 70.9%

non-Hispanic White, 5.8% African American, 17.8% Hispanic, 4.0% Asian, 1.0% American Indian/Alaska Native. Overall, 45.3% of patients were listed for ALD, of which 10.0% were acute alcohol-associated hepatitis. The proportion of LT waitlist registrants with ALD increased steadily from 38.7% in Era 1 to 46.2% in Era 2, and in Era 3, more than half (50.1%) of all adults ESLD waitlist registrants had ALD. The demographics of waitlist registrants with ALD have demonstrated a growing proportion of young adults (proportion of ALD age 18–39 years old: Era 1–13.6%, Era 2–17.4%, Era 3–17.5%) and women (Era 1–28.8%, Era 2–30.6%, Era 3–31.8%). Similar trends were seen in actual LT performed, with proportion of LT for ALD increasing from 37.8% in Era 1 to 46.8% and 51.2% in Eras 2 and 3, respectively. Rising proportion of young adults age (18–39 years) and women with ALD undergoing LT were also observed, and in Era 3, young adults and women represented 18.5% and 31.8% of adults with ALD receiving LT, respectively ($p < 0.01$ for trend).
Conclusion: ALD contributing to ESLD requiring LT represents more than half of waitlist registrations and LTs performed in the U.S. The rising burden of ALD-related ESLD among young adults and women emphasizes the need for concerted efforts to address unhealthy alcohol use among these at-risk populations.

SAT-514
High-risk PNPLA3 rs738409 genotype is associated with higher CCL2 concentrations in liver transplant candidates with alcohol - related liver disease
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Background and aims: Patients with GG rs738409 patatin-like phospholipase domain-containing protein 3 (PNPLA3) genotype have a greater risk of developing steatotic liver disease and hepatocellular carcinoma (HCC). We aimed to analyze the association between the PNPLA3 genotype and augmented inflammatory response in transplant candidates with alcohol-related liver disease (ALD).
Method: Sera concentrations of 13 cytokines (IL-1, IFN-α, IFN-γ, TNF-α, IL-6, CXCL8, IL-10, IL-12, IL-32 and IL-33, IL-17, IL-18 and CCL2) were measured in 106 ALD liver transplant candidates without HCC (40 with CC, 40 with CG and 26 with GG), 35 with HCC ($n = 35$) and 19 controls by cytometric bead array.
Results: Ten cytokines (IL-1, IFN-α, IFN-γ, TNF-α, IL-6, CXCL8, IL-10, IL-12, IL-32 and IL-33) had significantly higher sera concentrations in ALD patients in comparison to the controls, whereas there was no difference in IL-17 and IL-18 concentrations, and CCL2 concentration was significantly decreased. Patients with HCC had concentrations of all cytokines similar to those of ALD patients without HCC. Concentrations of CCL2 were in a negative correlation with INR ($\rho = -0.412$, $p < 0.001$), while a positive, but weaker, correlation with INR was found for IL-6 ($\rho = 0.278$, $p < 0.01$). Concentrations of CXCL8 ($\rho = 0.248$, $p < 0.05$) and IL-1 ($\rho = 0.232$, $p < 0.05$) correlated with bilirubin concentration. ALD GG carriers had significantly higher concentrations of CCL2 (212.6 (135.9–264.9)) than patients with CC/CG genotype (141.3 (104.1–201.6), $p = 0.002$, Mann-Whitney). We found no significant association for the remaining 12 measured cytokines ($p > 0.05$ for all conducted analyses).GG carriers also had significantly higher levels of AST and ALT and lower platelets.
Conclusion: The risk GG rs738409 PNPLA3 genotype is associated with increased concentration of CCL2 in patients with ALD, suggesting that increased concentration of CCL2 may contribute to the greater risk for development of HCC among the GG carriers.

Cirrhosis and its complications – ACLF and Critical illness

TOP-204
Efficacy of 5% albumin versus plasmalyte in combination with 20% albumin for fluid resuscitation in cirrhosis with sepsis induced hypotension. A randomized controlled trial (ALPS Plus)
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Background and aims: 5% albumin(5% Alb) is superior to normal saline for reversal of shock in critically ill cirrhosis (CIC) with sepsis induced hypotension (SIH) (FRISC). Plasmalyte was shown to be safer against 20% albumin with reduced incidence of pulmonary complications in CIC with SIH (ALPS trial). The comparison of 5% albumin against plasmalyte has never been studied in CIC.
Method: CIC with SIH underwent open label, 1:1 randomization to receive either 5% Alb alone (5 ml/kg bolus over half hour followed by 50 ml/hr) or plasmalyte (P+Alb20) (30 ml/kg bolus over half hour followed by 100 ml/hr) with 20–40 g of 20% albumin administered over 24 hours. Further, fluid boluses were guided by point of care ultrasound (POCUS) done every hourly for 3 hours. The primary endpoint was attainment of mean arterial pressure (MAP) >65 mm Hg without vasopressor at 3 hours.
Results: Baseline characteristics were comparable in both the groups; MAP (mm Hg) (59.47 ± 4.17 vs 59.90 ± 3.04; $p = 0.58$), arterial lactate (mmol/L) (2.51 ± 1.75 vs 2.60 ± 1.73; p value = 0.79), SOFA score (8.98 ± 2.09 vs 8.94 ± 2.47; $p = 0.93$), MELD score (28.38 ± 9.41 vs 29.43 ± 10.09; p value = 0.60), Inferior vena cava diameter (IVC) (mm) (14.4 ± 3.7 vs 15.2 ± 4.5; $p = 0.379$) with collapsibility index (IVCCI %) >40% and distensibility index (IVCDI %) >18% in all the patients and POCUS showed A pattern in all the patients. Majority of patients were alcohol related liver disease (67.7%), source of sepsis was pulmonary in 47%, Spontaneous bacterial peritonitis in 24% patients. Reversal of shock at 3 hours (45.8% vs 52%; $p = 0.54$) and 24 hours (59.6% vs 63%; $p = 0.73$) was similar in both the groups. The volume of fluid (ml) received at 3 hours was higher in P+Alb20 vs. 5% Alb (605.2 ± 257.2 vs 2248 ± 714.2 ml; $p = 0.0001$) while the dose of albumin per day (g/dl) was higher in 5% Alb (67.7 ± 19.9 vs 35 ± 8.6; $p = 0.0001$). The time to initiation of norepinephrine (hours) was similar 3.4 ± 4.5 vs 3.1 ± 3.6 hours ($p = 0.8$). The change in the IVC diameter, IVCCI and IVCDI was similar ($p = 0.34$, $p = 0.88$, $p = 0.38$), but more patients developed B lines on POCUS at 3 hours in 5% Alb (13.3% vs 2.1%; $p = 0.04$). At 28 days, 71.9% patients in P+Alb20 and 80% in 5% Alb had died (relative risk 0.64; 95% confidence interval [CI], 0.20 to 2.08; $p = 0.55$). The need for dialysis (52.1% vs 51%; $p = 0.91$), serum chloride level at 24 hours (mEq/L) (104.37 ± 9.55 vs 101.28 ± 6.35; $p = 0.161$), hypernatremia (sodium >145 mEq/L) (10.4% vs 9.8%; $p = 0.91$) and respiratory distress (12.5% vs 7.8%; $p = 0.44$) at 24 hours was similar in both groups. No patient developed pulmonary complication at 3 hours.
Conclusion: Plasmalyte with low dose 20% albumin is as effective as 5% albumin for reversal of shock in critically ill patients with SIH. The use of POCUS can reduce the incidence of pulmonary complications

and also guide effective fluid resuscitation. Trial registration - NCT06076330.

TOP-217-YI

Pathophysiological basis of acute on chronic liver failure (ACLF) triggered by alcohol-related hepatitis or infection using circulating biomarkers of inflammation, circulatory dysfunction and albumin modifications

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Background and aims: ACLF occurs in cirrhosis patients and characterized by multi-organ failure and high mortality. Although inflammation is important in the pathogenesis of ACLF, it is unclear what role circulatory dysfunction plays. The patterns of changes in biomarkers in the two commonest triggers of ACLF; infection (inf) and severe alcohol-related hepatitis (sAH) in patients with cirrhosis are also unknown. To better understand the pathophysiology, we compared a large panel of biomarkers in sAH- and inf-ACLF patients and their association with outcomes.

Method: 1019 patients from CANONIC, PREDICT, ACLARA with either sAH or inf-induced acute decompensation were included (sAH-AD, n = 546), sAH-ACLF (n = 239) or inf-ACLF (n = 234). Biomarkers assessed included those representing systemic inflammation, circulatory dysfunction and albumin function. Uni- and multivariable regression analyses were performed.

Results: IL-6, IL-17A, TNF-alpha, IL-10, IFN-gamma, G-CSF and copeptin were significantly higher in inf-ACLF, while IL-8 and eotaxin was elevated in sAH-ACLF. IL-6 and eotaxin levels independently differentiated sAH-ACLF from inf-ACLF. In univariable regression analyses for 28-day mortality, IL-6, IL-10, IL-1ra, G-CSF, GM-CSF, NGAL, and renin were associated with higher risk of 28-day mortality in both ACLF groups. In multivariate analyses, IL-10 (HR: 1.28; $p < 0.001$) was only predictor of sAH-ACLF mortality, while IL-8 (HR: 1.13; $p < 0.001$) predicted mortality in inf-ACLF. In sAH-AD compared to sAH-ACLF, IL-1 alpha, IL-17A, IFN alpha2 and gamma were significantly higher, whereas levels of IL-6, IL-8, IL-10, TNF alpha, IP 10, NGAL, HNA2 and copeptin were significantly lower. In the group of sAH-AD patients who developed ACLF within 28-days, IL-6, TNF alpha, NGAL, copeptin and HNA2 were significantly higher. IL-8 and HNA2 independently differentiated sAH-AD from sAH-ACLF.

Conclusion: Our study highlights significant differences between sAH-ACLF and inf-ACLF, not only in their clinical presentation but also in their cytokine profiles. In sAH-ACLF, the immunosuppressive cytokine, IL-10 emerged as an independent driver of mortality. In contrast, in inf-ACLF, pro-inflammatory IL-8, was the independent predictor of mortality. Additionally, we show that IL-8 and HNA2 independently differentiated AD from ACLF in patients with severe alcohol-related hepatitis. Our findings suggest that disease driving mechanisms are distinct in different ACLF entities and better characterization and personalized approaches are needed to impact on developing therapeutic strategies.

TOP-218

Yaq-001 positively impacts gut microbiome composition, virulence, antimicrobial resistance gene profile resulting in significant effects on ammonia, endotoxemia and inflammation in cirrhosis patients

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Background and aims: Yaq-001 is a novel, non-absorbable, gut-restricted nanoporous carbon bead adsorbent. Pre-clinical studies demonstrated its ability to reduce fibrosis, portal hypertension, and organ dysfunction, partially by restoring dysbiotic gut microbiome composition and endotoxemia. A Phase 2 clinical trial confirmed its safety in patients with cirrhosis. The aims of this study were to evaluate the effect of Yaq-001 on the gut microbiome and its association with ammonia metabolism, inflammation and endotoxemia.
Method: 28-patients with compensated cirrhosis were randomized (double-blind) to receive Yaq-001 (4 g once daily) or Placebo. Gut microbiome and biomarker analyses at baseline, after 4-weeks and after 12-weeks were performed. Shotgun sequence reads of the microbiome samples were mapped against the Integrated Gene Catalog of human gut microbiota to generate a gene count table and a species abundance table. Changes in biomarkers and relationship with microbiome composition were assessed.
Results: Yaq-001 was safe and no differences in liver function were observed. Alpha or beta diversity and the distribution distances of the different pairs at different time points were unaltered. Yaq-001 increased the abundance of bacteria associated with improved gut health such as *Adlercreutzia equolifaciens* ($p < 0.05$), a bacterium with anti-inflammatory properties commonly depleted in liver disease and decreased abundance of bacteria associated with infections and poor outcomes such as *Klebsiella pneumonia* and *Streptococcus mutans* ($p < 0.05$ each). Yaq-001 impacted positively and significantly on virulence factors such as siderophores, fimbriae structures and lipopolysaccharides (LPS) that are associated with inflammation and invasion ($p < 0.05$ each). Systemic LPS, NGAL, LBP, creatinine and ammonia showed the highest positive correlations with the virulence factors ($r > 0.28$, $p < 0.025$ each). Antibiotic resistance genes (ARGs) that are linked with negative disease outcomes, decreased in the Yaq-001 group. One gene associated with secondary bile acid metabolism decreased in the Yaq-001 group and showed significant correlations with serum and fecal secondary bile acid concentrations ($r > 0.5$, $p < 0.001$).
Conclusion: The results show that Yaq-001 impacts positively on the composition of the microbiome, significantly reduces its virulence and ARGs resulting on impacts on systemic inflammation and endotoxemia. Late phase clinical trials in cirrhosis are justified.
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Human cytomegalovirus reactivation in cirrhotic individuals with acute decompensation

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Background and aims: Human cytomegalovirus (HCMV) reactivation frequently occurs in immunocompromised host and is related to an excess of graft rejection and a major cause of fatal cases during the first year after transplantation. However, information about HCMV reactivation in cirrhotic population is very limited. In this study, we aimed to investigate its incidence and association with hepatic outcomes in acutely decompensation (AD) patients.
Method: Two sets prospective multicenter cohorts (Cohort 1 and Cohort 2, respectively) of AD patients who were HCMV seropositive were investigated. Cohort 1 was conducted from November 2020 to December 2023 in four tertiary hospitals in China. Cohort 2 was selected from the investigation cohort of Chinese Acute-on- Chronic Liver Failure study by using a simple random sampling technique. HCMV reactivation was diagnosed via commercially available real-time polymerase chain reaction with low limit detection at 100 copies/ml.
Results: HCMV reactivation at baseline was diagnosed with both 4.8% patients in Cohort 1 (35/722) and Cohort 2 (14/291). Patients with HCMV reactivation had higher MELD-Na scores than those without reactivation (27 [23–32] vs. 18 [11–26] in Cohort 1, $p < 0.001$; 27 [20–33] vs. 15 [10–23] in Cohort 2, $p = 0.001$) and a higher incidence of acute-on-chronic liver failure (ACLF) (48.6% vs. 16.4% in Cohort 1, $p < 0.001$; 35.7% vs. 9.7% in Cohort 2, $p = 0.011$) and bacterial infection (88.6% vs. 53.3% in Cohort 1, $p < 0.001$; 78.6% vs. 44.8% in Cohort 2, $p = 0.013$). In both cohorts, patients with HCMV reactivation at baseline had increased mortality compared with those without reactivation (49.6% vs. 18.1% in Cohort 1; 57.1% vs. 15.3% in Cohort 2; both $p < 0.001$) and was an independent risk factor for 90-day transplant-free mortality (HR: 1.740 in Cohort 1, $p = 0.038$; HR: 3.148 in Cohort 2, $p = 0.005$). This result appeared to be consistent across different MELD-Na scores and bacterial infection subgroups. As an opportunistic pathogen, patients with HCMV reactivation are both prone to developing ACLF during hospitalization or a 28-day follow-up period compared to non-infection individuals among non-ACLF patients at baseline (38.9% vs. 6.3% in Cohort 1; 33.3% vs. 2.0% in Cohort 2; $p < 0.001$). Among the total of 49 patients with HCMV reactivation in these two cohorts, 9 patients in Cohort1 and none in Cohort 2 had received antiviral therapy (ganciclovir) according to clinicians' decision. Due to the high fatality rate of patients with Grade-3 ACLF, they were excluded from the analysis of impact of anti-HCMV therapy on 90-day mortality. In the multivariable analysis with the inverse probability weighting, there was a significant association between antiviral treatment and death (HR:0.151, 95%CIs: 0.032–0.723).
Conclusion: HCMV reactivation was associated with increased 90-day mortality and development of ACLF. These observations support the use of HCMV reactivation as part of a risk stratification and potential interventional target in the management of AD patients.

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Efficacy of Granulocyte Colony-stimulating factor in hepatitis B virus-associated acute-on-chronic liver failure patients: a multicenter study

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Background and aims: The role of Granulocyte Colony-stimulating Factor (G-CSF) as a potentially effective drug in acute-on-chronic liver failure (ACLF) is still controversial. The aim of this study was to evaluate the efficacy of G-CSF in the treatment of patients with HBV-ACLF and to assess prognosis by selecting appropriate indicators for monitoring for early intervention.
Method: In this multicenter, nonrandomized, open-label prospective study, 284 patients who met APASL-ACLF criteria were screened and assigned to G-CSF group (300 mg/d G-CSF for the first 6 days and every other day to day 18 thereafter, n = 119) or standard drug therapy group (SMT group, n = 165) based on patient preference at 7 medical facilities in China, from June 2020 to June 2024. We assessed survival until day 90. The delta value (d-value) between each time point and the baseline was used to assess the change in the biomarker. The d-values of the two groups of biomarkers were compared, and the variables with differences were screened out and applied to establish the Cox proportional hazard regression model in G-CSF group, and the specific threshold was determined by X-tile software.
Results: The 90-day transplant-free survival rate was 80.2% in G-CSF treated patients versus 66.3% in the SMT group (p = 0.024).The dMon, dINR in G-CSF group was higher than that in SMT group at day 4,7 (p < 0.05). And the dWBC, dNeu, dGGT in G-CSF group was higher than that in SMT group at day 4,7,14 (p < 0.05). The d-values that differed between the two groups were taken out separately and modeled in the G-CSF group. In the G-CSF group, multivariate Cox regression showed that dMon14 (HR = 16.95, p = 0.021), dNeu14 (HR = 2.12, p = 0.04), dINR4 (HR = 4.92, p = 0.002) were associated with 90-day death. Patients in the high-risk group (dMon14 > 0.07, or dINR4 > 0.03) had worse survival rates, indicating the need for early intervention.
Conclusion: G-CSF can effectively improve the 90-day transplant-free survival of patients with HBV-ACLF (APASL criteria). In the process of G-CSF treatment, blood routine and coagulation should be dynamically monitored. When dMon14 >0.07 and dINR4 >0.03, the patient may have a poor prognosis after treatment with G-CSF, suggesting the need for early intervention.

FRI-165

Prevalence and characteristics of bacterial and fungal infections in end-stage liver disease: a multi-center, cross-sectional study from central China

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Background and aims: Patients with end-stage liver disease (ESLD) are at an elevated risk of bacterial and fungal infections due to their weakened immune systems and compromised liver function. This cross-sectional study aims to assess the prevalence, types, and risk factors associated with infections in ESLD patients, providing insights into the clinical characteristics and outcomes of these infections.
Method: A cross-sectional study was conducted, encompassing patients with stable decompensated cirrhosis (SDC), unstable decompensated cirrhosis (UDC), acute on chronic liver failure (ACLF) and Pre-ACLF from multiple tertiary hospitals in central China, spanning from January 2012 to December 2023. Data on demographics, laboratory results, complications, types of infections, identified pathogens, organ failure incidences and mortality were collected at admission and subsequently analyzed.
Results: Out of the 1328 patients enrolled, 935 were classified as SDC&UDC, 121 as Pre-ACLF, and 272 as ACLF, with bacterial infection rates of 38.3%, 52.1%, and 62.1% at admission, respectively. Within the ACLF group, bacterial infection rates for ACLF-1, ACLF-2, and ACLF-3 were 57.5%, 64.8%, and 56.3%, respectively. In each ESLD phenotype, spontaneous bacterial peritonitis (SBP) and pneumonia were the most common types of bacterial infections. Out of 67 identified bacteria, the most prevalent strains were *Enterococcus faecium* among Gram-positive organisms (9/32) and *Escherichia coli* (18/35) among Gram-negative organisms. Ascites was identified to be an independent risk factor for bacterial infections across all ESLD phenotypes (SDC&UDC, Pre-ACLF, and ACLF). SBP shows a moderate positive correlation with ascites (r = 0.675; $P < 0.001$), and pneumonia exhibits a moderate positive correlation with ACLF-2 (r = 0.730; $P = 0.007$). The 90-day mortality rates for patients with bacterial infections at admission in the SDC&UDC (10.4% vs 5.0%; $P = 0.002$) and ACLF-1 (38.6% vs 15.2%; $P = 0.028$) groups were significantly higher than those without infections. Fungal infections were identified in 7 SDC&UDC patients (0.7%), 6 Pre-ACLF patients (5.0%), and 5 ACLF patients (1.8%), with corresponding 90-day mortality rates of 14.3%, 66.7%, and 80%, respectively.
Conclusion: Bacterial infections are highly prevalent in ESLD patients and are associated with significant mortality. Early identification of risk factors and prompt initiation of targeted antimicrobial therapy are crucial for improving outcomes in this vulnerable patient population.

FRI-166

Real-world evidence on clinical outcomes and microbiome changes after healthy donor stool transplantation as palliative therapy compared to best supportive care in patients with unstable decompensations in alcohol-related end-stage liver disease

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Background and aims: Alcohol-associated hepatitis (AH) can trigger unstable decompensations in cirrhosis patients. In the absence of curative liver transplantation, they experience high rates of emergency department visits, hospitalization, and life-threatening events. In resource-poor setting, palliative care in such end-stage liver disease (ESLD) patients aims to improve quality of life but not survival. In this real-world experience report, we aimed to study clinical events and overall survival in unstable alcohol-related

cirrhosis (ALC) patients undergoing healthy donor stool transplant (FMT) as an adjunct to standard palliation compared to a control group on best supportive care (BSC).

Method: From July 2021 to April 2024, we enrolled ALC patients with severe unstable decompensations two months post index AH. Twenty-eight patients on palliative FMT along with BSC were compared with 37 patients on BSC. Patients on FMT received 150 ml daily freshly processed healthy donor stool infusion for five days through a nasoduodenal tube. Both groups were treated for symptoms and complications per standard recommendations. Patients were followed up for portal hypertension-related events, infections, hospitalizations, extrahepatic organ failure, as well as 6-, 12-months and overall survival. 16S rRNA sequencing on stool samples were collected at baseline and on follow up to analyze changes in relative abundance (RA) of bacterial communities between groups.

Results: Patients were matched for age, type of decompensation and liver disease severity at enrolment. Among those hospitalized at outset and with infection, septic shock was significantly lower in those receiving FMT (10.7% v 44.4%, P = 0.02). During first 90-days of follow up, hospitalizations (P < 0.001), overt hepatic encephalopathy (HE, 4% v 35.3%, P < 0.001), sepsis (28% v 58.8%, P = 0.02), and worsening ascites (28% v 67.6%) were significantly lower in FMT. Decompensation (90.6% v 58.3%, P = 0.005) beyond 90-days and unstable decompensations (72.7% v 28.6%, P = 0.005), overt HE (57.6% v 4%, P < 0.001) and variceal bleeding (48.5% v 7.7%, P < 0.001) were significantly higher in BSC group. Nonetheless, at median follow-up of 13- in BSC and 16.5-months in FMT, the overall, as well as 6- and 12-months survival were not significantly different between groups. Microbiome analysis revealed progressive expansion of Gram-negative genera in BSC, and beneficial Actinobacteria in FMT-treated patients at 3, 6, and 12 months from baseline.

Conclusion: Healthy donor FMT as an adjunct to palliative care ameliorated adverse clinical events, but not clinical outcomes (long-term survival) in ALC-ESLD compared to BSC. Nonetheless significant reduction in rates of hospitalization, portal hypertension events, HE, and severe infections reveal a strong palliative role for FMT in end-stage liver disease patients, which beckons prospective validation.

FRI-167

AI-AD score: a novel machine learning-based model for predicting acute liver decompensation progression – a prospective observational study

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Background and aims: Patients with advanced chronic liver disease (ACLD), including the new form of non-acute decompensated (NAD), are at risk for acute decompensation (AD) or acute-on-chronic liver failure (ACLF), with an increased risk of mortality. To date, no specific score has been developed for AD onset. The well-known CLIF-C AD score is the only score to predict prognosis in hospitalized cirrhotic patients, but not designed for AD onset. Aim of the study is to develop and validate, using artificial intelligence (AI) techniques, the AI-AD score, a prognostic score for outpatients with ACLD who may develop AD, and to compare its performance with CLIF-C AD, Child-Pugh, and MELD scores.

Method: a single-center cohort study enrolled consecutive ACLD patients, followed at Liver Unit in Verona between January 2017 and December 2022. AI-AD score was developed using machine learning and pattern recognition techniques, focusing on classification and feature selection. AI was able to select the feature most relevant for predicting AD onset and trough a linear classifier to applied it. The score was validated in both an internal and a validation cohort. To assess the performance of the different scores, we used the classic AUC.

Results: 456 patients (70.6% male, mean age 64 ± 11 years) were enrolled for a median follow-up of 43.3 months. Among ACLD patients, 91 developed AD, 62 developed ACLF, while 79 NAD patients progressed to AD. The selected features for AI-AD score were: previous hospital admissions, infection episodes before enrollment, history of ascites and encephalopathy, portal vein thrombosis, serum creatinine and albumin values. AUC for the AI-AD score was 0.80 (CI 95%:0.73–0.86), higher than other scores.

Conclusion: AI-AD score effectively predicts AD onset in ACLD patients. history of infections and PVT, were identified as a crucial complication in cirrhotic patients and may predispose individuals to AD and ACLF.

FRI-170

Acute-on-chronic liver failure in Australia: a non-transplant centre experience

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Background and aims: Acute on chronic liver failure (ACLF) is a clinical syndrome distinct from acute decompensation (AD) of cirrhosis characterised by systemic inflammation, organ failures and increased mortality. There is limited reported Australian data on ACLF outside of transplant centres. The aim of this study was to describe the prevalence, characteristics and outcomes of ACLF in a cohort of hospitalised patients at a non-transplant Australian tertiary centre.

Method: Adult patients with cirrhosis admitted acutely with decompensation to a single tertiary non-transplant health service between December 2017 and December 2021 were included for retrospective analysis. Data was collected on patient characteristics, clinical and laboratory parameters. ACLF presence and grades were defined using the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium criteria and scored on day of admission, day 3 and day 7.

Results: There were a total of 259 patients with a total of 500 admissions with acute decompensation. On index admissions, 80 patients (30.9%) met the criteria for ACLF (67 at admission and 13 developed during admission). There were no significant differences in basic patient demographics between the ACLF and AD groups. Both groups were predominantly male (66.7% and 72.1% respectively) with a median age at admission of 57 and 59 years respectively and the most common cirrhosis aetiology was alcohol (79.1%). The most common decompensating event was gastrointestinal bleeding for ACLF (30.0%) compared to ascites (48.0%) in AD. Patients with ACLF at index presentation had more severe liver disease than AD, indicated by higher median model for end-stage liver disease scores (23.5 vs 18.0, p < 0.001) and greater proportion with Child-Pugh class C disease (69.6% vs 50.3%, p < 0.004). ACLF patients at day 1 were also characterised by greater inflammation (WCC 9.75 vs 7.3 for AD, p = 0.001) and renal dysfunction (creatinine 90 vs 64 for AD, p < 0.001). The most common organ failure amongst both groups was circulation (26.2%) followed by coagulation (20.5%). Mortality was significantly higher in ACLF vs AD patients at both 30 days (53.2% vs 11.3%, p < 0.001) and 90 days (68.1% vs 28.2%, p < 0.01). The median survival post index admission was 29 days in the ACLF group compared to 257 days in the AD group (p < 0.001). Median survival was also

significantly shorter with progressive grades of ACLF(39.5 days for ACLF1 vs 20–25.5 days for ACLF2/3, $p < 0.001$).
Conclusion: ACLF was present in over a quarter of patients hospitalised with AD in this cohort and is associated with poor survival. The rate of ACLF was similar to previous studies in Europe and Australia with comparable survival rates in a non-transplant centre despite similar severities of liver disease at presentation. Further investigation in and comparison of different cohorts will be important to identify prognostic factors and inform management strategies.

FRI-171-YI
Oral anticoagulants are safe and may reduce risk of hepatic decompensation in patients with cirrhosis and atrial fibrillation
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Background and aims: Intrahepatic microvascular thrombi may elevate the portal pressure and increase the risk of hepatic decompensation in patients with cirrhosis, whereas resolving the thrombi may reduce such risk. Robust evidence from well-powered randomized controlled trials on the effect of anticoagulants on risk of hepatic decompensation is missing and has proven challenging to obtain. Therefore, we designed a hypothetical target trial aiming to estimate the effect of oral anticoagulants on risk of hepatic decompensation in patients with compensated cirrhosis and atrial fibrillation, and then emulated it using observational data. Further, we considered the risk of major bleeding as a potential side effect.
Method: Observational data from Swedish healthcare registers 2011–2022 were used to emulate a target trial of oral anticoagulants in patients with compensated cirrhosis and newly diagnosed atrial fibrillation. Inverse-probability weighted marginal structural models were used to compare 5-year risks of hepatic decompensation and non-portal hypertension-related major bleeding in initiators versus non-initiators of oral anticoagulants.
Results: Baseline characteristics were well balanced between treatment groups after inverse-probability weighting. The 5-year risk of hepatic decompensation was 10.3% (33 of 383) in initiators and 16.6% (112 of 777) in non-initiators in the intention-to-treat (ITT) analysis (risk ratio [RR] = 0.62, 95% confidence interval [CI] = 0.34–0.90). The corresponding per-protocol 5-year risk estimates were 10.2% (17 of 383) versus 16.6% (112 of 777) (RR = 0.62, 95%CI = 0.24–0.99). The effect of oral anticoagulants on the risk of hepatic decompensation was more pronounced in men (ITT RR = 0.53, 95% CI = 0.22–0.85) than in women (ITT RR = 0.85, 95%CI = 0.00–1.72), and primarily driven by a reduced risk of ascites (ITT RR = 0.58, 95%CI = 0.27–0.90). The 5-year risk of major bleeding was 19.3% (63 of 383) in initiators and 19.9% (149 of 777) in non-initiators in the ITT analysis (RR = 0.97, 95%CI = 0.65–1.30), and 14.4% (31 of 383) versus 19.9% (149 of 777) in per-protocol analysis (RR = 0.72, 95%CI = 0.25–1.19). Risks were similar between treatment groups regarding fatal, intracranial, gastrointestinal, and other bleedings.
Conclusion: Patients with compensated cirrhosis who initiated oral anticoagulants after the diagnosis of atrial fibrillation had a lower risk of hepatic decompensation and no increased risk of major bleeding compared to non-initiators. Results suggest oral anticoagulants are safe in compensated cirrhosis and may improve prognosis. Randomized trials are warranted to confirm these results.

FRI-172
Intraperitoneal administration of investigational drug VS-01 captures accumulated metabolites in patients with acutely decompensated liver cirrhosis
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Background and aims: Metabolites produced by altered gut microbiota may play an important role in acute decompensation (AD) of liver cirrhosis. Investigational drug VS-01 is an intraperitoneal pH-gradient liposomal infusion designed to enhance the clearance of ammonia and further disease-related metabolites. We evaluated the potential of VS-01 to capture gut-derived metabolites in 9 patients with decompensated liver cirrhosis, ascites, and covert hepatic encephalopathy (HE) from the Phase 1b safety clinical trial, EudraCT no.: 2018-004606-25.
Method: Patients received a single dose of either 15, 30 or 45 mL/kg of VS-01 which was administered intraperitoneally to dwell for 2 h following paracentesis. Peritoneal fluid and plasma samples were collected concomitantly at different timepoints: baseline (T0), 1 h (T1), 2 h (T2) and 24 h (T24) after VS-01 infusion start. Metabolomic analyses were first performed on all samples using an untargeted LC/MS approach. Among identified metabolites, we focused on 103 compounds which were described in the Gutsy Atlas as gut-derived metabolites. Fold changes (FC) and t-tests were computed to compare and detect significant differences ($p < 0.05$) in peritoneal samples at T0 vs T2, and in blood samples at T0 vs T24. Statistical analyses were performed using the R package "MetaboAnalyst" on the peak lists containing mass features of identified compounds.
Results: Of the 103 gut-derived metabolites, 64 were associated with a $\log_2(FC) \geq 0$ in the peritoneal fluid between T0 et T2, indicating an increased concentration in presence of VS-01. In particular, 12 of these metabolites showed a significant increase in peritoneal fluid with associated $\log_2(FC)$ ranging 1.12 to 4.47, and none of these metabolites were associated with significant increase in plasma at T24 vs T0. Among these 12 metabolites, 3 were xenobiotics (theophylline, norcotinine, (S)-nicotine) whose degradation occurs mainly in the liver, and 4 were previously described as accumulating in the context of AD (5-methyluridine, allantoin, methionine, formiminoglutamic acid). The remaining 5 included trigonelline, prolylglycine, methionine sulfoxide, carnosine and urocanic acid.
Conclusion: VS-01 appeared to capture gut-derived metabolites including xenobiotics. In the context of acute decompensation with impaired liver clearance, reducing metabolite accumulation may halt progression of AD and ACLF. Further analyses are warranted to confirm our findings.

FRI-173
Severe liver disease patients had dysfunctional platelets hypoergic to adenosine diphosphate
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Background and aims: Severe liver disease (Liver failure) patients has been documented with multiple organ dysfunctions and always leading to high mortality. Functions of blood cells, such as platelets, and its potential implications in diagnosis and therapy for liver failure patients, has not been widely studied.

Method: A prospective patient set for platelet functions assessment (n = 189) was hired for probing dysfunctional platelets in liver disease patients (n = 26). A prospective cohort was established to validate platelets functions and its prognostic values in liver failure patients (n = 260). The potential therapeutic benefit of platelets transfusion was further explored in liver failure patients (n = 73) from this prospective cohort. Unbiased and target proteomics with platelets concentrates, blood plasma samples from liver failure patients were adopted to explore underlying molecules for platelets dysfunction, respectively. In vitro experiments were further performed to establish the mechanism for dysfunctional platelets in liver failure patients.
Results: Platelets hypoergic to adenosine diphosphate (ADP) and arachidonic acid (AA), two common platelet agonists were found in patients with liver disease patients, tumor or severe infections, all of which were without anti-platelet therapy. With a newly established cohort, platelet hypoergic to ADP was validated in patients with liver disease which was significantly correlated with liver disease severity. Platelets function assessed with responsiveness to ADP (ADP inhibition) had independent impacts on 28-day survival of liver failure patients. Unbiased and target proteomics with platelets concentrates found descending pore-performing protein Orai-1 levels which is responsible for impaired extracellular calcium influx. Meanwhile, decreased calpain-2 level was found and validated in platelets which was responsible for impaired platelet shape changing and adhesion to endothelial cells or collagen. Continuous stimulation with high concentration of collagen, significantly elevated in circulation of liver failure patients was responsible for descending Orai-1 and calpain-2 of platelets. Liver failure patients with platelets highly hypoergic to ADP benefited from platelet transfusion(s) and had a higher 28-day survival than those without platelet transfusion.
Conclusion: Platelets hypoergic to ADP due to descending Oai-1 and Calpain-2 was found and validated in patients with severe liver diseases and manifested potential prognostic values. Platelets transfusions was a potential therapy for liver failure patients highly hypoergic to ADP.

FRI-174

The etiology of chronic liver disease is an independent prognostic factor in patients with acutely deteriorated chronic liver disease

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Background and aims: The prognosis for patients with acutely decompensated chronic liver disease (CLD) is very poor. There is a lack of research on the prognostic impact of underlying CLD in patients with acutely decompensated CLD.
Method: We enrolled a total of 1,352 patients, categorized into three groups: those with viral hepatitis (VH) (n = 206), alcoholic liver disease (ALD) (n = 1,017), and a combination of alcohol and viral hepatitis (Combination) (n = 129) based on etiology of underlying CLD. Subgroups analysis were conducted using Propensity Score matching (PSM). Primary outcome was 28-day liver transplantation free survival (TFS).
Results: The VH group had lower Child-Pugh, MELD, MELD-Na, CLIF-SOFA, and CLIF-C OF scores compared to the ALD and Combination groups, while the ALD and Combination groups had similar scores. The 28-day TFS was similar between the VH and ALD groups (P = 0.661), but significantly lower in the Combination group compared to other groups (P < 0.05). In the subgroup analysis comparing the VH and ALD groups after PSM (Subgroup 1), VH group (n = 193) had significantly lower 28-day TFS than ALD group (n = 197) (P = 0.01). In the subgroup analysis comparing the VH and Combination groups after PSM (Subgroup 2), there was no significant difference in 28-day TFS between VH group (n = 132) and Combination group (n = 90) (P = 0.7). In the subgroup analysis comparing the ALD and Combination groups after PSM (Subgroup 3), ALD group (n = 234) had significantly higher 28-day TFS than Combination group (n = 120) (P = 0.04). When comparing patients with a precipitating event of excessive alcohol consumption in the ALD group (n = 640) to patients with a precipitating event of hepatitis virus in the VH group (n = 52), there was no difference in 28-day TFS between the two groups (P = 1.0). However, after PSM, the patients with a precipitating event of hepatitis virus (n = 32) had significantly lower 28-day TFS than the patients with a precipitating event of excessive alcohol consumption (n = 35) (P = 0.04).
Conclusion: Patients with VH as the etiology of underlying CLD exhibit a poorer prognosis compared to those with ALD. Furthermore, the combined ALD and VH group also demonstrates a worse prognosis than the ALD-only group. Thus, different etiologies require different risk prediction methods.

FRI-175

Loss of hepatic leptin clearance is associated with development of acute-on-chronic liver failure

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Background and aims: Bacterial infections (BI) are the most frequent trigger for acute-on-chronic liver failure (ACLF) in patients with liver cirrhosis. Dysregulated systemic inflammation (SI) plays a key role in the development of ACLF. Leptin, a metabolic hormone primarily secreted by white adipose tissue, is critically involved in regulating SI as well as in the immune response to BI. However, the exact role of leptin in the progression to ACLF in patients with liver cirrhosis remains unclear.
Method: In this study, the relationship between leptin levels and liver disease was retrospectively analyzed in a cohort of patients with liver cirrhosis who underwent transjugular intrahepatic portosystemic shunt (TIPS) placement. Leptin concentrations were measured in plasma samples taken from the right atrium, hepatic vein, portal vein, and cubital vein at the time of TIPS implantation using enzyme-linked immunosorbent assay (ELISA). The absolute concentrations in the portal vein and hepatic vein were normalized to the cubital vein.
Results: A total of 180 patients were included in the study (58% male; median age: 58.87 years; 59% with alcohol-related liver cirrhosis; Child-Pugh classification: 17% A, 56% B, 15% C). Leptin concentrations

showed a significant positive correlation with body mass index (BMI) (p < 0.0001) and a negative correlation with the absolute leukocyte count (p = 0.0181). Neither age nor sex had a significant impact on leptin concentrations. Patients with liver cirrhosis (Child-Pugh A, B) exhibited significantly higher leptin concentrations in the portal vein compared to the hepatic vein (p = 0.0018). Interestingly, this difference was no longer detectable in advanced liver cirrhosis (Child-Pugh C) or in the presence of ACLF.
Conclusion: Our findings indicate hepatic uptake of leptin, likely originating from the splanchnic circulation, which may contribute to an attenuation in systemic inflammation (as evidenced by leukocyte counts). As liver cirrhosis progresses, the development of leptin resistance appears to exacerbate systemic inflammation and promote the onset of ACLF.

FRI-176
Elevated lipase levels during acute-on-chronic liver failure are linked to increased mortality
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Background and aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of chronic liver disease and a proinflammatory state mediating multiorgan failure. While some extrahepatic organ failures have been well characterized, involvement of the pancreas remains poorly understood despite shared risk factors with liver disease such as alcohol abuse. This study aims to determine the prevalence, dynamics, and prognostic significance of elevated lipase (eLIP) and (alpha-)amylase (eAMY) in ACLF.
Method: Patients diagnosed with ACLF, as per EASL-CLIF criteria, were retrospectively identified at the Vienna General Hospital between 11/2003 and 11/2022. eLIP and eAMY were defined as enzyme levels ≥3× the upper limit of normal (ULN). Blood and clinical data were collected at 30–180 days pre-ACLF (pre-ACLF), diagnosis (D0), and days 7 (D7), 28 (D28), and 90 (D90) post-diagnosis. Primary outcomes were post-ACLF survival at D28 and D90. Association with mortality was evaluated by uni- and multivariate Cox proportional hazards models adjusted for Model-of-end stage liver disease (MELD), age, sex, and C-reactive protein (CRP). Adjustments were made for all variables considering the respective values at the D0 and D7 timepoints.
Results: Among 193 ACLF patients (G1: 92 (47.7%), G2: 62 (32.1%), G3: 39 (20.2%) mortality was 39.9% at D28 and 53.9% at D90. No significant differences in pancreatic enzyme levels were observed across ACLF grades. At D0, lipase and (alpha-)amylase levels exceeded the ULN in 82 (43.4%) and 96 (54.5%) ACLF patients, respectively. Further, eAMY was detected in 14 patients (8.0%) at D0 and 14 (9.4%) at D7; while eLIP was found in 17 (9.0%) at D0 and 25 (15.7%) at D7, followed by a significant decline in lipase levels from D7 to D90 (p = 0.029). Lipase and alpha-amylase were strongly correlated (Spearman's rho: 0.687; p < 0.001). Only 2 eLIP patients had clinical and/or radiologic signs of de-novo pancreatitis. While neither D0 levels of lipase/(alpha-)amylase nor eLIP/eAMY at D0 were associated with D28 or D90 mortality (all p-values non-significant), eLIP at D7 emerged as an independent risk factor in univariate and multivariate analyses for both D28 mortality (adjusted hazard ratio [aHR]: 2.009, p = 0.035) and D90 mortality (aHR: 2.115, p = 0.010).
Conclusion: Elevated levels of lipase and (alpha-)amylase were common in ACLF patients - while overt clinical/radiologic signs of pancreatitis were mostly absent. Importantly, lipase levels exceeding ≥ 3x ULN during ACLF (at D7) showed a significant association with ACLF-related mortality, suggesting a potential role in disease progression. Further investigation is warranted to elucidate pathomechanisms linking ACLF with pancreatic inflammation and/or dysfunction in ACLF.

FRI-177
HDL-C, Cholesterol and the ALT/HDL-C ratio are predictors of survival in patients with acute-on-chronic liver failure
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Background and aims: The liver is central to lipid metabolism, with reduced levels of high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) and total cholesterol commonly seen in advanced chronic liver disease (ACLD), reflecting disease severity. HDL-C plays a key role in modulating immune responses and neutralizing endotoxins – critical mechanisms in acute-on-chronic liver failure (ACLF). This study investigates the alterations in lipid metabolism (HDL-C, LDL-C, total cholesterol, triglycerides) and their prognostic value in ACLF patients.
Method: Patients with ACLF (EASL-CLIF criteria) were retrospectively identified at the Vienna General Hospital from 11/2003 to 11/2022. Blood and clinical data were collected at multiple timepoints: pre-ACLF (30–180 days before ACLF), at ACLF diagnosis (D0), and at days (D) D7, D28 and D90 after ACLF diagnosis. Primary outcomes were survival at D28 and D90. Predictive performance was evaluated using area under the receiver operating characteristic curves (AUROCs) and compared by DeLong's test. Risk factors were identified by uni- and multivariate Cox proportional hazards models, adjusted for the Model for End-Stage Liver Disease (MELD), age, sex, and C-reactive protein (CRP) at D0. Risk stratification was assessed via Kaplan Mayer survival probabilities and log-rank tests.
Results: 193 patients with ACLF were included (G1: 92 (47.7%), G2: 62 (32.1%), G3: 39 (20.2%)); and 77 (39.9%) and 104 (53.9%) died at D28 and at D90, respectively. HDL-C and total cholesterol levels were higher pre-ACLF compared to D0 (p < 0.001) and replenished by D90 (p < 0.001 vs. D0). A similar pattern was observed for LDL-C (pre-ACLF vs. D0: p = 0.022; D0 vs. D90: p = 0.009), while triglycerides showed no significant dynamic. At D0, HDL-C yielded similar AUROCs as the CLIF-C ACLF score for D28 (0.724 vs. 0.787) and D90 (0.736 vs. 0.752) mortality prediction. Since alanine aminotransferase (ALT) was significantly elevated at D0 in higher ACLF grades (G1: 26 vs. G2: 31 vs. G3: 51 U/L; G1 vs. G3, p < 0.001; G2 vs. G3, p = 0.020), we assessed the D0-ALT/HDL-C ratio, which yielded numerically higher AUROCs than the CLIF-C ACLF score for D28- (0.817) and D90- (0.816) mortality. In multivariate analysis, the ALT/HDL-C ratio was an independent risk factor for D28 (adjusted hazard ratio [aHR]: 1.028,

p < 0.001) and D90 mortality (aHR: 1.030, p < 0.001). Effective stratification in low- and high-risk groups was shown by ALT/HDL-C ratio (<2 vs. ≥2, p = 0.002), HDL-C (<20 vs. ≥20 mg/dL, p < 0.001) and total cholesterol (<80 vs. ≥80 mg/dL, p < 0.001).
Conclusion: Lipid biomarkers such as total cholesterol and HDL-C, particularly when assessed as the ALT/HDL-C ratio are strong predictors of survival in ACLF, offering a straightforward and readily available method to stratify ACLF-related mortality risk based on routine lab values.

FRI-178

Development of an AI-driven predictive model and decision support system for managing acute-on-chronic liver failure: insights from the KACLiF cohort

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Background and aims: Acute-on-Chronic Liver Failure (ACLF) is associated with high mortality due to multisystem organ failure. Accurate prediction of mortality is crucial for guiding dialysis therapies and determining the optimal timing for liver transplantation. We hypothesized that artificial intelligence (AI) models are more precise than standard models in predicting outcomes in ACLF.
Method: A novel AI-based model was developed using data collected from patients with MELD scores ≥21. Data were prospectively collected from July 2015 to August 2018 and retrospectively from January 2013 to December 2013 from the Korean Acute-on-Chronic Liver Failure (KACLiF) cohort. The prospective data were split into training and validation sets in a 7:3 ratio and used as the derivation cohort (n = 294), while the retrospective data served as an independent validation cohort (n = 177). Logistic Regression, Random Forest Classifier, XGBoost Classifier, Decision Tree and Elastic Net were employed to refine the selection of significant features. Random Forest was used to evaluate the selected features' ability to predict survival.
Results: The mean MELD scores for the derivation and validation cohorts were 30.1 and 29.9, respectively. The 30-day mortality rates in the derivation and validation cohorts were 26.2% and 29.4%, while the 90-day mortality rates were 34.0% and 40.7%, respectively. In the validation cohort, XGBoost demonstrated the highest AUC of 0.82 for predicting 30-day mortality, and Logistic Regression achieved the highest AUC of 0.84 for predicting 90-day mortality. Baseline international normalized ratio (INR), prior acute deterioration events, circulatory failure, respiratory failure, ascites, hepatic encephalopathy, albumin levels, and systemic inflammatory response syndrome (SIRS) were identified as the top features influencing 30- and 90-day outcomes. The model demonstrated relatively high predictive power and outperformed previously reported models, including MELD (0.74 and 0.67), MELD-Na (0.62 and 0.68), MELD 3.0 (0.69 and 0.65), CLIF-ACLF score (0.63 and 0.63), and CLIF-SOFA score (0.74 and 0.74), in predicting 30- and 90-day mortality.
Conclusion: The AI-based model outperformed previously established models in predicting mortality among patients with severe ACLF, providing a more accurate tool for clinical decision-making.

FRI-179

Integrated analyses of cytokine and metabolomics profiles uncover pathways regulating acute-on-chronic liver failure induced mortality

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Background and aims: Acute-on-chronic liver failure (ACLF) is a high mortality clinical syndrome of acute hepatic dysfunction in patients with chronic liver diseases. Aside from liver transplantation, the treatment options for ACLF are limited. To develop new therapeutics, it is necessary to gain mechanistic understanding on ACLF pathogenesis. Impaired immunity and dysregulated metabolism are central to ACLF pathogenesis. However, there is lack of comprehensive and integrated analyses in cytokine profiles and metabolomics data to understand key alternations associated with ACLF clinical outcomes.
Method: Using an antibody array for 151 cytokines (covering chemokines, interleukins, tumor necrosis factors, colony-stimulating factors, and transforming growth factors) and a broad-spectrum metabolomics platform measuring over 1,000 annotated metabolites, we analyzed a cohort of 388 plasma samples collected from patients with chronic liver disease at hospital admission due to acute exacerbation. We classified the samples into three groups: non-ACLF (n = 239), ACLF survivor (at 90-day, n = 102), and ACLF non-survivor (n = 47). We used statistical analyses and machine learning methods to identify cytokines and metabolites associated ACLF mortality. We further performed correlation analysis between the cytokine and metabolomic profiles.
Results: Majority of the cytokines were altered between non-ACLF and ACLF survivor group, with intriguing interactions between pro- and anti-inflammatory cytokines. Among the most significant changes were cytokines in the interleukin-1 (IL-1) family, IL-6 family, chemokines, and death receptors in the TNF family. A number of these cytokines were further up-regulated in the ACLF non-survivor group, particularly death receptors TRAILR1, TNFR1 and DR6, 4-1BB, CCL20, CCL21, IL-6, IL18, IL36, IL37, IFN-beta, TGFbeta-2. We found that mitochondrial dysfunction, sphingomyelin metabolism, and polyamine metabolism were high correlated with IL-18 and death receptors, suggesting that these pathways may participate ACLF associated mortality.
Conclusion: Our analyses generated a comprehensive picture of cytokine cascade through ACLF pathogenesis and potential molecular mediators for ACLF pathogenesis. The findings may have therapeutic and diagnostic implications on ACLF patients.

FRI-180

Establishment of a sarcopenia decline curve for patients with liver cirrhosis to develop hepatic rehabilitation medicine

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Background and aims: Liver disease is a representative cause of secondary sarcopenia, and liver cirrhosis (LC) complicated by sarcopenia is associated with poor prognosis. Therefore, controlling sarcopenia progression is crucial. This study aimed to analyze factors related to muscle mass decline using the skeletal muscle index at the third lumbar vertebra (L3-SMI; cm^2/m^2), a representative indicator of sarcopenia. Furthermore, we sought to establish and validate a predictive model for muscle mass decline in LC patients.
Method: This multicentred retrospective study included 612 LC patients (375 males; mean age: 70 years) from four facilities who underwent annual CT imaging, including the pelvis, over five years. L3-SMI was measured annually, and factors related to muscle mass decline were analysed. A linear regression model predicting L3-SMI at year five (SMI_5) based on L3-SMI at year one (SMI_1) was developed using our institution's data and validated using external data from three other facilities.
Results: Patients were categorized by Child-Pugh score (A: n = 98, B: n = 75, C: n = 26). The average annual decline rates in L3-SMI were significantly steeper in Child C patients (-1.79 ± 1.92 cm^2/m^2/year) than in Child A (-0.99 ± 0.70 cm^2/m^2/year, p = 0.002). A multiple regression analysis yielded the following predictive formula: $SMI_5 = -1.194 + 0.731SMI_1$ - 2.609 (male) + 0.081BMI - 0.033*age - 4.077 (Child B) - 23.085 (Child C). Validation with data from 343 external patients demonstrated high accuracy ($R^2 = 0.8786$; root mean squared error [RMSE] = 5.39).
Conclusion: This study identified a significant correlation between liver functional reserve (Child-Pugh score) and the rate of muscle mass decline, with worse liver reserve associated with accelerated muscle loss. The developed model accurately predicts future L3-SMI values based on current L3-SMI, age, BMI, and Child-Pugh score. These findings support the potential for personalized hepatic rehabilitation protocols targeting sarcopenia in LC patients. This predictive model lays the foundation for establishing evidence-based hepatic rehabilitation strategies, potentially improving patient outcomes in the field of liver cirrhosis management.

FRI-181

Plasma interleukin-33 as a novel diagnostic marker for invasive pulmonary aspergillosis in patients with acute-on-chronic liver failure: a prospective study

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Background and aims: Invasive pulmonary aspergillosis (IPA) represents a critical and life-threatening complication in patients with acute-on-chronic liver failure (ACLF), characterized by a high rate of short-term mortality. Cytokines play a pivotal role in the pathogenesis of IPA and have been implicated as potential diagnostic biomarkers. The objective of this study is to conduct a comprehensive evaluation of the diagnostic efficacy of cytokines in the context of IPA among ACLF patients.
Method: In this single-center, proof-of-concept and prospective study, we enrolled 216 ACLF patients. Plasma samples and corresponding clinical data were collected throughout their hospitalization. Based on established diagnostic criteria for IPA, 16 patients were designated as the IPA group. For comparative analysis, 32 patients with bacterial pneumonia without IPA (BP group) and 32 patients without any infectious complications (non-infection group) were matched as controls based on gender, age and the severity of liver decompensation. Plasma levels of a panel of cytokines, including including interleukin (IL)-33, IL-17A, IL-23, IL-31, IL-1beta, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-13, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha and soluble IL-2 receptor (sIL-2r), were quantified at the time of IPA diagnosis. The diagnostic performance of these cytokines for IPA was evaluated using receiver operating characteristic (ROC) curve analysis.
Results: No significant difference was observed for patients baseline characteristics among IPA, BP and non-infection groups. Among the three groups, significant differences were observed in IL-33 levels (163.07 [IQR 108.30; 211.22] vs 12.82 [IQR 0.00; 50.55] vs 0.00 [IQR 0.00; 52.51] pg/ml, p = 0.033), IL-6 levels (33.82 [IQR 5.87; 50.04] vs 12.09 [IQR 5.56; 21.32] vs 7.67 [IQR 2.58; 11.47] pg/ml, p = 0.004), IL-4 levels (0.16 [IQR 0.11; 0.27] vs 0.11 [IQR 0.10; 4.92] vs 0.11 [IQR 0.10; 0.12] pg/ml, p = 0.025) and IL-23 levels (10.14 [IQR 9.03; 11.09] vs 10.95 [IQR 10.05; 12.87] vs 11.28 [IQR 9.67; 12.46] pg/ml, p = 0.033), in which only plasma IL-33 level (163.07 [IQR 108.30; 211.22] vs 12.82 [IQR 0.00; 50.55] pg/ml, p < 0.001) was significantly higher in the IPA group, when compared with BP group. ROC curve analysis and determination of cut-off values revealed that IL-33 (AUC = 0.871, cut-off = 66.97 pg/ml, p < 0.001) effectively discriminated between IPA and pulmonary bacterial infections, with a sensitivity of 93.80% and a specificity of 84.40%. Furthermore, IL-33 levels were significantly higher at the time of IPA infection compared to 5–7 days before infection (154.86 vs 2.01 pg/ml, p = 0.003) and 5–7 days after antifungal treatment (154.86 vs 28.01 pg/ml, p = 0.042).
Conclusion: Plasma IL-33 levels demonstrate robust diagnostic potential for IPA in ACLF patients, particularly in distinguishing aspergillus from bacterial infections.

FRI-182

Prediction of circulatory failure in patients with liver cirrhosis and acute-on-chronic liver failure on the intensive care unit

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Background and aims: Acute-on-chronic liver failure (ACLF) classification is based on the modified sepsis-related organ failure (SOFA) score, called CLIF-SOFA. Circulatory status is evaluated utilizing mean arterial pressure (MAP) and need of vasopressor therapy to define organ failure and predict outcome. Previous research failed to identify an optimal MAP target for critically ill patients with ACLF. Nevertheless, early detection of patients at risk for circulatory failure might improve survival. This study aimed to identify predictors of circulatory failure in patients with acute decompensation (AD) or ACLF on the intensive care unit (ICU).
Method: In this cohort study, we analyzed data from 498 cirrhotic patients with AD and/or ACLF admitted to the ICU between March 2015 and June 2019 at the Hospital of the Goethe University Frankfurt. Patients were stratified by presence or absence of circulatory failure according to CLIF-SOFA criteria using (i) a MAP threshold of 70 mmHg and (ii) vasopressor treatment at admission and on day 7. Logistic regression was used to test the predictive value of selected laboratory parameters and outcome measures for circulatory failure on day 7. An algorithm for an alternative circulation score was then developed and integrated into a modified ACLF grading and a recalibrated CLIF-C ACLF score to compare prognostic

precision of the original and modified CLIF-C ACLF scores regarding 28-day mortality.
Results: A MAP threshold < 70 mmHg could not discriminate patients with increased mortality on the ICU in absence of vasopressor treatment (p = 0.5). Lactate dehydrogenase (LDH) and lactate at admission were significantly associated with circulatory failure on day 7, as confirmed by logistic regression analysis. Using LDH and lactate, an algorithm for prediction of circulatory failure during follow-up was developed and aligned with CLIF-C organ failure (OF) score: (i) LDH < 400 U/l *and* lactate < 35 mg/dl (1 point), (ii) LDH ≥400 U/l *or* lactate ≥35 mg/dl (2 points) and (iii) LDH ≥400 U/l *and* lactate ≥35 mg/dl (3 points). Patients with circulatory failure at admission gained an additional point, with a maximum CLIF-C-OF score of 3. The predicted-to-observed mortality alignment within CLIF-C ACLF categories showed improved performance of the modified scores between 60–64 points (65% to 64% vs. 71% to 62%) and ≥65 points (81% to 84% vs. 72% to 85%), while performance in other ranges was comparable (<40, 50–59) or slightly lower (40–49) than original CLIF-C ACLF score.
Conclusion: In our study, MAP was not useful for the prediction of short-term mortality in patients with liver cirrhosis on the ICU. Instead, surrogates of tissue hypoxia, such as lactate and LDH at admission might be suitable to predict circulatory failure and optimize risk stratification in severely diseased patients.

FRI-183
Supporting unified management for patients with prior or first decompensation: evidence from three ACLF criteria
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Background and aims: Acute-on-chronic liver failure (ACLF) is a complicated syndrome associated with a high short-term mortality and reversibility. Whether the prior decompensation should be included in the definition of ACLF is controversial.
Method: A total of 532 patients with prior or first decompensation of chronic liver disease were retrospectively enrolled and analyzed from two Chinese tertiary hospitals from January 2018 to June 2023. Clinical data were used to identify the characteristics and determine prognosis.
Results: Of the 532 patients, 99 patients didn't meet APASL-ACLF criteria due to the exist of prior decompensation and 433 patients met the Asian Pacific Association for the Study of the Liver (APASL)-ACLF criteria. 442 patients met (Chinese Group on the Study of Severe Hepatitis B (COSSH)-ACLF criteria (73 prior decompensation and 369 first decompensation), and 217 patients met Chronic Liver Failure (CLIF)-ACLF criteria (47 prior decompensation and 170 first decompensation). Under three criteria, the two groups had similar characteristics including prognosis scores (APASL/COSSH/CLIF criteria: AARC score, p = 0.033/0.425/0.077; COSSH-ACLF II score, p = 0.934/0.310/0.898; CLIF Consortium ACLF score, p = 0.273/0.635/0.839) and the 28-/90-day mortality rates (APASL/COSSH/CLIF criteria: 28 days, p = 0.267/0.641/0.093; 90 days, p = 0.978/0.709/0.101). In all integrated ACLF patients, Receiver Operating Characteristic (ROC) curve analysis and decision curve analysis (DCA) showed that COSSH-ACLF IIs had higher prognostic efficiency and clinical net benefit than AARC score and CLIF-C ACLFs for 28-/90-day mortality under three criteria.
Conclusion: Prior decompensated patients exhibited clinical characteristics and high short-term mortality similar to those of first decompensated patients. The COSSH-ACLF IIs demonstrated the highest prognostic efficiency for all integrated ACLF patients. Including prior decompensation in the ACLF definition can help to simplify and improve clinical management.

FRI-184
Multidrug-resistant organism colonization and outcomes in critically Ill patients with cirrhosis: evidence from a tertiary care center
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Background and aims: Patients with liver cirrhosis are highly susceptible to multidrug-resistant organism (MDRO) colonization, which can influence clinical outcomes. This study evaluated the impact of MDRO colonization on survival and described MDRO prevalence and risk factors for colonization and MDRO infection in critically ill patients with cirrhosis.
Method: This retrospective cohort study included critically ill patients with cirrhosis admitted to a tertiary centre in Zagreb, Croatia (2018–2024). MDRO colonization was assessed via nasal, pharingeal, and rectal swabs at ICU admission and within 5 days. Data collected included clinical, demographic, and laboratory parameters, as well as severity (MELD) and organ failure (SOFA, CLIF-ACLF) scores.
Results: The cohort included 101 patients (median age 56.5 years, 69.3% male), with alcohol-related liver disease as the leading etiology (83.2%). Median MELD score was 14, and 75.2% presented with ACLF (median CLIF-ACLF score 60). MDRO colonization was found in 28.7% at admission and was not associated with 28-day survival (44.8% vs. 52.4%, p = 0.396), though it significantly increased the risk of MDRO infections (75.9% vs. 15.3%, p < 0.001). Risk factors for colonization included lower platelets (OR = 0.985, p = 0.024), diabetes (OR = 4.522, p = 0.011), lower PaO2/FiO2 (OR = 0.995, p = 0.018), and prolonged pre-ICU hospitalization (OR = 1.048, p = 0.049). MDRO infection was linked to prior colonization (OR = 17.604, p < 0.001) and lactulose use (OR = 4.334, p = 0.014). Predictors of mortality included MELD-Na (p = 0.001) and respiratory dysfunction (p = 0.014) in the whole cohort, and CLIF-ACLF score (p = 0.024) in the ACLF subgroup, with neither colonization nor infection affecting mortality.
Conclusion: MDRO colonization and infection were prevalent but did not affect mortality, which was primarily determined by disease severity markers such as MELD-Na, respiratory dysfunction, and CLIF-ACLF score. These findings suggest that once severe organ dysfunction develops, the impact of MDROs on survival diminishes. This highlights the importance of early infection prevention and treatment to mitigate their role in triggering or worsening organ failure, particularly in ACLF patients.

FRI-185
Outpatient sbp prophylaxis associates with higher sbp reccurence in a global cohort of cirrhosis inpatients with greatest impact in high- income countries
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Background and aims: Antibiotic resistant infections link with poor outcomes in cirrhosis. SBP prophylaxis (SBPPr) is recommended in selected cirrhosis patients, but recent US-based evidence shows that this results in resistant & recurrent SBP. Moreover, impact on subsequent infections in other regions is unclear. Aim is to determine the impact of pre-admission SBPPr on SBP as a cause of admission in a worldwide cohort of cirrhosis inpatients.

Method: CLEARED consortium enrolls non-electively admitted cirrhosis inpatients & collects inpatient clinical data & course. Comparisons between SBPPr/not vs SBP as a cause of admission was performed using univariate/multivariable analyses. Countries were divided per World Bank into high income (HIC), upper middle (UMIC) & low/low middle income (L/LMIC) countries. Separate analyses were performed for each group.
Results: 7306 patients from 115 centers in 35 countries were enrolled. Mean age was 56 yrs, 64% men, 42% alcohol etiology followed by HBV (19%) & MASH (18%). 35% from HIC, 44% UMIC & 21% from L/LMICs. History: 30%had diabetes, 28% prior HE, 19% prior infections, 29% prior variceal bleed, 18% prior AKI, and11% were listed for transplant. Admission details: 14% were on SBPPr, 10% statins, 34% β-blockers, 44% PPI, 17% HBV antivirals, 25% rifaximin, & 44% on lactulose. Median MELD-Na was 21.0, albumin 2.89 g/dl & WBC 6.21. Infections as a cause for admission: 22% had infections; most with SBP (29%), respiratory (17%), UTI (12%), & spontaneous bacteremia. Comparison SBPPr versus not: SBPPr was ↑in older men and was higher in L/LMICs (46%) vs UMIC (26%) & HIC (28%,p < 0.0001). SBPPr use was higher in alcohol & lower in HBV/Autoimmune etiologies. SBPPr use was higher in pts with prior cirrhosis complications & severity (↑MELD-Na, ↓albumin) and in those listed. PPI, HE-Rx, & β-blocker use was ↑ in SBPPr pts but statin & HBV were statistically similar. SBP as cause for admission and MV analysis: SBPPr pts had significantly higher rate of SBP (39% vs 27%, p = 0.003). MV analysis was done adjusting for SBP Prophylaxis, demographics, comorbidities, prior ascites/HE/AKI/variceal bleed, prior infections, hospitalizations within 6M and current LT listing. HICs: ↑ with SBPPr (OR1.73, p = 0.01), AKI (1.85, p = 0.001), prior infections (1.58, p = 0.02) & ↓with hypertension (0.65, p = 0.03). UMICs, SBPPr trended higher (OR 1.31, p = 0.11) & ↑ with prior infections (2.61, p < 0.0001) & ↓ with alcohol etiology (0.75, p = 0.05) & hypertension (OR 0.61, 0.39–0.97, p = 0.04) L/LMICs, Again ↓ in alcohol etiology (OR 0.75p = 0.04) & ↑ with prior infections (OR 2.31, p < 0.0001). SBPPr was not linked (1.02, p = 0.93).
Conclusion: Outpatient SBP prophylaxis is associated with a higher rate of SBP on admission, especially in high-income countries but not in lower-income countries in a global cohort of >7000 inpatients with cirrhosis.

FRI-186
Rifaximin use does not significantly affect the rate of 30-day mortality or liver transplant in patients with cirrhosis on Daptomycin in two national US-based cohorts
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Background and aims: Antibiotic resistance in cirrhosis leads to poor outcomes, especially near the stage of ACLF. Rifaximin is used extensively for preventing hepatic encephalopathy (HE) recurrence. A recent study showed in vitro and using metagenomics that rifaximin use increases resistance to daptomycin without data on real-world outcomes. We aimed to define the impact of rifaximin on mortality in cirrhosis patients on daptomycin in 2 national US-based cohorts.
Method: We used the Veterans affairs Corporate Data Warehouse (CDW, national database for US Veterans) & TriNetX (large national database of privately insured patients) to extract data using validated codes for cirrhosis patients who were prescribed daptomycin between 2010–19. Rifaximin use >60 days prior was determined. Data related to demographics, cirrhosis severity/complications, concomitant medications were collected. Outcome was 30-day mortality with secondary one being liver transplant (LT). Rifaximin vs not groups were compared & logistic regression for 30-day mortality/LT were performed.
Results: VA-CDW: 2,237 patients were given Daptomycin, of which 118 (5.3%) were on Rifaximin. 511 (22.8%) died 30-days post-Daptomycin and only 59 (2.6%) received LT. Rifaximin users were younger, more likely to be on PPI, diuretics, lactulose & beta-blockers & had higher admission MELD-Na. *Regression impact of rifaximin on 30-day mortality*: After adjusting for cirrhosis severity, patient history, other medication usage, and hospital course, rifaximin use was not statistically significant (adjusted OR: 0.97 [0.52–1.55], p = 0.92). Since < 3% received LT, a separate analysis was not performed here. TriNetX: 2,291 patients were given daptomycin, of which 643 (28.1%) were on Rifaximin. 753 (32.9%) died/ received LT [422 (18.4%) died without LT and 342 (14.9%) received LT]. Again, sicker pts with more advanced cirrhosis were likely to be on rifaximin. *Regression impact of rifaximin on 30-day outcomes*: Composite LT/death: No significant impact of rifaximin(adjusted OR: 1.14 [0.83–1.57], p = 0.411) after adjusting for cirrhosis severity & hospital course. LT-free mortality: This was non-significant (adjusted OR 1.39 [0.94–2.05], p = 0.10) after adjustment. LT alone: Not-significant after adjustment (adjusted OR 1.23 [0.81–1.87], p = 0.33).
Conclusion: In two large complementary US-based experiences, rifaximin use did not significantly impact 30-day mortality and was not a systematic barrier to LT in patients with cirrhosis on daptomycin therapy. This should be reassuring to clinicians after the recent report of potential rifaximin-induced resistance to daptomycin and shows that there is no real-world translation of this findings across large and diverse population experiences.

FRI-187
Long term abdominal drains: a five-year study of safety and efficacy of long-term abdominal drains in a tertiary referral centre
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Background and aims: Ascites is the most common cirrhosis complication with one-third of patients progressing to refractory ascites. Most patients are not candidates for liver transplantation or transjugular intrahepatic portosystemic shunt (TIPSS). Remaining options include recurrent large volume paracentesis or insertion of a palliative long-term abdominal drain (LTAD). Data on the efficacy and safety of LTADs is pending the results of the REDUCe2 trial. We aimed to review the LTAD service at Sheffield Teaching Hospitals (STH).
Method: Retrospective single-centre study of all LTAD insertions between December 2019 and October 2024. Inclusion criteria were refractory ascites secondary to cirrhosis, Child-Pugh ≥9, requiring >1 drain per month, life expectancy 3–12 months and not suitable for transplantation/TIPSS.
Results: 37 LTADs were inserted in 29 patients (52% male, age 74 (42–83) years). Underlying aetiology was MASLD (n = 14, 48%), ALD (n = 10, 35%), met-ALD (n = 4, 14%) and PSC (n = 1, 3%). There was a prior history of SBP in 55% (n = 16). 72% (n = 21) were commenced on prophylactic antibiotics post-drain insertion. Complications occurred in 68% of insertions (n = 25), including peritonitis (n = 12, 32%), colonisation (n = 7, 19%), leakage ± cellulitis (n = 7, 18%), displacement (n = 4, 15%) and drain blockage (n = 1, 3%). Peritonitis developed 15.5 (3–79) days post-insertion. Cultured bacteria included gastrointestinal (GI) bacteria in 17% (n = 2); skin commensals in 42% (n = 5); mixed GI and skin commensals in 33% (n = 4); and no growth in 8% (n = 1). 50% (n = 6) of peritonitis cases occurred within 14 days. Of these, skin commensals were cultured in 66% (n = 4). All cases of post-LTAD peritonitis were treated with intravenous antibiotics and 92% (n = 11) required LTAD removal. The time between date of insertion and date of death was 61 (24–206) days.
Conclusion: We believe this is the largest study to date of LTADs. Rates of peritonitis were higher than previously published data (32% vs 6%)[1], whilst rates of leakage, cellulitis, drain displacement and blockage were comparable. Our cohort was older (74 vs 66 years) and had a higher rate of prior SBP (55% vs 7%), which may account for the increased rate of post-LTAD peritonitis. Early infections with a skin commensal may suggest contamination at the point of insertion. This

is a palliative intervention aiming to improve quality of life. For practise, we recommend careful patient selection, to counsel regarding infective risks and to ensure a pre-procedure ascitic tap is completed. We await further data from the REDUCe2 trial.

Reference

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FRI-191

Modification of mortality risk scores with dynamic serum creatinine definition improves survival discrimination in patients with decompensated cirrhosis

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Background and aims: Acute-on-chronic liver failure (ACLF) is a severe manifestation of decompensated cirrhosis with high short-term mortality. Acute kidney injury (AKI) is a major driver of mortality in this patient group and kidney failure the most common organ failure encountered. Most scores including the Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) score assess short-term prognosis, and therefore also priority for liver transplantation, by employing static creatinine values and thus risk underestimating mortality. The aim of our study was to assess whether the addition of dynamic creatinine changes would improve mortality prediction of CLIF-SOFA ACLF grading.
Method: We prospectively included 449 patients in our biobanking system for acute and chronic liver diseases. We identified 225 patients with decompensated liver cirrhosis emergently hospitalized for an acute decompensation event. We screened for development of AKI at or during index hospitalization. We stratified according to Kidney Disease Improving Global Outcomes (KDIGO) AKI definition and assessed transplant-free short-term mortality. We created a modified score for grading of acute-on-chronic liver failure and compared it with the original CLIF-SOFA for mortality prediction.
Results: 75 (33,3%) of patients were female and 154 (68,4%) developed AKI of any stage. 36 (16,0%) of patients died within three months of baseline while 25 (11,1%) received liver transplantation (LT). Kaplan-Meier analysis showed excellent stratification capacity of KDIGO AKI definition (28 - day mortality: No AKI 0%, AKI stage I 6.1%, AKI stage II 15.5%, AKI stage III 31.0%, log-rank: $p < 0.001$) for short term mortality. A modified version of the CLIF-SOFA ACLF definition for kidney failure employing the KDIGO AKI definition reclassified ACLF grade in 30 (13,3%) patients and showed improved discriminative ability compared to the original CLIF-SOFA-ACLF score (Area under the curve (AUC) 0.841 vs. 0.751, $p = 0.0588$). This modification resulted in diagnosis of kidney failure in a subgroup of patients (24) with relevant mortality (28-day mortality: 17.4%) otherwise not classified or underclassified with CLIF-SOFA scoring.
Conclusion: Employment of static serum creatinine values in ACLF definitions underestimates mortality risk in patients with decompensated cirrhosis and renal dysfunction; modification of standard scoring systems to recognize dynamic changes in renal function improves survival prediction compared to CLIF-SOFA ACLF grading, showing excellent discriminative capacity. This is especially important in a time in which patients with ACLF are being short-tracked for liver transplantation.

FRI-192

Loss of paraspinal skeletal muscle tissue is independently associated with increased 90-, but not 28-day mortality in patients with acute-on-chronic liver failure

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Background and aims: The loss of skeletal muscle tissue is a highly prevalent complication in patients with cirrhosis carrying significant prognostic implications, whereas Acute-on-Chronic Liver Failure (ACLF) is characterized by a sudden and life-threatening deterioration in the clinical condition of said patients. This study aimed to assess the impact of skeletal muscle tissue loss on 28- and 90-day mortality on patients with ACLF.
Method: 195 patients with ACLF were retrospectively included in this study, conducted at the Charité, Berlin. ACLF was defined according to the EASL-CLIF criteria. Skeletal muscle was estimated by measuring horizontal psoas area adjusted for patients' abdomen height in CT scans. We performed multivariable regression analyses to determine independent risk factors for transplant-free mortality.
Results: In-hospital mortality in our cohort was 49.2% for all ACLF patients. Adjusted psoas area was significantly higher in surviving patients ($p < 0.038$). Univariate Cox analysis for 90-day mortality identified psoas area as a negative predictor, INR and bilirubin as positive predictors of death. Follow-up multivariable analysis revealed psoas area (HR: 0.43, 95% CI: 0.23–0.79, $p < 0.007$), INR (HR: 1.21 95% CI: 1.05–1.39, $p < 0.011$) and bilirubin (HR: 1.04 95% CI: 1.04–1.06, $p < 0.001$) as independent risk factors. No significant impact of psoas area on 28-day survival was observed in subsequent analysis. In the subgroup analyses of patients with a minimal survival of 28-day ($n = 115$), multivariable analysis on 90-day mortality showed again psoas area (HR: 0.24, 95% CI: 0.08–0.78, $p < 0.017$), and bilirubin (HR: 1.07, 95% CI: 1.03–1.1, $p < 0.001$), but not INR as independent risk factors for mortality. Further analysis revealed no significant differences among subgroups in the impact of psoas area on 28- or 90-day mortality when stratified by patient sex or ACLF etiology.
Conclusion: Our study highlights the loss of skeletal muscle tissue as an independent predictor of increased 90-day mortality in ACLF. No significant impact on 28-day mortality was observed, which might indicate that skeletal muscle tissue loss appears to be less relevant for patients in the acute phase of ACLF, rather than in the further course of disease. These findings have to be validated in further studies and may help to identify ACLF patients who are at risk of death medium-term and also could improve in-hospital management strategies.

FRI-193

A machine-learning algorithm using real-world data identified subpopulations at risk for adverse outcomes in patients with acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is associated with high morbidity and mortality, yet risk stratification in real-world settings remains challenging. This study aims to leverage real-world data (RWD) using machine learning (ML) algorithms to identify subpopulations of patients with varying risks for mortality, transplant-free survival (TFS), and time to hospital discharge (TTD).
Method: Using the U.S.-claims-based Komodo's Healthcare Map linked with Komodo Lab Results, routine and specialized laboratory tests curated by Komodo Health, from 2017 to 2024, we analyzed data from 278,593 patients with ACLF, defined according to EASL-CLIF criteria. Starting from more than 1,000 features related to ACLF, final subsets of features associated with mortality, TFS, and TTD were selected and used to build prognostic models at 90 days for each of these clinical outcomes. The cohort was randomly split into training (75%) and test (25%) sets. LightGBM modeled mortality and TFS, while Cox proportional hazards (CoxPH) estimated TTD. Feature importance rankings defined clinically relevant subpopulation. Models were validated on the test set, and mean risks for each subpopulation were computed.
Results: Models showed high performance with an Area Under the Receiver Operating Characteristic curve (AUROC) of 0.79 for mortality, 0.80 for TFS; the CoxPH model achieved a concordance index (C-index) of 0.70 for TTD. The mean risk of mortality estimated by the model in the whole study population was 0.21. Patients presenting with hepatorenal syndrome showed the highest increase in mean risk of mortality (0.42, 2-fold increase vs whole population), followed by patients with endotracheal intubation (0.40, 1.9-fold), cerebral or coagulation failure (0.39, 1.8-fold), respiratory failure (0.35, 1.7-fold) and circulatory failure (0.31, 1.5-fold). History of alcohol related liver disease was the etiology associated with the highest increase in risk of mortality (0.33, 1.6-fold increase). Patients presenting with hepatic encephalopathy or ascites (0.28, 1.3-fold), and sepsis (0.24, 1.2-fold) were also at higher risk of mortality. On the other hand, we identified subpopulations with lower risk of adverse outcomes (mortality, TFS, TTD), which included patients with history of Type 2 diabetes, insulin, statin, and metformin prescription. The decrease in mortality risk for the specified subpopulations ranged 0.7 to 0.8-fold vs the estimated mean risk in the whole ACLF population.
Conclusion: Using US RWD, this study identified subpopulations with higher and lower risks of mortality, TFS, and TTD compared with the whole ACLF population. These findings may inform clinical trial design, precision treatments, and multidisciplinary care to optimize outcomes and resource use in real-world settings.

FRI-194

Impact of home-based hepatology nurse-led care on disease knowledge in recently hospitalised patients with cirrhosis

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Background and aims: Insufficient disease knowledge in patients with cirrhosis contributes to suboptimal disease management and increased healthcare utilisation. We aimed to evaluate the impact of Liver At Home (L@H), a novel 3-month home-based program designed for recently hospitalised patients with cirrhosis, on patient disease knowledge. L@H provides continued outpatient care through regular hepatology nurse home visits/telehealth reviews with a focus on the management of cirrhosis-related complications and prevention of readmissions.
Method: Patients with cirrhosis admitted under the Gastroenterology Unit of a tertiary metropolitan tertiary hospital and enrolled to L@H between 01/03/2023–01/09/2024 were assessed on knowledge regarding cirrhosis. A cirrhosis knowledge questionnaire, previously validated in patients with cirrhosis, was offered on a voluntary basis at the time of enrolment (day of hospital discharge) and culmination of L@H. The questionnaire comprised 14 questions, each scored out of 1, covering the management of ascites (out of-5), varices (out of-3), hepatic encephalopathy (HE) (out of-3), hepatocellular carcinoma (out of-1), and diet/lifestyle (out of 3). Primary outcome was total knowledge score, and secondary outcome was breakdown scores for each knowledge category. Results at the beginning and end of L@H were compared using Chi square and Mann-Whitney U tests for categorical and continuous variables, respectively.
Results: Of 89 patients enrolled to L@H in the study period, 20 completed the questionnaire at both enrolment (baseline) and discharge from the program [median age 56 years (IQR 43.5–70.5), 30% (n = 6) female, Child Pugh score 7 (IQR 7–10), MELD-Na score 17.5 (IQR 12.5–20.5)]. Of these patients, 80% (n = 16) had ascites, 10% (n = 2) had variceal bleeding, and 25% (n = 5) had ≥ Grade II HE during hospital admission. Baseline median total knowledge score was 7.5/14 (IQR 7–9), which significantly improved to 9/14 (IQR 9–12) at discharge from L@H ($p < 0.001$). Most patients (n = 17, 85%) demonstrated improved knowledge scores at the culmination of the program. Median breakdown scores revealed significantly improved knowledge regarding ascites [4/5 (IQR 3–5) vs. 3 (IQR 2–3.5), $p = 0.003$], trend towards improved knowledge regarding HE [2/3 (IQR 1–3) vs. 1 (IQR 0.5–2), $p = 0.084$], and stable knowledge regarding varices [2/3 (IQR 2–3) vs. 2 (IQR 1.5–3)] on discharge from L@H.
Conclusion: Patient education is a pivotal aspect of chronic disease management. The findings of this study highlight the potential of specialist hepatology nurse-led transitional care programs for recently hospitalised patients with cirrhosis as an intervention to help improve their disease knowledge and awareness regarding the major complications of this complex condition.

FRI-195

Single-cell multimodal analysis reveals cellular dynamics underlying divergent immune response trajectories in HBV-ACLF progression

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Background and aims: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome involving dysfunction of multiple immune cell types. This study aimed to comprehensively depict the dynamic trajectory of immune responses throughout the disease course of hepatitis B virus-related ACLF (HBV-ACLF).
Method: Single-cell RNA sequencing (scRNA-seq) and single-cell proteomics were performed on the peripheral blood mononuclear cells (PBMCs) of 45 samples from 17 hospitalized patients (progressive/stable/recovering course of HBV-ACLF, 6/5/6) and 15 control subjects (liver cirrhosis, chronic hepatitis B and healthy controls, 5/5/5). Bulk RNA-seq and flow cytometry of PBMCs were performed for external validation.
Results: Single-cell transcriptomics revealed specific alterations in the peripheral immune response in ACLF. VCAN+CD14+-monocytes with activated interferon-stimulated genes and increased inflammatory functions expanded in ACLF-1, contributing to early inflammatory storm. Low-density hyperinflammatory CXCR2+-neutrophils and M2 macrophage-like CD163+-monocytes predominated in progressive ACLF patients, serving as significant markers of disease deterioration. Elevated anti-inflammatory signalling, including ENTPD1-TMIGD3 and IL1B-IL1R2 interactions, correlated with disease severity. Highly activated cytotoxic T cells were increased in recovering patients. Natural killer cells decreased during ACLF progression, exhibiting impaired cytotoxic and metabolic functions. Six cellular modules were identified, highlighting a specific immune pattern (CM3) that could be focused as an optimal therapeutic window. The proteomic profiling showed high concordance with the transcriptomic data. External validation with bulk RNA-seq and flow cytometry confirmed the immune cell clusters involved in ACLF progression.
Conclusion: Our longitudinal multiomics study revealed the dynamic evolution of the immune response in HBV-ACLF and characterized diverse immune patterns for the precise management and therapeutic intervention.

FRI-196

Outperformance of the COSSH diagnostic framework for acute-on-chronic liver failure: a global aetiology cohort

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Background and aims: Acute-on-chronic liver failure (ACLF) of various aetiologies is a complicated syndrome with high short-term mortality. A globally applicable diagnostic framework and accurate prognostic score for ACLF are urgently needed.
Method: Clinical data from 7388 prospectively enrolled patients with acute deterioration of chronic liver disease across various aetiologies were used to evaluate the performance of European Association for the Study of the Liver (EASL)-ACLF and Chinese Group on the Study of Severe Hepatitis B (COSSH)-ACLF criteria. Three non-Asian cohorts were performed to validate the results.
Results: Among 5288 enrolled patients, 844 patients were diagnosed with ACLF using EASL-ACLF criteria (321 with non-hepatitis B virus (HBV) aetiology, 523 with HBV aetiology), while 2038 patients were diagnosed using COSSH-ACLF criteria (602 with non-HBV aetiology, 1436 with HBV aetiology). COSSH-ACLF criteria identified 22.6% more patients compared to EASL-ACLF, including 14.2% more patients with non-HBV aetiology. COSSH-ACLF criteria also produced a more reasonable diagnostic distribution (Grade 1–3: 63.4%/27.5%/9.1%) compared to EASL-ACLF (Grade 1–3: 25.8%/56.3%/17.9%). The 28-/90-day mortality rates for patients diagnosed using COSSH-ACLF criteria were significantly lower than those under EASL-ACLF criteria (27.3%/41.0% vs. 40.7%/57.0%, both $p < 0.0001$), which may help to identify more patients with a golden window receiving early treatment. COSSH-ACLF II score showed the highest predictive values for 28-/90-day mortality in both cirrhotic and all ACLF patients (n = 844/2038) with various aetiologies, outperforming the CLIF-C ACLF and other scores. The similar outperformance of China-CLIF score was validated in three non-Asian cohorts.
Conclusion: COSSH-ACLF criteria and COSSH-ACLF II score can effectively diagnose and accurately prognose ACLF patients with all aetiologies. These findings could pave the way for improved global clinical management of ACLF.

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The AMMON-OHE model predicts liver-related complications in outpatients with cirrhosis: a prospective cohort study of the AMMON consortium

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Background and aims: A simple, cost-effective and objective tool remains an unmet need for risk stratification of liver-related events (LRE) and death (LRD) in outpatients with cirrhosis. Recently, the AMMON-OHE model has been validated for the prediction of overt hepatic encephalopathy (OHE) occurrence, with a superior predictive performance than traditional psychometric tests and disease severity scores. This study was performed to test the ability of the AMMON-OHE model compared with other prognostic scores for risk stratification regarding development of LRE, acute-on-chronic liver failure and LRD in outpatients with cirrhosis.
Method: This observational, prospective international cohort study included 1575 outpatients with cirrhosis from 5 independent liver units. The primary endpoint was a composite of bacterial infection, variceal bleeding, new onset or worsening of ascites and OHE (defining LRE). Secondary endpoints were ACLF and LRD. Random forest methods were used and Integrated Brier Scores (IBS) were calculated to evaluate performance of each model.
Results: Overall, 597 (38%) patients developed LRE, 143 (10%) ACLF and 202 (13%) died over a median follow-up of 17 (IQR 4–46) months. The AMMON-OHE model showed an IBS of 0.180 for liver-related complications, with a lower prediction error than MELD (0.212), MELD-Na (0.210), MELD 3.0 (0.206), Child-Pugh (0.185), and other combinations of albumin, creatinine, INR, sodium and white blood cell count (0.183–0.104). Its higher predictive accuracy was reproduced for bacterial infection (IBS 0.135), variceal bleeding (IBS 0.069) and ACLF (IBS 0.085).
Conclusion: The results of the study show that the AMMON-OHE model performs better than the currently used prognostic models to identify outpatients with cirrhosis at highest risk for developing LRE.

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Benefit-to-risk profile in the label-specific population of patients with hepatorenal syndrome-acute kidney injury treated with terlipressin

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Background and aims: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a deadly but potentially reversible form of AKI that occurs in patients with cirrhosis and ascites. Terlipressin, a vasopressin analogue, is FDA-approved to treat adult patients with HRS with a rapid worsening in kidney function, and is recommended as first-line treatment (in combination with albumin) for HRS-AKI per EASL and AASLD guidelines. A mitigation strategy to increase effectiveness and decrease the risk of respiratory failure adverse events (AEs) was developed to identify patients with a more favorable benefit-to-risk profile with terlipressin; these patients are referred to as the "label-specific population" (LSP) and include acute-on-chronic liver failure (ACLF) grade < 3, serum creatinine (SCr) < 5 mg/dL, and Model for End-Stage Liver Disease (MELD) score < 35 (if transplant listed). This study evaluated efficacy and safety outcomes in the LSP compared with those patients who do not meet any of the label-specific criteria (ie, the non-label-specific population [non-LSP]).
Method: HRS reversal—defined as a SCr level of ≤1.5 mg/dL—and the incidence of AEs and death were retrospectively assessed in the LSP and non-LSP of patients with HRS-AKI from the Phase III placebo-controlled CONFIRM study (NCT02770716).
Results: The incidence of HRS reversal in the terlipressin arm was 44.7% (59/132) in the LSP vs 19.4% (13/67) in the non-LSP; 18.3% (13/71) vs 13.3% (4/30) among patients in the placebo arm, in the LSP vs non-LSP, respectively. The incidence of AEs in the terlipressin arm was 87.9% (116/132) vs 88.2% (60/68); in the placebo arm, 88.7% (63/71) vs 89.3% (25/28), in the LSP vs non-LSP, respectively. The incidence of respiratory failure in the terlipressin arm was 6.1% (8/132) vs 19.1% (13/68); in the placebo arm, 4.2% (3/71) vs 7.1% (2/28), in the LSP vs non-LSP, respectively. The incidence of AEs leading to death up to 30 days posttreatment in the terlipressin arm was 34.1% (45/132) in the LSP vs 55.9% (38/68) in the non-LSP; in the placebo arm, 40.8% (29/71) in the LSP vs 39.3% (11/28) in the non-LSP. Respiratory failure was the cause of death in the terlipressin arm in 5.3% (7/132) of patients in the LSP vs 14.7% (10/68) in the non-LSP; in the placebo arm, in 1.4% (1/71) of patients in the LSP vs 0% (0/28) in the non-LSP.
Conclusion: Terlipressin improves the rate of HRS reversal vs placebo, especially in the LSP, as compared with the non-LSP. In the terlipressin arm, selection of the LSP vs the non-LSP resulted in approximately a 3.1-times lower incidence of respiratory failure, and a 2.8-times lower incidence of respiratory failure as a cause of death up to 30 days posttreatment. Selection of patients in the LSP leads to an improvement in the benefit-to-risk profile of patients with HRS-AKI treated with terlipressin.

FRI-199

Fibroblast growth factor 19 (FGF-19) predicts transplant free-survival in critically ill patients with acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is a complex syndrome characterized by acute decompensation of cirrhosis (AD) and multiorgan dysfunction, leading to high short-term mortality. Fibroblast growth factor 19 (FGF-19), involved in regulation of bile acid synthesis and cellular stress response, has been linked to liver disease progression; however, its role in ACLF remains to be elucidated. This study aimed to evaluate its prognostic relevance in critically ill patients with ACLF.
Method: Data of 161 patients admitted to the medical intensive care unit (ICU) at RWTH Aachen University Hospital between 2015 and 2021 due to ACLF were retrospectively analysed. Serum samples were collected at ICU admission and after 48 hours. Serum samples from 20 healthy individuals were used as controls. All samples underwent

measurement of FGF-19 concentrations by enzyme linked immunosorbent assay (ELISA).
Results: FGF-19 serum concentrations were significantly elevated in patients compared to controls ($p = 0.004$) and correlated with ACLF severity ($p = 0.002$). Moreover, a positive correlation of FGF-19 was observed with total bilirubin, aspartate aminotransferase (AST), international normalized ratio (INR) and the model of end stage liver disease (MELD) score (all corrected $p < 0.001$). Patients who deceased or were transplanted had significantly higher FGF-19 concentrations at all investigated time points, including short-term (30, 60, and 90 days) and long-term (180 and 365 days) survival analyses (all $p < 0.001$). Cox regression analysis identified FGF-19 as an independent predictor of transplant-free survival ($p < 0.001$). An FGF-19 serum concentration of >168 pg/mL at ICU admission was associated with a reduced one-year transplant-free survival ($p < 0.001$).
Conclusion: FGF-19 serum concentrations correlate with disease severity in critically ill patients with ACLF and predict transplant-free survival. Further studies should address underlying mechanisms and evaluate the therapeutic potential of anti-FGF-19 targeted therapies in these patients.

FRI-200
Interleukin-22 is a predictor for pre-ACLF and short-term mortality in cirrhosis
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Background and aims: Interleukin-22 (IL-22) is known to promote hepatoprotective or detrimental properties. Schwarzkopf et al. elucidated the role of IL-22 in acute-on-chronic liver failure (ACLF). In summary, serum levels of IL-22 were associated with ACLF ($p < 0.001$) and increased mortality ($p < 0.01$). In this study we analyzed associations between IL-22 plasma levels and clinical endpoints of patients with liver cirrhosis. Thereby we focused on different courses of decompensation as outlined in the PREDICT study.
Method: A retrospective analysis was conducted in clinical data of patients ($N = 204$) diagnosed with liver cirrhosis. Baseline IL-22 plasma concentrations were quantified and correlated with clinical endpoints observed over a 90-day follow-up period. IL-22 levels were assessed using enzyme-linked immunosorbent assay (ELISA) methodology.
Results: Plasma IL-22 concentrations in patients with compensated cirrhosis were comparable to those of healthy controls. In contrast, patients experiencing decompensation showed significantly higher IL-22 levels (healthy vs. decompensated, $p = 0.005$), with further increases noted in those with ACLF (healthy vs. ACLF, $p < 0.0001$). No significant variations in IL-22 levels were observed across different decompensation courses (chronic, acute stable, acute unstable); however, patients classified as pre-ACLF demonstrated significantly higher IL-22 concentrations in comparison to chronic, acute stable, and acute unstable decompensated cohorts ($p = 0.028$; $p = 0.029$; $p = 0.001$, respectively). Additional analyses indicated low IL-22 concentrations in patients without current ACLF and those who did not progress to ACLF. Patients who recovered from ACLF during the 90-day observation period showed intermediate IL-22 levels. Highest IL-22 concentrations were observed in patients with pre-ACLF and persistent ACLF. Furthermore, IL-22 plasma levels were significantly higher in patients who died within 30 days, regardless of ACLF status ($p = 0.04$). Strongest correlation was identified between IL-22 plasma levels and 7-day mortality ($p < 0.0001$).
Conclusion: IL-22 is associated with adverse outcomes in liver cirrhosis, particularly in the context of pre-ACLF and ACLF. These findings support the potential utility of IL-22 as a biomarker for predicting the dynamics of ACLF and short-term mortality in affected patients.

FRI-205
Non-acute decompensation of cirrhosis is a clinically and biologically distinct phenotype in cirrhosis
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Background and aims: The presentation patterns of decompensations in cirrhosis are heterogeneous, conferring varying outcomes. While acute decompensation (AD) is associated with the poorest prognosis, the clinical profile and outcomes of non-acute decompensation (NAD) remain unclear. This study aimed to characterize the clinical and pathophysiological features of NAD.
Method: A prospective, two-center study enrolled patients across the cirrhosis spectrum between 2020 and 2023: compensated cirrhosis (CC, $n = 29$), NAD ($n = 311$), and AD ($n = 201$). Clinical and laboratory parameters, cytokine levels (IL-6, TNF, IL-10, MCP-1), and cell death markers (M30, M65, Gasdermin-D, Receptor-interacting-protein-kinase; RIPK3, Mixed lineage kinase domain-like; MLKL) were assessed at baseline and patients were followed-up for 12 months. Overall survival and its determinants were evaluated in patients presenting as NAD.
Results: Patients with NAD had a poorer 12-month survival (81.7%) compared to CC (100%), but superior to AD (31.2%) ($p < 0.001$). Although the inflammatory cytokine levels were not different between CC and NAD ($p > 0.05$), cell death markers, particularly Gasdermin-D and RIPK3 (median with IQR)-in ng/ml were significantly elevated in patients with NAD [2.5 (2.2–2.9) and 2.4 (2.3–2.9)] compared to healthy [0.9 (0.8–1.0) and 0.9 (0.8–1.0)] and patients with CC [1.8 (1.6–1.9) and 1.8 (1.2–1.9)], $p < 0.001$, each. Both inflammatory and cell death markers were most pronounced in AD. Over 12 months, the cumulative incidence of progression to AD among NAD was 55.1%, significantly reducing their survival (68.2% vs. 95.3%, $p < 0.001$). Predictors of such progression to AD in competing risk survival models included severe ascites, lower IGF-1, albumin, BMI, and higher bilirubin, CTP, MELD, Gasdermin-D, and RIPK3 levels.
Conclusion: NAD represents a clinically, prognostically and pathophysiologically distinct clinical phenotype in cirrhosis. Patients with NAD had elevated cell death markers and severity scores and are at risk of progression to AD and mortality. Identifying NAD and high-risk populations within NAD should trigger enhanced protocols to prevent the progression to AD. Modulation of cell death is a novel and potentially disease-modifying target in cirrhosis.

FRI-206
Excess ICU mortality in septic patients with cirrhosis compared to a population without cirrhosis in two contemporary prospective cohorts
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Background and aims: Sepsis is common in patients with cirrhosis and may require admission to intensive care units (ICU). Previous studies suggested that short-term mortality exceeded 50%, which has

limited ICU access for these patients, due to perceived futility. Our hypothesis is that this excess in mortality is not as high and may be partly due to a higher number and severity of organ failures at ICU admission. Our aim is to analyze ICU mortality from sepsis in a cohort of patients with cirrhosis compared to a cohort without cirrhosis.
Method: This is a prospective cohort study including all consecutive patients with sepsis admitted to the Liver ICU at Clínic Barcelona from February 2022 to September 2024. ICU mortality was analyzed using logistic regression, adjusted for scales measuring the number and severity of organ failures, such as SOFA and APACHE II at admission.
Results: Of 1,475 admissions, 502 (34%) presented sepsis. Of these, 207 (41%) had cirrhosis, and 295 (58%) did not. The most common infection sources in patients with cirrhosis were abdominal (22%), respiratory (15%), and bloodstream infections without a clear focus (14%). In non-cirrhotic patients, the most common source was abdominal (38%), followed by respiratory (22%). Among cirrhotic patients, 68% required vasoactive support and 31% required respiratory support, compared to 51% and 18%, respectively, in non-cirrhotic patients. ICU mortality in cirrhotic patients was 24%, compared to 10% in non-cirrhotic patients. SOFA and APACHE scores were higher in patients with cirrhosis. The risk of mortality was higher in cirrhotic patients, with an odds ratio (OR) of 2.6 (95% CI 1.6–4.48). When adjusted for APACHE, the risk of mortality decreased to an OR of 1.96 (95% CI 1.14–3.39) and was no longer significantly higher when adjusted for SOFA, with an OR of 1.31 (95% CI 0.74–2.3).
Conclusion: Patients with cirrhosis admitted to the ICU for sepsis have higher mortality than a similar cohort without cirrhosis. However, this does not justify reduced access to intensive care. This excess mortality is partly due to the greater number and severity of organ failures at admission.

FRI-207

A retrospective study of puncture counts and diagnostic accuracy in 119 patients undergoing transjugular liver biopsy

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Background and aims: Transjugular liver biopsy (TJLB) is a vital diagnostic tool for liver disease patients, particularly those with ascites or coagulopathy. Unlike percutaneous liver biopsy, which uses a 16–18G needle and typically requires a single puncture, TJLB often involves multiple punctures with an 18G needle due to challenges like fragmented or insufficient tissue samples. This study retrospectively analyzed 119 TJLB cases over 15 years, evaluating puncture counts, tissue acquisition success rates, and diagnostic accuracy.
Method: We reviewed 119 cases of TJLB performed between December 2009 and November 2024, using an 18G needle for all procedures at our institution. Patients undergoing TJLB were those with ascites, coagulopathy, or cases where discontinuation of antithrombotic therapy was deemed challenging. Additional indications included suspected hematologic disorders, amyloidosis, or idiopathic portal hypertension requiring hepatic venous pressure gradient (HVPG) measurement. The procedure was concluded once a sufficient tissue sample was obtained, confirmed by visual inspection. We assessed the number of punctures, tissue acquisition success rates, and diagnostic outcomes.
Results: The cohort included 119 patients (50 males, 69 females) with a mean age of 54.2 years (range: 17–86). The average platelet count was 134,000/mm³ (range: 2,000–70,900/mm³), and the average PT-INR was 1.5 (range: 0.5–4.3). Key indications for TJLB were ascites (53.8%), PT-INR >1.5 (37.8%), ongoing anticoagulation (5.0%), platelet count < 50,000/mm³ (4.2%), and prior blood transfusions (27.7%). Suspected hematologic disorders were noted in 27.7% of cases, and HVPG measurement was performed in 77.3%. Tissue was successfully obtained in 104 cases (87.4%), with complications in 3 cases (2.5%, 1 bleeding, 2 renal biopsy). Among 103 cases with recorded puncture counts, the average number of punctures was 2.8 (range: 1–6), and the average number of tissue samples was 2.3 (range: 0–1). Puncture distributions were: 10 cases with 1 puncture, 39 with 2, 32 with 3, 13 with 4, 5 with 5, and 4 with 6. The success rates for obtaining tissue were 90% for 1 puncture, 97.4% for 2, 88.5% for 3, 76.9% for 4, 68% for 5, and 70.8% for 6 punctures. The percentage of cases with adequate tissue samples for diagnostics was 70% for 1 puncture, 100% for 2, 96.9% for 3, 92.3% for 4, 60% for 5, and 100% for 6.
Conclusion: This study highlights that TJLB is a safe procedure enabling the reliable collection of tissue samples. Additionally, it analysed tissue acquisition rates in relation to the number of punctures performed during TJLB cases. Despite an average of 2.8 punctures, a higher number of punctures did not correlate with better tissue acquisition. It was found that cases requiring multiple punctures often had underlying challenges that made tissue collection difficult in a single attempt. Further studies are needed to identify which case characteristics predict successful tissue acquisition.

FRI-208

Pre-existing sarcopenia as the 7th organ failure and one of the leading predictors of 90-day mortality in acute decompensated cirrhosis

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Background and aims: The short-term mortality of acute decompensation (AD) of cirrhosis is dependent on the development of organ failures. Sarcopenia is common in decompensated cirrhosis but its prognostic implications are poorly understood. Intense systemic inflammation has also been reported as a predictor of mortality. This study aims to determine the transplant-free short-term mortality (90-day) of AD and investigate the role of sarcopenia and inflammatory mediators in AD.
Method: In this multicentre prospective study, 249 patient visits were analysed. AD and acute-on-chronic liver failure (ACLF) were defined according to EASL-CLIF consortium definitions. Sarcopenia was assessed using psoas muscle index (PMI) calculated at the third lumbar vertebra level on computed tomography scan done within the last one year. PMI cut-offs for sarcopenia were 6.36 cm^2/m^2 for men and 3.92 cm^2/m^2 for women. Systemic inflammation was assessed using white cell count (WCC) and neutrophil to lymphocyte ratio (NLR). Standard statistical tests were used for group comparisons. Predictors of mortality were analyzed using Cox-proportional hazards regression. Multivariable logistic regression analysis was done to determine the independent predictors of 90-day mortality.
Results: Majority were male (66.7%). Alcohol was the predominant etiology (44.2%) followed by MASLD (27.7%). 57 patients (22.9%) had ACLF; 32 (12.9%) had grade-1, 16 (6.4%) had grade-2, and 9 (3.6%) had grade-3 ACLF. 61 patients (24.5%) had sarcopenia, of which 14 had ACLF as well. The 28- and 90-day mortality of the overall cohort were 11.6% and 28.1% respectively. Mortality in AD were 6.3% and 22.4% while in ACLF, were 29.8% and 47.4% at 28- and 90-day respectively. In the univariate analysis, predictors of 90-day mortality were presence of sarcopenia ($p < 0.001$), MELD score ($p < 0.001$), NLR ($p < 0.001$), WCC ($p = 0.008$), high serum bilirubin ($p = 0.002$), high creatinine ($p = 0.003$), circulatory failure ($p < 0.001$), liver failure ($p = 0.001$), renal failure ($p = 0.005$), cerebral failure ($p = 0.008$), coagulation failure ($p = 0.019$) and respiratory failure ($p = 0.043$). A multivariate logistic regression analysis with MELD, sarcopenia, WCC, respiratory, cerebral

and circulatory failure showed that MELD, sarcopenia and circulatory failure were the independent predictors of mortality (p < 0.05 for all). In another multivariable model involving EASL-CLIF defined organ failures, sarcopenia (aHR: 2.79 (95%CI: 1.70–4.58); p < 0.001), circulatory failure (aHR: 3.76 (95%CI: 1.77–7.98); p < 0.001), liver failure (aHR: 2.64 (95%CI: 1.31–5.32); p = 0.007), renal failure (aHR: 1.89 (95%CI: 1.03–3.48); p = 0.040) and cerebral failure (aHR: 2.23 (95%CI: 1.01–4.92); p = 0.048) were independent predictors of 90-day mortality.

Conclusion: The result of this study shows that in addition to CLIF-C OF score, presence of sarcopenia should be treated as the 7th organ failure as it is one of the independent predictors of 28- and 90-day mortality in acutely decompensated cirrhosis.

FRI-209

Prevalence of advanced liver fibrosis and accuracy of non-invasive tests in primary, secondary and tertiary care in Austria

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Background and aims: Background and aims: Identifying individuals with steatotic liver disease (SLD) and advanced fibrosis is crucial, as these are at increased risk for liver and non-liver-related morbidity and mortality, and subject to intensified medical management and potential new therapies. Therefore, we studied patient characteristics, fibrosis prevalence and accuracy of emerging blood-based non-invasive tests (NITs) throughout elastography-based screening initiatives in primary, secondary and tertiary care.

Method: Five cohorts spanning primary-tertiary care including unselected individuals (colonoscopy screening, n = 1197, Cohort I), those at risk of SLD (metabolic risk factors/prediabetes, n = 1333/n = 996, Cohort II/III), and after referral to hepatology outpatient clinics (n = 2397/n = 2598, Cohort IV/V) between 2016 and 2024 were retrospectively included. All subjects underwent liver stiffness measurement (LSM) with controlled attenuation parameter (CAP), clinical and laboratory examination on the same day (Cohort I-IV) or within 90 days (Cohort V). NITs included LiverPRO, LiverRisk score, and CORE.

Results: Mean age was 49.1–58.3 years (range across cohorts), 51%-61% were male, mean BMI was 26.8–31.3 kg/m², 21–59% were obese (BMI ≥30 kg/m²), 25–100% had prediabetes. Mean CAP was 262–294 dB/m and 57–82% showed hepatic steatosis (defined by CAP ≥248 dB/m). Suspected advanced fibrosis (LSM ≥8 kPa) was found in 6.4% of Cohort I, 7.3/6.8% of Cohort II/III, and 21/30% of Cohort IV/V. This prevalence was especially high in obese subjects (15, 10/14, 38/38%) and individuals with diabetes (11. 17/NA, 52/49%). However, the prevalence in individuals with overweight, prediabetes or elevated ALT/GGT was not increased. Applying possible referral strategies, sensitivity of LiverPRO ≥25% (71, 51/51, 87/88%) was higher for LSM ≥8 kPa across primary, secondary and tertiary care as compared to FIB-4 >1.3 (44, 33/37, 69/62%) and LiverRisk score ≥6 (52, 31/39, 86/78%) at lower specificity and comparable PPV. However, screening based on lab-based tests did only marginally increase net-benefit for true- and false-positives (using LSM ≥8 kPa as a reference) in primary/secondary care. Overall diagnostic accuracy for LSM ≥8 kPa was numerically higher for LiverPRO (area under the curve: 0.755, 0.595/0.632), LiverRisk (0.746, 0.607/0.621) and CORE score (0.726, 0.583/0.636) in primary/secondary care as compared to FIB-4 (0.612, 0.576/0.571).

Conclusion: Prevalence of suspected advanced fibrosis/cirrhosis was 6–7% in primary/secondary care populations undergoing liver fibrosis screening in Austria, and 20–30% in tertiary care, being pronounced in individuals with diabetes or obesity, but neither overweight, prediabetes nor elevated ALT/GGT. In low-prevalence settings, LiverPRO had higher sensitivity to detect individuals with LSM ≥8 kPa as compared to FIB-4 and LiverRisk score.

FRI-210

Impact of blood cell count derived inflammatory markers on the outcome of critically ill cirrhotic patients

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Background and aims: Neutrophil-to-lymphocyte (NLR) and monocyte-to-lymphocyte-(MLR) ratios and systemic immune-inflammation index (SII) have been associated with adverse outcomes in critically ill cirrhotic patients with acute decompensation (AD) or acute on chronic liver failure (ACLF). The aim of this present study is to investigate the performance of leukocyte markers, including NLR, MLR and SII in predicting mortality of cirrhotic patients admitted to the ICU with AD and ACLF.

Method: All patients admitted to the ICU with decompensated cirrhosis with and without ACLF were retrospectively evaluated. All leukocyte markers were calculated in the first three hours of ICU admission. Their ability to predict mortality was measured using the analysis of the area under the receiver operating characteristic curve (AUC). Primary outcome was in-hospital mortality.

Results: Six hundred and two patients (444 males, mean age 67 ± 12 years) with either AD (n = 360) or ACLF (n = 242) were investigated. Baseline NLR, MLR and SII of those patients were, respectively, 12.7 ± 7, 0.96 ± 0.67 and 1.547 ± 717. Mortality was observed in 102 (17%) patients. NLR (21.5 [16.4–21.5] *vs.* 10.9 [9.7–12.3] in survivors, (p < 0,001), MLR (1.20 [0.96–1.49] *vs.* 0.95 [0.81–1.00] in survivors, p < 0,001) and SII (2617.6 [1966.1–3.269.1] *vs.* 1.328.4 [1088.4–1568.5] in survivors, p < 0,001) were associated with in-hospital mortality. After exclusion of patients with ACLF, even higher AUCs were observed for SII (0.754) and NLR (0.746).

Conclusion: Leukocyte ratios, particularly SII and NLR are readily available and low-cost biomarkers capable of predicting mortality in patients with decompensated cirrhosis irrespective of the presence of concurrent ACLF.

FRI-211

Vasopressin is safe and effective as a second vasopressor in patients with cirrhosis and septic shock: results of the VITEL-C trial. NCT05315557

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Background and aims: Septic shock in critically ill patients with cirrhosis (CIC) is associated with high mortality and requires targeted management. Terlipressin (TERLI) and vasopressin (VASO) are used as second-line vasopressors after norepinephrine (NE), but their comparative efficacy and safety have not been established. Additionally, vasopressin has not been studied in CIC. We hypothesized that VASO would be non-inferior to TERLI as an add-on agent for reversing septic shock in CIC.
Method: Open-label randomized controlled trial; CIC patients in septic shock unresponsive to NE at 0.05 μg/kg/min were randomly assigned to either VASO (0.03 U/min) or TERLI (1 mg/24 hours). NE doses were titrated to maintain a target mean arterial pressure (MAP) of ≥65 mmHg. The primary outcome was shock reversal at 6 hours(h), defined as cessation of NE.
Results: Patients with septic shock with mean age 46.7 ± 10.4 years, 97% males, 41% alcohol-related, with 67% pneumonia, mean SOFA score 12.5 ± 1.9 were randomized to receive VASO (n = 50) or TERLI (n = 50). Baseline characteristics were similar: MAP [(63.36 ± 12.59) vs. (62.18 ± 10.4) mmHg; p = 0.61], arterial lactate [(3.76 ± 1.65 mmol/L) vs. (3.40 ± 1.35 mmol/L); p = 0.240], KDIGO stage of acute kidney injury [0 (34% vs. 38%), 1 (34% vs. 22%), 2 (16% vs. 20%), 3 (16% vs. 20%); p = 0.61], MELD scores [(28.38 ± 8.62) vs. (30.13 ± 8.62); p = 0.313]. The reversal of shock at 6 h [(58% vs. 48%); p = 0.32] including dose of vasopressors in norepinephrine equivalents (0.15 ± 0.19 vs. 0.17 ± 0.12 ug/kg/min) was similar in TERLI vs. VASO. The reversal of shock at 72 h was also comparable [(34% vs. 50%); p = 0.11], however, rapid reversal of shock at 3 h (22% vs. 6%; p = 0.02) and significantly improved urine output at 6 h [(55.1 ± 21.9) vs. (41.6 ± 22.93); p = 0.003], and at 12 h [(49.0 ± 25.1) vs. (39.8 ± 20.7); p = 0.048] were observed in TERLI vs. VASO, respectively. KDIGO stage at 72 h [0(14% vs. 28%), 1(40% vs. 30%), 2(8% vs. 6%), 3(38% vs. 6%); p = 0.36], need for dialysis (42% vs. 42%; p = 0.10), 28-day mortality (84% vs. 80%; p = 0.60), days of mechanical ventilation [(5.28 ± 3.59) vs. (4.48 ± 2.86); p = 0.22] were similar in TERLI vs. VASO. A significant improvement in systemic vascular resistance (SVR) at 12 h and 24 h (p < 0.05) and lactate clearance at 6 h [(−2.69 ± 16.48) vs. (−10.65 ± 18.23); p = 0.02] and 24 h [(−0.067 ± 17.42) vs. (−14.76 ± 21.90); p < 0.001] was seen with VASO compared to TERLI. Adverse events (34% vs. 8%; p = 0.001) and rebound hypotension (44.1% vs. 21.2%; p = 0.046) were significantly higher with TERLI. The majority of adverse events were ischemic and occurred after 12 h.
Conclusion: In CIC with septic shock, vasopressin is comparable to terlipressin as an adjunct to NE in reversing shock. While terlipressin led to a faster reversal of shock, it was associated with a higher incidence of adverse events and rebound hypotension. Vasopressin is a safer and effective second-line vasopressor for CIC with septic shock.
[Trial Registration: NCT05315557].

FRI-212
The COPPTRIAHL randomized controlled study, a preliminary analysis

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Background and aims: Critically ill patients with cirrhosis and ascites are at high risk of developing intra-abdominal hypertension (IAH), which is associated with increased mortality. Clinical guidelines recommend maintaining intra-abdominal pressure (IAP) below 16 mmHg. However, over 75% of these patients develop IAH within the first week of ICU admission. Large-volume paracentesis (LVP) is the standard treatment to relieve abdominal wall tension in these patients, resulting in intermittent reduction of IAP associated with transient improvements in renal and pulmonary function. Continuous passive paracentesis (CPP) offers a strategy to treat and prevent IAH, potentially improving clinical outcomes. However, no studies have compared paracentesis strategies for IAH management. This study aims to compare clinical outcomes of patients with cirrhosis and ascites treated with CPP versus LVP in intensive care.
Method: A randomized clinical trial in a tertiary hospital center, open to collaboration with other centers, with an estimated duration of 36 months. A total of 72 patients with liver cirrhosis and grade 2 ascites will be enrolled and randomly allocated (1:1) to either the LVP (control) or CPP (intervention) groups. Randomization within the initial 24 hours of admission will be stratified based on maximum values of serum creatinine concentration (sCr) and IAP. LVP will be performed intermittently according to clinical guidelines, while CPP will drain ascitic fluid for up to 7 days. The primary outcome is sCr measured up to day 7, with secondary outcomes including 28-day mortality.
Results: Between September 2022 and November 2024, 89 patients were screened, and 26 (29%) were included in the study and in this preliminary analysis (LVP n = 10 vs. CPP n = 16, henceforth). The most frequent exclusion criterium was minimal ascites (n = 21). The median patient age was 58 (50–62) years-old and male gender represented 73%. Clinical severity at admission showed SAPS II 44 (30–76), MELD-Na 31 (25–38), ACLF 3 (1–3) and CLIF-SOFA 13 (9–17) and CLIF-C 56 (37–63) median score values. The baseline sCr was similar between groups (2.0 vs 1.9 mg/dL, p = 0.9). The results for sCr from days 1 to 4 post-randomization are presented. No significant differences between groups were observed (general linear model repeated measures, p = 0.06). The overall 28-day mortality rate was 42%, with no significant group difference (50% vs. 38%, p = 0.7), as depicted by Kaplan-Meier analysis.
Conclusion: This preliminary analysis of the COPPTRIAHL clinical trial revealed a slow patient recruitment rate. There was no significant difference in sCr or 28-day mortality between critically ill patients with cirrhosis and ascites submitted to LVP or CPP.
The study remains open for collaboration with other centers. ClinicalTrials.gov registration NCT04322201. Protocol published in Trials, 24, 534 (2023).

FRI-213-YI
The presence of chronic kidney disease does not worsen 28- or 90-day survival in cirrhotic patients with acute on chronic liver failure

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Background and aims: With the rise in metabolic associated steatotic liver disease (MASLD), patients presenting with acute decompensation (AD) of cirrhosis with pre-existing chronic kidney disease (CKD) is increasing. AD with organ failures is known as acute on chronic liver failure (ACLF) and exhibits high mortality. The CANONIC study showed that kidney failure (KF) was the strongest prognostic factor for worse outcomes in ACLF. Currently however, there is no clarity on the prognostic implication of CKD in either AD or ACLF as published literature [1, 2] excluded these patients. The aim of

this study thus is to evaluate the impact of underlying CKD on 28- and 90-day mortality in patients with AD and ACLF.
Method: In this multicenter prospective study of "predictors of decompensation, ACLF and mortality in cirrhosis (SoLiDaRity-DAM), 396 AD patients visits were analyzed. AD and ACLF was defined as per e-CLIFF consortium definitions [1]. CKD was defined as glomerular filtration rate (eGFR) < 60 for minimum 3 months and loss of corticomedullary differentiation on renal ultrasonography. The study was approved by the institutional review board and was in accordance of declaration of Helsinki. Standard statistical tests were used for group comparison. Predictors of mortality was analyzed using Cox-proportional hazards regression. Patients were characterized in 4 groups, No ACLF with and without CKD and ACLF with or without CKD for Kaplan-Meier survival function.
Results: Out of 396, majority were male (67.2%) with mean age of 64.4 ± 11.5 years. Alcoholic was the predominant etiology (43%) followed by MASLD (30%). CKD was adjudicated for 75 (18.9%), whereas 62% of the cohort has at least 1 metabolic dysfunction. A total of 89 (22.5%) had ACLF of which 53 (60%) had grade-1, 22 (25%) grade-2, and 12 (13%) had grade-III ACLF. The 28 and 90- day mortality was (44/396) 11% and (99/396) 25% respectively. The important predictors of 90-days mortality were serum creatinine (p = 0.005), CRP (p = 0.036), procalcitonin (p = 0.022), Bilirubin (p < 0.001) and MELD score (p < 0.001). Of the organ failures, liver, renal, circulatory and brain (p < 0.001 for all) were, whereas coagulation and respiratory failure were not 90-days mortality predictors. The prevalence of CKD was 19%. CKD was adjudicated in 43% patients with ACLF and 12% without ACLF and most importantly presence of CKD was not a predictor of 90-days mortality. The highest probability of 90-day survival corresponded to patients with CKD but no ACLF (81%) which mirrors the survival of patients without CKD or ACLF (p = NS between the groups). The worst survival was seen in patients with ACLF but no CKD (57%) which mirrors the survival of patients with CKD who developed ACLF (p = NS).
Conclusion: The result of our study shows that the presence of CKD does not impact the survival in patients admitted with AD or ACLF. Further large-scale prospective, multicenter studies with biomarkers of CKD are suggested.

FRI-214
Predicting the risk of clinically relevant bleeding in patients with acute-on-chronic liver failure and acute decompensated liver cirrhosis
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Background and aims: Hemostasis in acute decompensated liver cirrhosis (AD) and acute-on-chronic liver failure (ACLF) is complex and a challenge in the clinical setting. This study aims to predict clinically relevant bleeding in patients with AD or ACLF using two new point-of-care laboratory methods: the Quantra hemostasis system (Quantra) and the Total Thrombus formation Analysis System (T-TAS).
Method: In this interim analysis, individuals with decompensated liver cirrhosis were prospectively included at a tertiary hepatology center. Hemostasis was assessed with T-TAS and Quantra at inclusion and patients were followed up for 28 days for clinically relevant non-variceal bleeding. Non-variceal bleeding was defined as major bleeding, relevant minor bleeding and non-relevant minor bleeding according to the International Society on Thrombosis and Haemostasis. Quantra is a viscoelastic test that uses sonic assessment to evaluate the elasticity and formation of a clot, measuring clotting time. T-TAS measures the elevation of flow pressure during platelet plug formation (PL-chip) and fibrin clot formation (HD-chip) and is presented as the area under the curve (AUC). Individuals with clinically relevant bleeding (major bleeding or relevant minor bleeding) were compared to a combined group of non-relevant bleeding and no bleeding using the Mann-Whitney U-test.
Results: 47 consecutive patients, 17 with ACLF and 30 with AD, were included. The ACLF group had significantly (p = 0.02) lower AUC using the PL-chip suggesting smaller and/or less stable platelet plugs in the ACLF group. In contrast, no difference in fibrin clot formation and/or stability was observed between ACLF and AD using the HD-chip (p = 0.33). Quantra clotting time was significantly longer in the ACLF group than the AD group (p = 0.01). We documented 19 bleedings in the first 28 days: 8 major bleedings, 5 relevant minor bleedings and 6 non-relevant minor bleedings. The T-TAS showed a significantly reduced AUC of the PL-chip in patients with clinically relevant bleeding (major or relevant minor bleeding) compared to patients with non-relevant or no bleeding (p = 0.029) indicating a diminished capacity for platelet aggregation in patients with clinically relevant bleeding. HD-chip did not show a difference between the groups (p = 0.087). Quantra clotting time showed a significantly increased clotting time (p = 0.02) in the group with clinically relevant bleeding compared to the others, suggesting a risk for clinically relevant bleeding in patients with a clotting time over 150 seconds.
Conclusion: T-TAS and Quantra both show promising potential to predict the risk of clinically relevant bleeding in patients with ACLF and AD. The result of the T-TAS PL-chip indicate a compromised primary hemostasis in patients with subsequent clinically relevant non-variceal bleeding. This will be further evaluated in our ongoing study.

FRI-215
An argument for risk-based case-finding in chronic liver disease
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Background and aims: Most Liver disease is preventable, if diagnosed early, yet 75% of cirrhotic patients are diagnosed at presentation with liver failure. 25% die within 60 days. There is no strategy for optimium identification of patients. This study aims to identify what proportion of patients admitted were known to have prior alcohol excess, type 2 diabetes mellitus (T2DM), or abnormal liver function tests (LFTs), to provide evidence for targeted case finding to reduce presentations with decompensated cirrhosis.
Method: Records of patients aged 18 and over admitted to NHS Tayside with an ICD-10 code for liver disease between August 2018 and July 2023 were interrogated to quantify the proportion who presented because of decompensated liver disease, and if these were known to have T2DM, consume excess alcohol, or had an LFT in the 3–12 months prior to admission.
Results: Of the 7387 admissions, 634 individuals were primarily admitted for liver disease (541 in liver failure) of which 408 (64%) presented due to alcohol-related liver disease (ALD), 82 (13%) due to metabolic dysfunction-associated liver disease (MASLD), 52 (8%) due to hepatocellular carcinoma (HCC), 31 (5%) due to MASLD and increased alcohol intake (MetALD), 22 (3%) with other/unspecified aetiology (including cryptogenic cirrhosis), 19 (3%) due to

autoimmune hepatitis, 10 and 3 (2%) due to primary biliary cirrhosis and primary sclerosing cholangitis, respectively, 6 and 2 (1%) due to hepatitis C and B viruses, respectively, and 1 due to Wilson's disease. Overall, 355 (53%) had a history of excess alcohol use prior to admission and 173 (27%) had T2DM. For the ALD + MetALD subgroup, 333/439 (76%) had a history of excess alcohol use. For the MASLD + MetALD subgroup, 79/113 (70%) had T2DM. 316 (50%) of patients had LFTs checked by primary care 3–12 months prior to admission; this increased to 65% if LFTs taken in secondary care were counted. Of these 316, median alanine aminotransferase (ALT) was 43 U/L, interquartile range (IQR) 26–61. For ALD and MASLD it was 46 U/L (31–65) and 29 U/L (22–44), respectively. 67% had ALTs ≤55 U/L (lab's upper limit of normal (ULN)), 34% had ALTs ≤30 U/L (the true ULN), and 17% had both an ALT ≤30 U/L and alkaline phosphatase (ALP) ≤130 U/L. For the combined ALD + MASLD + MetALD subgroup, 448/521 (86%) patients could be identified before presentation if they had a known history of excess alcohol use, T2DM, or LFTs demonstrating an ALT >30 U/L or ALP >130 U/L.

Conclusion: Of patients admitted to hospital for liver disease, 50% had LFTs checked in primary care (65% in total), 3–12 months before admission. For those, depending on ULN used, 34% and 67% of ALTs were within reference intervals Knowing whether patients have T2DM, alcohol excess or abnormal LFTs could mean up to 86% of patients with ALD, MASLD or MetALD are identified, and it remains to be seen whether non-invasive fibrosis scores could pick up the remainder, provided these patients are tested.

FRI-216

Interprofessional therapeutic drug monitoring of Piperacillin/Tazobactam enhances care for patients with acute-on-chronic liver failure in the ICU

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Background and aims: Acute-on-chronic liver failure (ACLF) is a rapidly progressive and severe condition in patients with underlying liver cirrhosis, frequently precipitated by bacterial infections. Effective and timely management of these infections, particularly with targeted antibiotic therapy, is critical. Piperacillin/Tazobactam is a key agent for treating severe infections in critically ill patients. However, optimizing its dosing is challenging due to altered pharmacokinetics in ACLF patients. Therapeutic drug monitoring (TDM) offers a precise, evidence-based approach to achieving optimal drug concentrations, especially for time-dependent antibiotics like Piperacillin/Tazobactam. This study aimed to evaluate the impact of an interprofessional TDM strategy on optimizing Piperacillin/Tazobactam dosing in ACLF patients in the intensive care unit (ICU).

Method: This analysis was conducted in a medical ICU with a strong interprofessional framework, including physicians, clinical pharmacists, and nursing staff. Twenty-seven ACLF patients underwent initial TDM, and eight received follow-up TDM. Serum concentrations of Piperacillin/Tazobactam were measured weekly using high-performance liquid chromatography (HPLC). Patient severity was characterized using Child-Pugh, SOFA, MELD, and CLIF-C-ACLF scoring systems. TDM results guided individualized dosing adjustments, and the outcomes were compared to a seasonally adjusted control cohort without TDM intervention. The adherence to interprofessional recommendations for dose adjustments or antibiotic switches was assessed.

Results: Initial TDM revealed that 63% of patients achieved Piperacillin/Tazobactam serum concentrations within the target range, while 22% exceeded and 15% fell below the target. Follow-up TDM demonstrated improved outcomes, with 75% of patients achieving target concentrations, 25% exceeding the range, and none falling below. In five cases, antibiotic switches were recommended due to resistance or clinical necessity, and all recommendations for dose adjustments or therapy changes were fully implemented. The interprofessional approach ensured consistent adherence to evidence-based dosing strategies, reflecting robust team collaboration.

Conclusion: The integration of an interprofessional TDM strategy significantly optimized Piperacillin/Tazobactam dosing in critically ill ACLF patients. This approach led to higher rates of target achievement and facilitated individualized antibiotic management. Beyond improving clinical outcomes, this strategy underscores the importance of rational antibiotic use in critically ill patients and contributes to global efforts to combat antimicrobial resistance. The findings highlight the value of TDM in achieving precision medicine in complex patient populations, such as those with ACLF.

FRI-221

APASL ACLF research consortium (AARC) liver failure score and first week(transplant window) defines the limits of medical management and time frame for liver transplant in acute on chronic liver failure patients

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Background and aims: Acute-on-Chronic Liver Failure (ACLF) is associated with a high risk of short-term mortality in the absence of liver transplantation (LT). This study aimed to evaluate the AARC score's effectiveness in predicting 90-day survival and determining the appropriate timing for LT in ACLF patients.
Method: We analysed data from the AARC registry data of 7721 patients enrolled between Dec 2012 to Nov 2023. Patients aged 18 to 70 years with a diagnosis ACLF according to the APASL criteria were enrolled in the study and prospectively followed for up to 90 days or liver transplantation. Predictors of 90-day mortality were identified through multivariate Cox regression analysis. To evaluate the predictive accuracy, a propensity matching analysis was performed for ACLF patients who underwent liver transplantation (n = 265) with 3 times matched non-transplant cohort (n = 795). The AARC score was dynamically evaluated at time points (days 4, 7, 15, and 28 post-hospitalization) to predict 90-day outcomes by repeated measures analysis with a General Estimating Equations (GEE) model.
Results: Of the 7,721 ACLF patients, mean age of 44.4+12.4 years and 85% being male. The cohort is relatively sick with MELD (29.5 ± 7.3), SOFA (9.2 ± 3.2), CLIF SOFA (11.6 ± 2.7) and AARC Score (10.2 ± 1.4) with only 421 cases (5.45%) had undergone LT. The survival among the non-transplanted cohort is 45.6% at 90 days. In multivariate analysis, age >55 years (HR = 1.013, 95% CI 1.005–1.022, p = 0.002), new-onset sepsis within the first week (HR = 3.02, 95% CI 2.15–4.02, p < 0.001), and baseline AARC score (HR = 1.435, 95% CI 1.37–1.50, p < 0.001) as independent predictors of mortality. The mortality rate was 29% for patients with an AARC score of 5–8, rose sharply to 62% for those with a score of 10, and exceeded 92% for patients with a score of 13 or higher. For patients with a baseline AARC score of 10 or greater, the 90-day mortality rate was 76.5%, which increased to 92.8% if the score remained unchanged at day 7. Conversely, patients with an AARC score below 10 had a 90-day mortality rate of 30.2%, which further decreased to 12% if the score remained stable after 7 days. Median survival was significantly higher in the LT group (76.8%, 95% CI 73.2–80.5 days) compared to the non-LT group (50.9%, 95% CI 48.7–53.8days) (p < 0.001). Among non-survivors, cumulative mortality was 31% by the end of the first week, escalating sharply to 55% by the second week and 78% by the fourth week, highlighting the importance of first week.
Conclusion: The AARC score is a reliable tool for stratifying ACLF patients, guiding the timing and necessity of liver transplantation. Patients with an AARC score of 10 or more during the first week of hospitalization i.e. the "transplant window" should be considered for early LT to improve clinical outcomes. This model will assist clinicians in making timely decisions regarding whether to escalate to LT or manage conservatively.

FRI-222

One-week criteria of potential care inappropriateness for patients with acute-on-chronic liver failure not eligible for liver transplantation

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Background and aims: Patients with Acute-on-Chronic Liver Failure (ACLF) had very poor short-term prognosis and required frequently intensive care with organ supports. The definition of inappropriate care where the recovery is highly improbable is an urgent medical need to limit unnecessary and expensive management and to stimulate palliative care.
Method: This analysis investigated 791 patients with EASL-CLIF-defined ACLF enrolled in two independent prospective multicenter cohorts (PREDICT and ACLARA) according to baseline and 1-week number of organ failures (OF), organ supports and CLIF-C ACLF scores. A threshold of 100% of 90-day transplant-free mortality rate was used to define inappropriate care.
Results: Overall, there were 55%, 26% and 19% patients with initial ACLF-1, 2 and 3, respectively. 34% of the patients were admitted to ICU and the overall 90-day transplant-free mortality rate was 60%. Neither number of OF, organ supports or value of CLIF-C ACLFs at baseline, were associated with inappropriate care, as defined above. The accuracy of 1-week CLIF-C ACLF score in distinguishing patients who died from those who survived by 90 days was significantly higher than that of the baseline CLIF-C ACLF score (AUROC 0.83 (95% CI 0.79–0.87) vs. 0.73 (0.67–0.78); p < 0.001). A 90-day mortality rate of 100% was found in patients with baseline ACLF-1 or 2 who had at 1 week 5 or more OFs and/or CLIF-C ACLF score ≥70 and in those with initial ACLF-3 who had at 1 week 4 or more OFs and/or CLIF-C ACLF score ≥60. Importantly, the definition of inappropriate care was not reached with any number of organ supports at 1 week.
Conclusion: The number of OF and CLIF-C ACLF scores one week after ACLF onset should be used to define future inappropriate care and to

suggest palliative care when curative treatments, as liver transplantation, are not available. On behalf of the PREDICT and ACLARA study groups.

FRI-223

Intermediate-term survival in patients with hepatorenal syndrome-acute kidney injury treated with terlipressin

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Background and aims: Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a deadly but potentially reversible complication of decompensated cirrhosis resulting in rapid (days to weeks) mortality if left untreated. Terlipressin is FDA-approved to treat adult patients (pts) with HRS with a rapid worsening in kidney function and is recommended as the first-line treatment (in combination with albumin) for HRS-AKI per EASL and AASLD guidelines. While for most pts liver transplantation (LT) may be the only definitive treatment for the underlying disease, some pts with HRS-AKI survive for >90 days without LT. Identification of factors associated with the intermediate-term survival of pts with HRS-AKI could facilitate their treatment optimization.
Method: Data from pts treated with terlipressin in 3 Phase III placebo-controlled clinical studies, OT-0401(NCT00089570), REVERSE (NCT01143246), and CONFIRM (NCT02770716), were pooled for the retrospective analysis of factors associated with intermediate-term survival, defined as >90 days without LT, using univariable and multivariable logistic regression.
Results: In the terlipressin group (N = 352), 87 (24.7%) pts survived >90 days without LT, and 265 (75.3%) pts survived ≤90 days or received LT. The rate of HRS reversal—defined as a serum creatinine level of ≤1.5 mg/dL—was 63.2% (55/87) among pts who survived >90 days without LT vs 23.4% (62/265) who survived ≤90 days or had LT ($p < 0.001$). In the univariable analysis, survival >90 days without LT was significantly associated with the following parameters: HRS reversal (odds ratio [OR] = 5.63, $p < 0.001$); acute-on-chronic liver failure (ACLF) score (OR = 0.51, $p < 0.001$); baseline Model for End-Stage Liver Disease (MELD) and MELD-sodium (Na) scores (OR = 0.89 and OR = 0.88, respectively, both $p < 0.001$); MELD ≥35 (OR = 0.45, $p = 0.004$); alcohol-related etiology of cirrhosis (OR = 1.90, $p = 0.016$); and systemic inflammatory response syndrome (SIRS; OR = 1.85, $p = 0.022$). In the multivariable analysis, HRS reversal (OR = 3.99, $p < 0.001$); MELD ≥35 (OR = 0.38, $p = 0.006$); SIRS (OR = 2.80, $p = 0.002$), and alcohol-related etiology (OR = 2.57, $p = 0.011$) were independent predictors of survival > 90 days without LT.
Conclusion: Significantly more pts with HRS reversal experienced intermediate-term survival >90 days without LT, compared with pts without HRS reversal. Lower ACLF score correlated with >90-day survival without LT in the univariable but not in the multivariate analysis. In the multivariable analysis, HRS reversal was the strongest independent predictor of survival >90 days without LT, followed by the presence of SIRS, lower MELD score, and alcohol-related etiology of disease.

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Time-varying effect of acute-on-chronic liver failure on post-liver transplant survival accounting for selection bias

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Background and aims: Prior studies show severe acute-on-chronic liver failure (ACLF) at liver transplantation (LT) negatively impacts short-term, but not long-term, post-LT outcomes. However, not accounting for ACLF's time-varying effect on the waitlist may underappreciate its dynamic nature. Moreover, excluding those who died or dropped off the waitlist raises concerns about selection bias.
Method: This US nationwide retrospective cohort study estimated the effect of severe ACLF (grade 3) on post-LT outcomes, including adult, first-time deceased donor LT candidates listed from June 2013 to May 2023. A counterfactual pseudopopulation was constructed using a marginal structural model (MSM) to address selection bias and time-varying exposure (ACLF grade-3). Cox proportional hazard (PH) models and an extended Cox model with a Heaviside step function assessed the hazard of death post-LT.
Results: Among 31,267 eligible LT candidates (baseline cohort), 11.2% (n = 3,518) had ACLF-3 at listing; 13.6% (n = 4,243) died or dropped out while on the LT waitlist. Of the 27,024 patients who received LT (transplanted cohort), 12.3% (n = 3,333) had ACLF-3 at LT. In the inverse probability weighted, extended Cox model, ACLF-3 at LT (but not at waitlisting) was associated with a higher hazard of death (HR1.87, 95%CI; 1.15–3.05) within one-year post-LT but not thereafter. This MSM effect size was 12% higher than conventional multivariable Cox PH models. Sensitivity analyses corroborated these findings.
Conclusion: Compared to previous studies, ACLF-3 at LT in our MSM was associated with a discernible increase in short-term mortality post-transplant, presumably due to our addressing of selection bias, while long-term survival was similar to those without severe ACLF at LT. However, potential vulnerability to post-transplant complications warrants further investigation.

FRI-225

Predictors of shock reversal and outcomes in acute-on-chronic liver failure with septic shock

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Background and aims: Acute-on-chronic liver failure (ACLF) patients with septic shock have high mortality. Identifying predictors of shock reversal and survival can modify our therapeutic strategies.
Method: In this prospective cohort study, two hundred and three ACLF patients diagnosed per the Asia-Pacific Association for the Study of the Liver (APASL) criteria and presenting with septic shock were enrolled. Septic shock was defined according to Sepsis-3 criteria. Shock reversal was defined as sustained MAP ≥65 mmHg without vasopressors for at least 12 hours within 3 days of onset or admission.
Results: The cohort had a mean age of 45.0 ± 9.3 years; 94.2% were male, 52% had alcohol-related liver disease, the mean baseline MELD score was 34.0 ± 6.0, and the mean SOFA score was 12.5 ± 2.5. The mean baseline Asia Pacific ACLF Research Consortium (AARC) score was 11.5 ± 1.5. Pneumonia was the predominant infection focus (75%, n = 152). The mean norepinephrine equivalent dose was 0.12 ± 0.06 μg/kg/min. CRRT was initiated in 84 patients (41.4%). The mean length of ICU stay was 7.9 ± 3.2 days. At 7 days, 72% of patients were alive. Shock reversal within 3 days occurred in 81 patients (39.9%). Univariate analysis showed that patients who achieved shock reversal had significantly lower baseline lactate levels (3.5 ± 1.6 mmol/L vs. 4.8 ± 1.7 mmol/L; $p = 0.01$), higher lactate reduction at 6 hours (−35% ± 15% vs. −10% ± 18%; $p < 0.001$), lower baseline AARC scores (10.8 ± 1.2 vs. 12.5 ± 1.4; $p < 0.001$), lower MELD scores (32.5 ± 5.5 vs. 35.8 ± 6.2; $p = 0.02$), and lower SOFA scores (11.8 ± 2.3 vs. 13.5 ± 2.6; $p = 0.01$). They also received higher volumes of fluid resuscitation (35 ± 8 mL/kg vs. 22 ± 9 mL/kg; $p < 0.001$), required fewer vasopressors (1.5 ± 0.5 vs. 2.1 ± 0.7; $p < 0.04$), and had shorter ICU stays (6.5 ± 2.8 days vs. 9.2 ± 4.5 days; $p < 0.03$). Rebound hypotension was less frequent in patients who achieved shock reversal (20% vs. 45%; $p < 0.001$). Multivariable analysis showed lactate reduction ≥15% at 6 hours [odds ratio (OR) = 5.8; 95% confidence interval (CI): 3.0–11.2; p <

0.001], lower AARC score [OR = 1.5; 95% CI: 1.3–1.8; p < 0.001] absence of mechanical ventilation requirement [OR = 2.5; 95% CI: 1.3–4.7; p = 0.006]. Patients who achieved shock reversal had a higher 28-day survival rate compared to those who did not (60% vs. 15%; log-rank p < 0.001).
Conclusion: In ACLF patients with septic shock, early lactate reduction of more than 15%, lower baseline AARC scores, and absence of need for mechanical ventilation are significant predictors of shock reversal. Achieving shock reversal is associated with improved survival outcomes.

FRI-226
The burden of extrahepatic organ failures in european patients with cirrhosis
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Background and aims: The impact of acute-on-chronic liver failure (ACLF, the most severe form of decompensated cirrhosis characterized by the presence of extra-hepatic organ failures [EHOF]) on the European health care systems has not been well characterized, in part due to the lack of a code for ACLF in the International Classification of Diseases (ICD). We used ICD-codes for extrahepatic organ failure to assess the burden of cirrhosis with EHOFs from routinely collected data of a number of European health care systems.
Method: We searched national health care system databases from Germany, France, Italy and Denmark for admissions between 2017 and 2020 with an ICD diagnosis of cirrhosis and analyzed in those renal, cerebral, respiratory or circulatory failures. Healthcare claims refer to reimbursement requests for medical expenses submitted by healthcare providers to insurers. In this study, we also analyzed the healthcare claims incurred during admissions for EHOFs and calculated their proportion relative to all cirrhosis-related admissions.
Results: During the 4-year period, 1,599,680 hospital admissions for cirrhosis, which included 329,093 (20.6%) admissions with at least one EHOF, were recorded across the 4 countries. The most frequent failing organ systems were kidneys (52.9%) and respiratory (41.2%). The annual number of admissions for cirrhosis decreased over time (from 414,093 in 2017 to 375,112 in 2020), whereas the percentage of admissions with EHOF rose from 19.9% to 21.5%. Overall, in-hospital mortality rate of admissions with diagnosis of EHOF was high (29.2%), markedly exceeding mortality of admissions with diagnosis of cirrhosis alone (7.9%). The estimated median hospital stay was 12 days of each admission due to EHOF, and proportion of estimated healthcare claims of all hospital admissions between 2017 and 2020 due to EHOF accounting for almost half (44.9%) of the admissions for liver cirrhosis.
Conclusion: This study reveals that the burden of cirrhosis with EHOF was high and rising over time in 4 European countries studied, and associated with high mortality.

Cirrhosis and its complications – Experimental and pathophysiology

TOP-201-YI
MeCP2 as epigenetic mechanosensor of liver sinusoidal endothelial cells in cirrhosis
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Background and aims: Chronic liver disease (CLD) arises from progressive liver injury, fibrosis and tissue remodeling, leading to cirrhosis and liver failure. Increased tissue stiffness is a powerful biomechanical stimulus driving extracellular matrix (ECM) deposition and causes liver sinusoidal endothelial cell (LSEC) dedifferentiation. Mechanical forces transmitted to the nucleus influence chromatin, shifting euchromatin to heterochromatin to prevent DNA damage. MeCP2, an epigenetic regulator, modulates chromatin and nuclear structure, influencing gene expression. While MeCP2 knockout reduces liver fibrosis, its role in high stiffness-induced LSECs dysfunction remains unclear. This study aimed at investigating this aspect.
Method: MeCP2 expression was measured in healthy and cirrhotic human liver tissue slides via immunofluorescence. Liver cirrhosis was induced by thioacetamide (TAA) administered at 200 mg/kg twice a week for 12 weeks in male and female Sprague-Dawley rats. Freshly isolated LSECs were cultured on polyacrylamide (PAA) gels with stiffness of 0.5 kPa (healthy) and 30 kPa (cirrhosis) with and without cytoskeleton disruptors. Transcriptomic analysis and nuclear-proteomic analyses were employed to provide insights on the LSECs phenotype. Enrichr tool was used to identify genes co-expressed with MeCP2 and predict related pathways.
Results: Immunofluorescence analysis of human liver tissue revealed significant MeCP2 upregulation in patients with cirrhosis, as also observed in cirrhotic rat livers by nuclear deformation and reduced circularity. Gene set expansion via Enrichr linked MeCP2 to bZIP domain transcription factors, including CREB-binding protein (CBP), suggesting that stiffness-induced MeCP2 upregulation impacts transcription factors. MeCP2 protein levels increased under high stiffness. Its distribution near lamina-associated domains confirmed a mechanosensory role. Intracellular tension regulated MeCP2 in vitro of healthy and cirrhotic LSECs. Cytoskeletal inhibition reversed its upregulation in cirrhotic LSECs under high stiffness. Transcriptomic analysis on healthy LSECs cultured at 0.5 and 30 kPa, revealed 586 dysregulated genes with a repressive epigenetic profile, showing negative enrichment for euchromatin and transcription. Pathway analysis indicated dysregulation of bZIP transcription factors like CBP and AP-1 components (e.g., JUN). Proteomic analysis of LSEC nuclei identified 491 dysregulated proteins in response to

high stiffness, linked to cell cycle arrest and transcriptional repression.
Conclusion: MeCP2 is upregulated in cirrhotic LSECs in response to high stiffness in CLD. Moreover, MeCP2 provided for mechanical support as well as repressed transcription factors related to endothelial dysfunction. These findings highlight MeCP2 as a key transcription factor regulator in CLD.

TOP-202-YI
Matrix remodeling and versican upregulation in mesenteric lymph nodes modulate bacterial phagocytosis and migration of activated CD4+ T cells, fueling systemic bacterial infections in cirrhosis
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Background and aims: Mesenteric lymph nodes (MLN) act as a critical barrier against bacterial dissemination. In cirrhosis, enhanced gut bacterial translocation (BT) through MLN promotes systemic inflammation. Here, we investigated mechanisms underlying the failure of MLN to effectively contain bacteria in cirrhosis through a series of proteomic, in vitro, in vivo, and human studies.
Method: Cirrhosis was induced in rats using 12 weeks of CCl_4 treatment. Endogenous bacterial load and exogenous BT using GFP bacteria were assessed in MLN, lymph, blood, and other organs. MLN proteome profile and immune response to infection were analyzed. The role of one of the extracellular matrix proteins (ECM), versican (Vcan), was deciphered using $CD45^-$ $CD31^-$ $Pdpn^+$ fibroblastic reticular cell (FRC). Effects of FRC on bacterial phagocytosis, T cell migration, and function were studied *in vitro*. Effect of in vivo siRNA-mediated Vcan inhibition in CCl_4 models was delineated. Plasma Vcan levels and T cells were quantified in cirrhotic patients with and without bacterial sepsis.
Results: High endogenous bacterial load was present in cirrhotic rats' MLN, efferent lymph, portal blood, and all organs vs none in control. In control, GFP bacteria were retained in MLN; in cirrhotic rats, bacteria were translocated from MLN (3-fold high vs control) to lungs, liver, spleen, lymph, and blood. In cirrhotic MLN, CD134+ CD4+ activated Th cells and antigen-presenting CD80+ DC were significantly higher than control. Conversely, in systemic circulation, activated Th cells and DC were reduced in cirrhosis vs control. Proteome analysis of MLN from healthy and cirrhotic rats revealed 73 differentially expressed proteins (DEP), of which many ECM proteins were upregulated in cirrhotic MLN. From the top 10 upregulated DEP, we selected the ECM protein, Vcan, which was found to be highly expressed in FRC of cirrhotic MLN compared to control FRC. *In vitro*, cirrhotic FRC had reduced bacterial phagocytosis activity than control FRC and Vcan-siRNA treated cirrhotic FRC. Coculture of T cells with cirrhotic FRC resulted in increased T cell clumping and attachment, reduced T cell migration, and Th cell activation compared to when cultured with control FRC. *In vivo* inhibition by Vcan siRNA in CCl_4 rats led to increased Th cell migration in systemic blood with reduced BT compared to that in control siRNA treated CCl_4. Plasma Vcan levels were higher (by 35%) in cirrhotic patients with bacterial sepsis than in non-septic cirrhotics. Patients with high Vcan levels had reduced activated Th cells than those with low Vcan levels.
Conclusion: In cirrhosis, ECM remodeling and elevated Vcan expression in MLN cause impaired bacterial clearance, reduced activation, and migration of Th cells from MLN to systemic circulation, fostering systemic bacterial dissemination. Targeting Vcan in MLN presents a potential therapeutic target to treat systemic bacterial infections. Also, plasma Vcan may serve as a biomarker for MLN dysfunction and bacterial sepsis in cirrhosis.

TOP-203
Recombinant insulin-like growth factor-1: a novel therapy for patients with cirrhosis and ACLF
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Background and aims: Acute-on-chronic liver failure (ACLF) is associated with high short-term mortality and its treatment is an unmet need. Hepatocyte senescence and lack of regeneration are important mechanisms underlying poor recovery. Insulin-like growth factor system (IGFs), IGF-1, its receptor (IGF-1R) and binding proteins (IGFBPs), are involved in the regulation of hepatocyte proliferation. This study was conducted to explore whether IGF-1 could reduce liver injury whilst enhancing liver regeneration.
Method: *Patients:* Serum samples from patients with hepatitis, stable cirrhosis, acute decompensation cirrhosis (AD), pre-ACLF or ACLF from European DASIMAR cohort (n = 103) and Chinese cohort (n = 304) were used to explore the association between IGFs and liver diseases. *Animal models*: Hepatic IGFs was measured in cirrhosis and ACLF animals treated with TAK-242 (Toll-like receptor-4 antagonist); Nec-1 (Receptor interacting serine/threonine kinase-1 inhibitor); combination of granulocyte colony stimulating factor and TAK-242 (G-TAK). Each of the interventions protected from liver injury and ACLF. *Recombinant IGF-1 (rhIGF-I) therapy*: rhIGF-1 (1 mg/kg/day, i.p.) was administered for 2-weeks prior to sacrifice. The clinical effect of rhIGF-I administration in models of cirrhosis (4 wk, bile duct ligation, BDL) and ACLF (BDL + lipopolysaccharide) were observed.
Results: *Patients*: Serum level of IGF-1 and IGFBP-3 were significantly lower in patients with AD, pre-ACLF and ACLF, than in the healthy subjects in both the European and Chinese cohorts while IGFBP-1 was increased significantly ($p < 0.001$, $p = 0.004$, $p < 0.001$, for both cohorts). *Animal models*: mRNA level of IGF-1 in liver was decreased in both BDL (3.4-fold) and CCl4 cirrhosis models (2.4-fold) compared with Sham, while IGF-IR and IGFBP1 were increased, which was confirmed with immunohistochemistry. The decrease of IGF-1 and IGFBP3 were reversed with TAK-242, Nec-1 or G-TAK. Conversely, IGFBP1 decreased significantly after TAK-242 (11-fold), Nec-1 (8.7-fold) and G-TAK (13.5-fold). *rhIGF-1 therapy*: Administration of rhIGF-1 resulted in a significant reduction in sarcopenia in cirrhosis and ACLF animals, significant reduction in bilirubin, ammonia and creatinine in ACLF animals and reduced hepatic fibrosis. Liver gene profiling showed that rhIGF-1 modulated senescence pathways, inhibited p53/pRb signalling and reduced IFN signalling in the liver of rhIGF-1 treated mice.
Conclusion: IGFs were reduced in cirrhosis and partially corrected with interventions targeting inflammation. Treatment with rhIGF-1 improved organ function and sarcopenia in cirrhosis and ACLF animals and should be further as a novel therapeutic.

THURSDAY 08 MAY

THU-131-YI
Expression signatures of IL-18 and IL-18BP characterize stages of cirrhotic decompensation
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Background and aims: Cirrhosis-associated immune dysfunction (CAID) is characterized by systemic hyperinflammation and impaired immune responses in patients with advanced liver disease that favors infections and organ dysfunction to precipitate acute-on-chronic liver failure (ACLF). Molecular CAID networks remain poorly defined but may involve interleukin (IL)-18 and its antagonist IL-18BP as targetable agents. IL-18 is a potent inflammatory cytokine involved in liver inflammation, fibrosis, and cell death. However, the contribution of intrahepatic and systemic IL-18/IL-18BP balance to CAID is unknown. The study aimed to delineate IL-18 and IL-18BP expression patterns in decompensated cirrhosis (DC) and ACLF and evaluate their associations with established inflammatory markers and disease severity.
Method: Hepatic mRNA expression was quantified via RNAseq from 36 patients (compensated cirrhosis [CC] n = 13, DC n = 13, ACLF n = 10). Plasma IL-18, IL-18BP, sCD14, LPS-binding protein (LBP), and intestinal fatty acid binding protein (iFABP) levels were measured via ELISA in a prospective cohort of 111 cirrhosis patients (CC n = 12, DC n = 24, ACLF n = 75) and correlated with CRP, IL-6, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), organ dysfunction, and clinical outcomes.
Results: Expression levels of IL-18 and IL-18BP were progressively upregulated in DC and ACLF livers. Circulating IL-18 levels increased with progressing hepatic decompensation, independent of cirrhosis etiology, with a particularly high IL-18/IL-18BP ratio in ACLF (median ratio DC vs. ACLF 0.4 vs 0.8, p = 0.009). IL-18 was more robustly correlated with ACLF grade, MELD, MELD-Na, and Child-Pugh scores compared to CRP, IL-6, WBC, and NLR. Notably, IL-18, IL-6, WBC, and NLR were significantly lower in ACLF survivors compared to non-survivors and patients requiring liver transplantation, whereas CRP and IL-18BP were not. The correlation between IL-18 and IL-18BP with IL-6 was only moderate (<0.5), and remarkably low with markers of intestinal barrier dysfunction.
Conclusion: This study demonstrates that intrahepatic and systemic IL-18 induction characterizes hepatic decompensation and is especially pronounced in ACLF. The expression pattern of IL-18 is distinct from IL-6, WBC, CRP, and NLR. In ACLF, the disproportionate IL-18/IL-18BP ratio, driven by a relative IL-18BP deficiency, may contribute to organ dysfunction and adverse outcomes. These findings highlight the need for further research to elucidate the specific contributions of IL-18 to CAID.

THU-132
Hepatocyte derived extracellular vesicles promote endothelial dedifferentiation in chronic liver disease through the miR-153-3p – pyroptosis axis

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Background and aims: Liver cells paracrinally affect neighbouring cells through the release of extracellular vesicles (EVs). The aim of this study was to investigate the role of microRNAs (miRNAs) enclosed in hepatocyte-derived EVs (hepEVs) in sinusoidal endothelial dedifferentiation in chronic liver disease (CLD).
Method: Healthy (CT) or cirrhotic (CH) hepEVs were obtained from human and rat livers. Healthy rats received fluorescently labelled hepEVs-CT or hepEVs-CH (200 µg/day, 3 days, i.v.) or vehicle (n = 10/group) to evaluate their biodistribution and their effects on the phenotype of liver sinusoidal endothelial cells (LSECs) using RNAseq, IF, and WB. The profile of deregulated miRNAs in human and rat hepEVs-CH was analysed, and common miRNAs were exogenously overexpressed in LSEC-CT for transcriptomic and pathway analysis. The most deregulated pathway was studied in LSEC-CH, in human and rat cirrhotic livers, and in LSEC-CT treated with hepEVs overexpressing a specific miRNA. Cirrhotic rats were treated with the caspase-1 (casp1) inhibitor VX-765 (15 mg/kg, 10 doses, 2 weeks) or vehicle (n = 11/group) to evaluate hepatic hemodynamic, liver function, and endothelial phenotype.
Results: LSEC-CT *in vitro* treated with hepEVs-CH exhibited increased expression of pro-inflammatory, fibrogenic, angiogenesis, and cell death-related genes. *In vivo* administration of hepEVs-CH mainly accumulated in the hepatic endothelium, resulting in marked dysregulation of genes associated with fibrogenic and inflammatory pathways, together with increased vWF expression and alterations in nitric oxide synthase, suggesting a direct effect on endothelial dysfunction. Characterization of hepEVs-CH from patients revealed significant dysregulation of 37 miRNAs, with upregulation of miR-200a-3p and miR-153-3p validated in rat hepEVs-CH. Transfection of LSEC-CT with miR-153-3p dysregulated 771 genes implicated in inflammation and cell death pathways, particularly pyroptosis, with 51% homology to the transcriptome of LSEC-CH. Additional analyses in liver tissue showed increased expression of active casp1 and GSDMD-N, indicating activation of the pyroptosis pathway during CLD progression. Furthermore, activation of pyroptosis was observed in LSEC-CT upon treatment with miR-153-3p-enriched hepEVs. Finally, cirrhotic rats treated with VX-765 exhibited reduced hepatic pyroptosis (−60% active casp1), leading to significant amelioration in portal hypertension (−16.5%), fibrosis (−11.4%), and endothelial phenotype (−42% vWF). All results p < 0.05.
Conclusion: miRNAs contained in hepEVs actively contribute to hepatic endothelial dedifferentiation in CLD through the activation of the miR-153-3p-pyroptosis pathway, suggesting caspase 1 inhibition as a novel therapeutic strategy for endothelial dysfunction in CLD.

THU-133-YI
Risk of hypoglycemia in people with cirrhosis without diabetes

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Background and aims: People with cirrhosis have disrupted glycemic metabolism which puts them at risk of dangerous hyper- and hypoglycemia. People with cirrhosis are encouraged to have high protein snacks before bedtime due to impaired endogenous glucose production while they sleep. While studies of hypoglycemia focus on people with cirrhosis with diabetes, little is known about the risks of hypoglycemia in people with cirrhosis who do not have diabetes. The low blood glucose index is a calculated score based on continuous glucose monitor measures that assesses risk for severe hypoglycemia.
Method: We enrolled people with cirrhosis without a diagnosis of diabetes presenting for liver transplant evaluation. Thirteen subjects (10 male, 3 female, mean age 50.3 years) were given a blinded Abbott Libre Pro continuous glucose monitor (CGM) for 14 days and a Fitbit Inspire 3 wristwatch. After an overnight fast blood was sampled for insulin, glucagon, and A1c. Using the Fitbit-designated wake and sleep events, we classified our CGM glucose measurements as occurring during wake or sleep.
Results: Seven out of thirteen subjects had greater than 4% of the time in hypoglycemic ranges of glucose less than 70 mg/dL (3.9 mmol/L), which is above the American Diabetes Association's goal for patients with diabetes. Eight out of nine subjects had CGM-estimated A1c greater than laboratory hemoglobin A1c (mean ±

standard deviation 5.7 ± 0.2 vs 5.1 ± 0.6, respectively). Fasting glucagon was strongly correlated with the overall CGM coefficient of variation (Pearson r = 0.815, p < 0.02), strongly correlated with the sleeping low blood glucose index (LBGI, an indicator of hypoglycemic risk) (r = 0.95, p < 0.02) and inversely correlated with the number of Wakes after Sleep Onset (WASO) (r = –0.72, p < 0.03). Fasting insulin was not correlated with the fasting glucagon (r = 0.34, p < 0.24), but was also strongly correlated with the sleeping LBGI (r = 0.977, p < 0.005), and negatively correlated with the WASO (r = –0.67, p < 0.05).
Conclusion: Even people with cirrhosis who do not have diabetes are at risk of dangerous hypoglycemia. We found that two straightforward and readily available blood tests, the fasting insulin and fasting glucagon, were strongly associated with hypoglycemia. These tests were also associated with disrupted sleep, as measured by wakes after sleep onset. This suggests that obtaining fasting insulin and glucagon could help risk stratify people with cirrhosis without diabetes into further evaluation of hypoglycemia and sleep. Further work will need to validate these findings in larger cohorts.

THU-134-YI
Bone morphogenic protein 9 (BMP9): a novel therapeutic agent for the prevention of circulatory and renal failure in animal models of acute-on-chronic liver failure (ACLF)

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Background and aims: Endothelial dysfunction in ACLF is associated with extrahepatic organ failure, reduced organ perfusion and lactatemia. Bone morphogenic protein 9 (BMP9) regulates endothelial cell (EC) function, is produced by the liver and is reduced in decompensated cirrhosis. We hypothesise that administration of BMP9, by virtue of its known positive effect on the endothelial function may prevent extrahepatic organ dysfunction, organ injury and improve survival in models of ACLF.
Method: *Animal Models*: Two animal models of ACLF: (1) Rat model induced by 4-week bile duct ligation (BDL) ± 0.025 mg/kg ip Lipopolysaccharide (LPS) (2) Mouse model induced by 12-week oral gavage of 0.5 mL/kg carbon tetrachloride (CCL4) ± 2 mg/kg LPS (ACLF). Both models received BMP9 ip or placebo (±90 µg/kg/day) daily for two weeks prior to LPS. Survival, mean arterial pressure (MAP), biochemistry, liver histology and kidney qPCR and RT^2 PCR profiler for EC dysfunction related genes were evaluated. *Experiments in endothelial cells (EC)*: human ECs were exposed to plasma from ACLF patients (n = 7), decompensated patients (n = 4), or healthy control (n = 5), supplemented with BMP9 (0, 0.37, 3.7 ng/ml). EC morphological responses to exposure were quantified by image-based high-content morphological profiling. Shifts in EC morphology for BMP9 titration and disease status were scored and compared by linear discriminant analysis model.
Results: *Animal models*: BMP9 administration significantly increased survival of ACLF rats [75% vs 22%, p = 0.03], which was associated with significantly higher MAP in ACLF animals [82.1 to 108.5 mmHg, p = 0.01], reduction of renal injury [plasma creatinine: 82.3 to 65.4 µmol/L, p = 0.056] and significantly improved tissue perfusion [plasma lactate: 10.4 to 6.6 mmol/L, p = 0.019]. The effects seen in BDL animals were validated in the CCL4 mouse model. qPCR analysis of kidney tissue showed BMP9 treatment reduced gene expression of markers of endothelial dysfunction in ACLF with a reduction in KDR [p = 0.079], and significant reduction in eNOS [p < 0.05] and AQP1 [p < 0.05]. RT^2 PCR profiler showed a significant reduction in genes including CAV1, IL-1β, IL-6, PLAT and PAI-1 following BMP9 treatment. *EC experiments:* Plasma from decompensated cirrhosis and ACLF patients induced a highly activated EC morphology compared to healthy plasma. No effect of BMP9 was observed in healthy plasma. EC activation and disturbances of the EC border morphology induced by decompensated and ACLF plasma was prevented in a dose dependent manner by BMP9 (p < 0.001), indicating BMP9 modulates the inflammatory response in ECs.
Conclusion: This data suggests that BMP9 may be a novel treatment to prevent the progression of circulatory and renal failure in ACLF by modulating endothelial function and organ perfusion, which results in reduced mortality. The data provide the rationale to initiate clinical studies.

THU-135
Associations between cardiorespiratory fitness and physical frailty in patients with cirrhosis

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Background and aims: Cirrhosis leads to severe impairment in cardiorespiratory fitness and frailty, both of which are strong predictors of poor prognosis. Our objectives were twofold: first, to validate the Liver Frailty Index (LFI) as a practical tool for assessing the physical fitness of patients with cirrhosis by studying its correlation with cardiorespiratory fitness (CRF); and second, to evaluate the impact of liver function on maximal oxygen consumption (VO_2).
Method: Each participant with confirmed compensated cirrhosis (by hepatic elastography) or decompensated cirrhosis underwent the Liver Frailty Index (LFI) assessment. Patients also performed an incremental test on a cycle ergometer to determine maximal oxygen consumption (VO_{2Peak}).
Results: 10 females and 28 males, aged of 60.6 ± 7.9 years (females are older (p = 0.042)) completed the study. The mean VO_{2Peak} value was 16.1 ± 6.1 $ml.min^{-1}.kg^{-1}$ corresponding to 68.2 ± 28.5% of predicted VO_{2Peak}. According to the LFI, 28.9% are frail, 57.9% are pre-frail and 13.2% are robust with a mean LFI of 3.99. Concerning the Child-Pugh (CP) groups, 52.6% are in CPA, 21.1% are in CPB and 26.3% in CPC. The LFI was negatively correlated with CRF variables: absolute VO_{2Peak} ($l.min^{-1}$) (r = –0.538, p < 0.001), relative VO_{2Peak} ($ml.min^{-1}.kg^{-1}$) (r = –0.537, p < 0.001), and percentage of predicted VO_{2Peak} (r = –0.682, p < 0.001). The LFI was positively correlated with liver failure, as reflected by the Child-Pugh (CP) score (r = 0.476, p = 0.016) and MELD score (r = 0.384, p = 0.011). CPA and CPB patients were less frail than CPC patients (p < 0.001 and p = 0.007, respectively), but no significant difference was found between CPA and CPB (p = 0.792). Similar differences were observed for absoluteVO_{2Peak} ($l.min^{-1}$): CPA and CPB patients had higher values compared to CPC patients (p < 0.001 and p = 0.006, respectively), with no difference between CPA and CPB (p = 1.000). For relative VO_{2Peak} ($ml.min^{-1}.kg^{-1}$), values were

higher for CPA and CPB patients versus CPC ($p < 0.001$ and $p = 0.029$, respectively), with no significant difference between CPA and CPB ($p = 0.959$). A difference was also noted for the percentage of predicted VO_{2Peak} achieved by CPA and CPB, CPB and CPC, and CPA and CPC patients ($p = 0.031$, $p = 0.008$, and $p < 0.001$, respectively).
Conclusion: The LFI is associated with both cardiorespiratory fitness and liver failure severity. As a simple tool, it could be included in pre-transplant evaluations, provided its independent prognostic value is confirmed in diverse populations, including European and Asian cohorts. Our findings also demonstrate that cardiorespiratory fitness is reduced in CPC patients but remains relatively preserved in CPA and CPB patients.

THU-136
Clinical relevance of the evaluation of cardiorespiratory fitness in patients with cirrhosis: a systematic review with meta-analysis
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Background and aims: Cirrhosis is a major public health issue, with a high prevalence of associated morbidity and mortality. It also leads to severe impairment in cardiorespiratory fitness (CRF). Some studies have suggested that reduced CRF is linked to an increased risk of early mortality. The primary objective of this systematic review is to determine whether cardiopulmonary exercise testing (CPET) can predict the mortality and morbidity of patients with cirrhosis.
Method: The literature was reviewed across electronic databases (PubMed, Scopus, Embase, Google Scholar) from their inception to April 2024. Two independent researchers applied inclusion criteria to assess the eligibility of articles. Studies were eligible if they involved maximal exercise testing and reported oxygen consumption at anaerobic threshold (AT) and at maximum (VO_{2Peak}).
Results: This review includes sixty-one articles' data from 2,991 patients with cirrhosis. The mean values were: 11.80 $ml.min^{-1}.kg^{-1}$ [95% CI 11.16; 12.45] for AT, 19.51 $ml.min^{-1}.kg^{-1}$ [95% CI 18.75; 20.26] for VO_{2Peak}, and 61.1% [95% CI 60.7; 67.6] of predicted VO_{2Peak}. Concerning analysis between Child-Pugh (CP) groups, we found for AT, CPA and CP B have higher values than CP C with 12.75 $ml.min^{-1}.kg^{-1}$ (95%CI, 11.65; 13.85), 11.43 $ml.min^{-1}.kg^{-1}$ [95%CI, 10.22; 12.65] and 9.15 [95%CI 7.55; 10.75], respectively. Relating to VO_{2Peak} values, CP A have B superior results than CP C with 20.68 $ml.min^{-1}.kg^{-1}$ [95% CI, 17.92; 23.43], 17.95 [95%CI and 14.95 $ml.min^{-1}.kg^{-1}$ [95%CI 13.51; 16.38], respectively. CRF was identified as a predictor of mortality in eight of nine studies (n = 1,193 patients). Additionally, eight studies found CRF to be predictive of morbidity, including two studies with 160 patients for sepsis, four studies with 538 patients for hospitalization duration, and four studies with 551 patients for intensive care unit (ICU) stay duration. One study (n = 98) reported no significant effect on ICU stay duration.
Conclusion: Evaluating CRF should be recommended to improve the ability to predict prognosis by providing a better understanding of patients' physical function. This meta-analysis of CRF levels across studies establishes reference values that can serve as practical and efficient tools for clinical decision-making.

THU-137-YI
The metabolome of patients with cirrhosis hospitalized with overt hepatic encephalopathy and association with clinical course
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Background and aims: Although ammonia is a known toxin associated with overt hepatic encephalopathy (OHE), the metabolic basis remains unknown. OHE is part of the acute-on-chronic liver failure (ACLF) definition and often occurs with other organ failures making it difficult to understand whether OHE has a particular metabolic basis. The aims of this study were to define the metabolome of OHE patients and whether they are distinct from ACLF and other organ failures. Other aims were to identify metabolites associated with clinical course.
Method: This study was performed on a subset of 252-unselected patients with cirrhosis hospitalized with acute decompensation [PREDICT study] in whom the metabolomic profile (using high-resolution mass spectroscopy) were available. Differences in mean metabolite expression levels were quantified by using pairwise t-tests. Univariable Cox regression models were fitted on each metabolite to identify those that were associated with survival. All p-values were controlled for false discovery rate.
Results: 15-metabolites were significantly different between OHE(−) [n = 211] and OHE(+) [n = 41] from which 13-overlapped with ACLF. Two metabolites in OHE(+) patients were independent of ACLF, namely alanine/sarcosine and lactic acid, which represent altered amino acid metabolism and gut permeability. There were no significant different in metabolites between OHE(+) ACLF(−) and single liver failure. There were 3-significant metabolites between OHE(+) ACLF(−) [n = 14] and single kidney failure, namely N-acetyl-L-alanine, reduced hexoses and 2,2′-thiodiacetic acid. Among OHE(+) ACLF(+) patients, [n = 27], 64-metabolites were significantly associated with 90-day mortality. Of these metabolites, those with the highest coefficients included cis/trans aconitic acid, lactic acid, carnitine and N-acetyl-L-alanine. Among OHE(-) ACLF(+) patients [n = 81], 3-[(R)-butyryl-carnitine, carnitine, hexanoylcarnitine)] were significantly associated with 90-day mortality. No metabolites were significantly associated with 90-day mortality among OHE(+) ACLF(−) and OHE(−) ACLF(−) [n = 128] patients. No metabolites were associated with progression or regression of OHE.
Conclusion: The data show for the first time that OHE patients exhibit a distinct metabolic profile that provides novel pathophysiological insights. Metabolites significantly associated with mortality were only found in the ACLF(+) groups suggesting that mortality attributed to OHE are due to non-metabolome factors.
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THU-138

Albumin infusion improves albumin binding capacity in patients with cirrhosis and MHE on gut-specific therapy

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Background and aims: Minimal hepatic encephalopathy (MHE), or cognitive impairment that affects patient's quality of life (QoL), can persist despite adequate HE gut-directed therapy such as lactulose/rifaximin. Albumin has been investigated in HE for its potential therapeutic benefits related to non-oncotic functions, particularly on its capacity to bind, transport and modulate biologically active molecules such as fatty acids, proinflammatory mediators and reactive oxygen species. In the HEAL study (NCT03585257), albumin infusions in patients with cirrhosis and MHE were associated with improved cognitive function and psychosocial QoL. The aim of the present study was to characterize the albumin binding capacity of patients from the HEAL study and its correlation with cognitive parameters.
Method: Serum samples from 47 patients included in the HEAL study were analyzed. This was a double-blind, placebo-controlled randomized clinical trial in outpatients with cirrhosis and MHE on HE therapy, who received either weekly intravenous infusions of albumin 1.5 g/kg or saline over 5 weeks. The impairment in the drug albumin binding capacity to Sudlow Binding Site II (ABiC) was determined using a specific fluorescent marker. Results were compared with age-matched healthy controls (HC) (n = 13). Cognitive response was evaluated with psychometric hepatic encephalopathy score (PHES). Wilcoxon test was used to assess the differences in ABiC of patients versus HC at baseline. Lasting effects were analyzed with a mixed model for repeated measures. Relationship between cognitive impairment and ABiC was assessed through Spearman correlations. All analyses were performed with R (v4.3.0).
Results: At baseline, albumin from patients with cirrhosis and MHE tended to present lower binding capacity compared to HC (80.1% [72.4–92.6] vs 93.2% [82.2–96.3]; median [IQR]; p = 0.086), which led to a statistically significant decrease in effective albumin for transport (30.2 mg/mL [25.9–32.8] vs 35.1 mg/mL [33.1–36.6]; p < 0.001). Albumin infusions increased progressively the content of albumin binding capacity, reaching 36.1 mg/mL at the end of the study (p = 0.022, compared to placebo). Moreover, the increased functionally active albumin for transport correlated with a higher PHES at the end of treatment (binding capacity: p = 0.04, r = 0.33; total binding: p = 0.06, r = 0.29).
Conclusion: Albumin binding capacity was impaired in patients with cirrhosis and MHE on lactulose and rifaximin, which was restored to normal levels in parallel with improvement in cognitive function after albumin administration. Our data suggested that albumin treatment could exert its beneficial effects through the restoration of albumin transport functionality, over and above traditional HE therapies.

THU-139

Glycated albumin is increased in patients with cirrhosis and hepatic encephalopathy already on gut-directed therapy and links with cognitive and quality of life impairment

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Background and aims: Cognitive impairment in cirrhosis can persist despite adequate treatment of HE with gut-directed therapies such as lactulose and rifaximin. This impairment, or minimal hepatic encephalopathy (MHE), negatively impacts outcomes. Albumin has shown benefit in HE patients with improved cognitive function and psychosocial quality of life (QoL) (HEAL study, NCT03585257). The aim of the present study was to describe albumin post-translational modifications (PTMs) of patients with cirrhosis and MHE compared to healthy controls (HC) and its correlation with clinical parameters, since structural modifications of albumin could alter albumin's non-oncotic functions.
Method: Serum samples from 24 cirrhosis patients in the HEAL study without diabetes and 10 age-matched HC were evaluated. Albumin PTMs were assessed on the intact mass protein (top-down) by using ultra HPLC coupled to electrospray ionization mass spectrometer (LC_ESI_qTOF-MS) and expressed as percentage of relative intensity. Principal Component Analysis (PCA), limma Bioconductor package and Wilcoxon test were used to assess the differences in PTMs of patients versus HC. Relationship between cognitive impairment, QoL and PTMs was assessed through Spearman correlations. All analyses were performed with R (v4.3.0).
Results: PCA showed good separation between samples from HC and non-diabetic patients with cirrhosis and MHE. Fourteen out of 25 PTMs presented statistically significant differences between both groups. In comparison to HC, albumin from patients showed less native albumin (50.1% [44.6–55.9] vs 56.1% [54.5–57.3]; median [IQR]; p = 0.05) and less truncated forms (5 PTMs) (6.3% [5.4–7.0] vs 7.0% [6.5–8.7]; p = 0.025), as well as more overall glycated forms (13 PTMs) (14.8% [12.4–16.1] vs 10.5% [9.5–10.9]; p < 0.001) being the forms HSA+Glyc and HSA+Cys+Glyc the most relevant. Decreased native albumin correlated with worse cognitive testing (psychometric hepatic encephalopathy score) (p = 0.05, r = 0.41), and the increase of HSA+Glyc, HSA+2Glyc and HSA+3Glyc forms correlated with poor QoL (p < 0.01, r = 0.58; p = 0.01, r = 0.56; p = 0.02, r = 0.46, respectively).
Conclusion: Albumin from patients with cirrhosis and MHE even without diabetes shows higher glycation versus HC. These structural alterations contributed to decrease native albumin levels that could impair non-oncotic albumin functions in these patients.

THU-140

The in vitro immune response of mononuclear cells to Escherichia coli is not dependent on antibiotic multidrug resistance

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Background and aims: Multidrug-resistant organisms (MDRO) pose a serious global health threat. Infections caused by MDRO are increasing and are associated with poor outcomes, especially in patients with cirrhosis, although the underlying mechanisms are not fully understood and may involve variations in the elicited immune response. The aim was to evaluate whether the immune response to multidrug-resistant *Escherichia coli* isolates from cirrhotic patients differs from the response to antibiotic-susceptible *E. coli* strains.
Method: Surface and nuclear protein extracts were obtained from multidrug-resistant *E. coli* (n = 6) and antibiotic-susceptible *E. coli* (n = 6) strains isolated from bacteremia and spontaneous bacterial peritonitis in patients with cirrhosis. These extracts were used to

stimulate *in vitro* peripheral blood mononuclear cells from healthy donors (n = 8). After 48 hours of culture, we quantified several mediators of immune response (IFN-gamma, IL-1beta, IL-10, IL-12p70, MCP-1, IL-8, IL-6, MIP-1alpha, and MIP-1beta) in the supernatant using Luminex or ELISA. The results were normalized using a ratio to mediator production by a reference *E. coli* strain (ATCC® 25922) and analyzed with the Mann-Whitney test and multivariable linear regression models.

Results: The mediators with the highest production were IL-1beta in surface extracts (ratio of 2.15 ± 2.87 for multidrug-resistant vs. 2.47 ± 2.56 for sensitive strains, p = 0.54) and IL-10 and MCP-1 in nuclear extracts (ratios of 1.24 ± 2.38 vs. 2.46 ± 4.07, p = 0.19, and 1.71 ± 1.84 vs. 1.29 ± 1.56, p = 0.33, respectively). No statistically significant differences were observed in the production of any mediators between multidrug-resistant and susceptible strains. However, differences in mediators production were noted among the various healthy donors, except for IFN-gamma and IL-6 in surface extract and MCP-1 in nuclear extract, in which production was similar across donors.

Conclusion: Multidrug-resistant *E. coli* strains produced an *in vitro* immune mediator profile similar to that of antibiotic-susceptible strains. However, differences in mediator production were significantly associated with donor variability. The poor prognosis linked to infections caused by multidrug-resistant *E. coli* does not appear to be related to a different immune response compared to susceptible strains.

THU-142-YI

Early detection of hepatic encephalopathy using wearable sensors: preliminary data

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Background and aims: Hepatic encephalopathy (HE) is a common complication of liver cirrhosis, with clinical manifestations ranging from mild neuropsychiatric symptoms to coma. Covert HE (cHE) diagnosis is difficult because specific symptoms and validated tests are lacking. This study evaluates its presence by using wearable sensors.

Method: Thirty-four cirrhotic patients and five control cases (without liver disease) were enrolled at the Medicine and Hepatology Unit of the University Hospital of Messina between August 2024 and October 2024. Study cohort was evaluated by positioning 6 sensors on the dorsum of both hands and the flexors/extensor muscles of forearms: 2 configured as Inertial Measurement Units (IMUs) (continuously measuring linear acceleration and angular velocity on 3 axes) and 4 configured as IMUs with additional electromyography channels. Data were recorded during arm extension with palms facing up/down (repeated twice) and arm extension with palms extended for at least 10 seconds. The frequency domain analyzed all the documented signals, extracting features from each signal power spectrum. ANOVA, Kruskal-Wallis, and Eta Squared tests were applied for feature sampling, and the Birch method was used for unsupervised clustering.

Results: Twenty-two subjects were males (mean age 63 ± 14 years). Available clinical data identified 22 of 34 (64.7%) cirrhotic patients without overt HE (oHE), with a possible cHE, and 12 (35.3%) with an overt HE (oHE). Diseased subjects exhibited frequency peaks between 3 and 8 Hz, with significantly higher energy content than the control group. Five features were found to be relevant in the selection process: Left-hand Mean Frequency (LHMF) Gyroscope X, LHMF Gyroscope Y, LH Difference between Power inside boundaries and outside Accelerometer Y, LH Amplitude spectrum outside ratio Gyroscope Z, and Right-Hand MF (RHMF) Gyroscope Y. A comparison of features showed significant differences between the 3 groups (controls vs. non-HE vs. oHE): LHMF Gyroscope X (5.5 ± 0.5 vs. 5.9 ± 1.3 vs. 7.2 ± 1.6 Hz, p = 0.04), LHMF Gyroscope Y (11.0 ± 2.5 vs. 7.9 ± 2.5 vs. 9.9 ± 2.3 Hz, p = 0.04), LH Difference between Power inside boundaries and outside (−1.1 ± 1.3 vs. −4.5 ± 11.2 vs. −0.2 ± 1.9 m/s^2, p = 0.01), LH Amplitude spectrum outside ratio (356.6 ± 272.6 vs. 266.7 ± 140.8 vs. 374.2 ± 143.2, p = 0.01), and RHMF (11.1 ± 1.4 vs. 7.7 ± 2.7 vs. 7.9 ± 2.9 Hz, p = 0.04). The unsupervised clustering identified 3 groups of patients: 4 in cluster 1, 15 in cluster 2, and 11 in cluster 3. Nine patients did not cluster with others. The unsupervised analysis clustered 68.2% of cases as potential cHE, 13.6% as healthy, and 18.2% as oHE. Clustering identified original diagnosis in 77% of patients, but 4 cases clinically evaluated as non-HE showed typical features for oHE.

Conclusion: Wearable IMUs present a promising, noninvasive, objective method for early diagnosis of cHE and oHE. However, increasing the sample size would be crucial for broader use.

THU-143-YI

TLR7-mediated immunomodulation in experimental liver fibrosis

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Background and aims: Cirrhosis, a global healthcare burden, is characterized by liver fibrosis, immune dysregulation, and impaired pathogen clearance that contribute to an increased infection risk and mortality. Here, we assessed the administration of a Toll Like Receptor (TLR) 7 agonist (R848) in toxin- and diet-induced mouse models of liver fibrosis with or without infectious challenge, as a novel immune-modulatory strategy to restore antimicrobial responses.

Method: Fibrosis was induced in C57BL/6J male and female mice by a) Choline-Deficient, L-Amino-Acid defined High-Fat-Diet (CDA-HFD) for 8 weeks compared to normal diet (ND), or b) intraperitoneal (i.p.) injections of CCl_4 (0.4 μl/g) twice-weekly for 6 weeks compared to control (oil). During the last week of treatments, mice received three i.p. injections of saline (PBS) or TLR7 agonist (R848; 1 mg/kg). Liver immune cells were assessed by flow cytometry; tissue fibrosis and hepatic damage were quantified in Picro Sirius Red (PSR) stained liver sections and serum, respectively. In separate experiments (6-week control vs CCl_4), *Escherichia coli (E. coli)* was intravenously administered. After 24 hours, mice were culled; liver and spleen were harvested, and tissue lysates were plated on agar to quantify bacterial load.

Results: Compared to PBS, R848-treated CDA-HFD and CCl_4-fibrotic mice displayed increased numbers of conventional dendritic cells (cDC1, cDC2), NK, $CD8^+$ and $CD4^+CD25^-FoxP3^+$ T_{reg} cells. Moreover, monocyte, neutrophil, Kupffer cell and liver-recruited monocyte-derived macrophage numbers did not differ between groups.

Interestingly, liver fibrosis (percentage of PSR^+ area) and tissue damage (serum ALT and AST) were not impacted by R848 treatment. Compared to control, CCl_4-fibrotic mice showed increased liver and spleen bacterial load (*E. coli* CFU per tissue gram); notably, R848 treatment of CCl_4-fibrotic mice led to significantly reduced tissue bacterial burden.

Conclusion: Our findings demonstrate that, in the mouse fibrotic liver, R848 treatment reshapes the hepatic immune compartment resulting into improved *E. coli* clearance following systemic infection. Future studies will elucidate the underlying mechanisms of TLR7-mediated immunomodulation in fibrosis, and potentially translate TLR-targeted therapies in a clinical setting.

THU-144

Epigenetic regulation of LSECtin in hepatic antigen presenting cells during experimental cirrhosis

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Background and aims: LSECtin/*Clec4 g* is a pattern recognition receptor and T cell ligand expressed in Kupffer Cells (KCs) and Liver Sinusoidal Endothelial Cells (LSECs). Its expression is reduced during advanced chronic liver disease (CLD). The main aim of this work is to characterize the epigenetic regulation of LSECtin.

Method: DNA methylation levels and histone post-translational modification (HPTMs) profile where studied by methylation array and ChIP-Seq experiments carried out on KCs and LSECs isolated by FACS from untreated and cirrhotic (12 weeks of CCl_4 gavage) mice. Immortalized KCs and LSECs were treated with epigenetic effector inhibitory drugs (OTS186935-Suv39h2i, UNC0642-G9a/Glpi, UNC1999-EZH2/1i, 5-Aza-2′-deoxycitidine-DNMTi), alone and in combination with IL-4, an LSECtin expression inductor. Drugs with relevant regulatory potential were intraperitoneally injected to untreated and CCl_4 mice.

Results: Statistically significant changes were observed in specific loci methylation levels in both KCs and LSECs, being macrophages especially susceptible to methylome modification by CCl_4 treatment. Significant changes were also observed in gene body and promoter region of *Clec4 g*, primarily in KCs. ChIP-Seq experiment allowed the study of HPTMs profile of chromatin associated to H3K3me3/H3K27me3. KCs and LSECs showed a specific peak profile at the genomic level; however, no significant differences were identified in proximal promoter region of *Clec4 g*. Immortalized cell lines treatment with epigenetic effectors inhibitory drugs caused a slight reduction in LSECtin expression, which was further retrieved by IL-4 +drug treatment. Additionally, LSECtin expression was increased by 5-Aza-2′-deoxycitidine, a passive DNA demethylating agent; causing a higher increment of expression by the combined treatment of Aza +IL-4. Cirrhotic mice treated with OTS186935 and UNC1999 showed an increment of LSECtin expression studied by WB, qPCR and flow cytometry, as well as an improvement in hepatic transferases and other liver damage markers. These animals also had a reduction in activation and proinflammatory profile of T CD4+/CD8+ cells, which in combination with a reduction of IL-17+ T cells population, mechanistically correlates with LSECtin expression recovery.

Conclusion: The increment of LSECtin expression by passive demethylation of DNA and methylation array results point out methylation of *Clec4 g* promoter is a key mechanism in expression regulation. Modulation of LSECtin expression both *in vitro* and *in vivo* by epigenetic effector inhibitory drugs strongly suggest that HPTMs profile alteration contributes to protein regulation during CLD, thus positioning periodical administration of epigenetic inhibitors as a candidate for LSECtin expression recovery in the pathological scenario.

THU-145-YI

Propranolol reverses splanchnic β-adrenergic induced small intestinal barrier disruption stabilizing gut-liver axis in experimental cirrhosis

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Background and aims: Propranolol (PROP) exerts beneficial effects in cirrhosis by reducing portal pressure and decreasing pathological bacterial translocation (PBT). The mechanisms underlying its effect on the intestinal barriers (IB) however, are largely unknown. This study investigates (1) the effect of splanchnic β-adrenergic hyperstimulation on the IB, and (2) whether PROP reverses the potential harmful effects of β-adrenergic hyperstimulation in experimental models with and without cirrhosis.

Method: *Models*: A) Wistar rats and C57BL/6 mice with cirrhosis induced by CCl_4 or bile duct ligation (BDL), treated with PROP or placebo for 2 weeks. B) β-adrenergic hyperstimulation model: C57BL/6 mice treated with peritoneal osmotic pumps delivering isoproterenol (ISO), ISO plus PROP or vehicle for 7 days. C) β-Catenin gain-of-function (GOF) mice: generated from β-catenin-lox(ex3)/lox(ex3) and Cdh5(PAC)-CreERT2 strains presenting with VE-cadherin-dependent stabilized gut-vascular barrier (GVB). *Methods:* i) Muco-epithelial barrier: ileal tight junctions (TJ: ZO-1, claudin 1 and 5) by immunofluorescence (IF) and RT-qPCR, and mucus thickness (PAS). ii) Vascular barrier: PV1, VE-cadherin expression (IF), fecal albumin (ELISA), in-vitro transwell-permeability for FITC-albumin in murine endothelial cells, in-vivo extravasation of FITC-albumin (by laser endomicroscopy) iii) hepatic 4KDa-FITC-dextran recovery after ileal loop injection (=translocation to liver).

Results: ISO increased endothelial FITC-albumin permeation and down-regulated VE-cadherin (0.20 vs 0.09, $p < 0.05$) and claudin-5 (0.07 vs 0.03, $p < 0.05$) in the duodenal vasculature. ISO induced pathological albumin extravasation in small intestinal microcirculation (15 vs 10 AUC, $p < 0.05$), being mitigated by PROP and not observed in GOF mice, indicating VE-cadherin as key driver of GVB-disruption induced by β-adrenergic hyperstimulation. In CCl_4-cirrhotic rats, PROP restored the ileal mucosal-epithelial barrier by

increasing mucus thickness and TJ expression (each, $p < 0.01$, respectively). PROP reduced PV1 expression in ileal vessels (PROP vs. placebo; 0.81 ± 0.11 vs 0.42 ± 0.09U, $p < 0.01$), dextran translocation to the liver (0.81 ± 1 vs 0.42 ± 4 part., $p < 0.05$), and fecal albumin loss (from 24,579 ± 1,040 to 1,187 ± 373 ng/mg feces, $p < 0.01$). Similar results were seen in BDL-cirrhotic rats, with PROP attenuating also duodenal albumin extravasation. PROP improved intestinal dysbiosis in CCl_4-induced cirrhosis but not in BDL, and reduced PBT in both models (CCl_4: 86 vs 34%, $p < 0.01$. BDL: 64 vs. 42%).
Conclusion: β-adrenergic hyperstimulation impacts on the IB by increasing endothelial and epithelial permeability through direct cellular mechanisms. PROP restores both the structure and function of the IB in cirrhosis, thereby limiting PBT. The beneficial effects of PROP in cirrhosis are largely associated with the stabilization of the gut-liver axis, an effect at least partially being independent of hemodynamic mechanisms.

THU-146
Global trends in antimicrobial resistance in chronic liver disease patients with bacteremia: a systematic review and meta-analysis of observational studies
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Background and aims: In cirrhotic patients, bacteremia can rapidly progress to sepsis and multi-organ failure, contributing to significant morbidity and mortality. This systematic review and meta-analysis assess global trends in antimicrobial resistance (AMR) among bacterial pathogens responsible for bacteremia in patients with cirrhosis.
Method: We conducted a systematic review and meta-analysis following PRISMA guidelines, registered on PROSPERO (CRD42024539347). Searches across PubMed, Embase, Web of Science, and Scopus were completed up to September 30, 2024. Pooled proportions (PPs) and 95% confidence intervals (CIs) were calculated using random-effects models. Heterogeneity was assessed with the I^2 statistic, and subgroup analyses were conducted by geographic region, bacterial species, and AMR type.
Results: A total of 26 studies comprising 5,488 bacteremia cases in patients with cirrhosis were included in the analysis. The pooled bacteremia infection proportion was 21.53% (95% CI: 13.07–31.37), with 76.56% (95% CI: 63.66–87.49) identified as nosocomial. *Escherichia coli* was the predominant pathogen (27.07%; 95% CI: 16.66–38.84), followed by *Staphylococcus aureus* (15.25%; 95% CI: 11.36–19.58). The overall pooled proportion of multidrug-resistant (MDR) bacteria was 30.77% (95% CI: 19.03–43.88), with higher rates in Asia (35.10%, 95% CI: 22.41–48.93) and Europe (35.05%, 95% CI: 25.80–44.87). Methicillin-resistant *Staphylococcus aureus* (MRSA) infections were observed at 11.46% (95% CI: 0.00–57.88) in Asia and 9.96% (95% CI: 2.97–19.79) in Europe. Extended-spectrum beta-lactamase (ESBL) *E. coli* had a pooled proportion of 13.81% (95% CI: 7.04–22.24), with rates in Asia reaching 20.91% (95% CI: 12.26–31.10). The global pooled proportion of carbapenem-resistant *Enterobacteriaceae* (CRE) was 4.86% (95% CI: 0.69–11.49).
Conclusion: Bacteremia represents a significant global burden among chronic liver disease patients, marked by geographic variability in resistance patterns. This necessitates targeted regional strategies and collaborative efforts to effectively combat the increasing incidence of infections in this vulnerable population.

THU-149-YI
Sex-specific estradiol signaling in liver cirrhosis and portal hypertension
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Background and aims: Recently, it has been shown that estradiol (E2) may have long-term anti-fibrotic and metabolic effects in liver disease mediated through the nuclear estradiol receptor alpha (ERalpha). Additionally, E2 was shown to cause rapid, non-genomic effects in human heart disease via the G-protein-coupled ER (GPER) receptor - cyclic guanosine monophosphate (cGMP) - nitric oxide (NO) pathway, but its role in liver cirrhosis remains unclear. Therefore, this study investigated the sex-specific effects of estradiol on GPER and cGMP-NO pathway in liver cirrhosis and portal hypertension.
Method: Liver cirrhosis was induced using bile duct ligation (BDL) in male, female and female ovariectomized rats. Animals received either (i) a single high dose of E2 one day before sacrifice, (ii) an acute dose of phosphodiesterase-5-inhibitor (PDE-5-I) for cGMP augmentation directly before sacrifice, or (iii) a combination of both. Male and female BDL rats without E2 and PDE-5-I served as controls. Subsequently, portal and systemic hemodynamics were assessed using colored microspheres and vascular contractility using *ex vivo* aortic ring contraction. Furthermore, expression of E2 receptors and NO signal pathway in aorta and liver tissue was analyzed using Western blot and qPCR.
Results: In male BDL rats, E2 did not affect portal and systemic hemodynamics, ERalpha and GPER expression, or response to PDE-5-I. In female BDL rats, ovariectomy led to an increased hepatic portal vascular resistance (HpVR), a decreased hepatic GPER expression, and a reduced hepatic NO pathway activity compared to non-ovariectomized female BDL rats. In addition, ovariectomized female BDL rats exhibited a decreased systemic vascular resistance, but higher contractility of aortic rings *in situ* compared to female BDL control rats. Additionally, GPER and ERalpha expression was increased in aorta of ovariectomized rats compared to female rats without ovariectomy. PDE-5-I significantly reduced portal pressure (PP) in male and female control BDL rats but had no hemodynamic effect on ovariectomized female BDL rats. The substitution of E2 in ovariectomized female BDL rats caused a significant decrease in HpVR and PP and restored susceptibility to PDE-5-I.
Conclusion: Estradiol deficiency after ovariectomy deteriorates portal hypertension in female cirrhotic rats, which can be reversed by estradiol substitution. These effects might be mediated by the cGMP-NO pathway. Thus, targeting the GPER – NO pathway could be a therapeutic approach in postmenopausal women with liver cirrhosis and portal hypertension.

THU-150
Comparative analysis of surrogate markers of intestinal permeability, bacterial translocation, and gut vascular barrier damage across different stages of cirrhosis
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Background and aims: Portal hypertension, impaired gut barrier function and pathological bacterial translocation are hallmarks of advanced liver disease driving complications of cirrhosis. As measuring gut barrier function is demanding, surrogate markers have been proposed but their intercorrelation and applicability across different stages of advanced liver disease, particularly in acute-on-chronic liver failure (ACLF) is largely unknown.

Method: Proposed markers of gut barrier dysfunction and bacterial translocation were quantified in sera from 160 patients with cirrhosis across different disease stages of compensated and decompensated cirrhosis as well as in hepatic and portal vein serum before and after the insertion of transjugular intrahepatic portosystemic stent (TIPS) using ELISA.
Results: Across all stages of liver disease, the gut vascular barrier marker plasmalemma vesicle protein-1 (PV-1) correlated with the bacterial translocation markers endogenous endotoxin-core IgA antibodies (EndoCAb) and LPS-binding protein (LBP) but not with intestinal damage markers intestinal fatty acid binding protein (I-FABP) and Zonulin-family peptides (ZFP). PV-1 and EndoCAb were higher in decompensated cirrhosis without further increase in ACLF. Among investigated markers, only I-FABP correlated with the portosystemic pressure gradient and TIPS insertion significantly reduced portal concentrations within 24 h hours. Higher PV-1 levels indicated poor transplant-free survival in univariate and multivariable analysis.
Conclusion: The investigated surrogate markers of bacterial gut barrier dysfunction and bacterial translocation appear of limited use in advanced stages cirrhosis and are differently confounded by the hepatic synthesis capacity, portal congestion, and acute phase responses. The prognostic implications of circulating PV-1 in decompensated cirrhosis levels demands further investigation.

THU-151-YI

Aberrant monocyte function promotes systemic inflammation in decompensated advanced chronic liver disease and can be therapeutically targeted

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Background and aims: Systemic inflammation has been proposed as a key driver of disease progression in advanced chronic liver disease (ACLD), with monocyte dysfunction suggested to play a pivotal role. However, the exact causes and mechanisms are not fully understood, limiting therapeutic opportunities. We aimed to study differences in monocyte phenotype, function and molecular mechanisms that drive the development of systemic inflammation in cirrhosis and identify novel anti-inflammatory therapeutic targets for ACLD.
Method: Four study groups were defined as: healthy controls, non-cirrhotic CLD (fibroscan < 10 kPa in the absence of other signs of cirrhosis), compensated ACLD (cACLD, fibroscan ≥10 kPa without clinical signs of decompensation) and stable decompensated ACLD (dACLD, stable clinical signs of decompensation regardless of fibroscan). 28-colour spectral flow cytometry panels were designed for the immunophenotyping of whole blood to determine cell counts, inflammatory cytokine expression and phagocytic capacity using pHrodo green E. Coli bioparticles. Proteomics (mass spectrometry) was performed on monocytes from dACLD and cACLD (n = 9, 6 respectively) subjects.
Results: Samples from 13 healthy, 17 non-cirrhotic CLD (9 PBC, 8 MASLD), 59 cACLD (31 MASLD, 16 ALD, 7 other, 5 PBC) and 20 dACLD (7 MASLD, 6 ALD, 6 PBC, 1 PSC) patients were analysed. Quantitation of cell numbers demonstrated significant reductions in $CD8^+$ (cytotoxic), $CD4^+CD45RA^+$ (naïve), NKT and gamma delta T cells in patients with dACLD. No difference was observed in monocyte numbers, but there was a significant phenotypic shift in monocytes between cACLD and stable dACLD. dACLD monocytes were more activated (upregulated CD9 and CD64), showed higher phagocytic capacity ($p < 0.05$) and increased inflammatory cytokine production (IL-1β, $p < 0.005$, TNF-α, $p < 0.05$, IL-6 $p = 0.08$) compared to cACLD. Quantitative proteomics analysis of monocytes identified a significant increase in proteins related to interferon signalling (including STAT1, TBK1, IRF3) and pattern recognition receptors (PRRs) in dACLD, which could drive excessive inflammatory mediator production.
Conclusion: Our analyses show a step-change in monocyte phenotype between cACLD and dACLD, with aberrant monocyte function contributing to the systemic inflammation observed in dACLD. Our proteomic data identified candidate mechanisms and PRRs driving this monocyte activation. Ongoing work is focused on modulating candidate dACLD-associated PRRs to attenuate inflammatory activity.

THU-152

CLM-022, a dual inhibitor of priming and activation steps of NLRP3 inflammasome, as a potential treatment for acute and chronic inflammatory late-stage liver diseases

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Background and aims: Inflammasomes are intracellular multi-protein complexes involved in liver diseases that, in response to cellular danger signals, activate caspase-1 and release pro-inflammatory cytokines IL-1beta and IL-18 (Ribeiro et Szabo 2022). NLRP3 activation requires two signals: the first signal inducing cell priming is the first step of NLRP3 inflammasome activation leading to up regulation of NLRP3 expression, and the second signal includes a broad variety of activators leading to the NLRP3 inflammasome complex activation. The ability of investigational drug CLM-022 to inhibit the NLRP3 inflammasome has been shown through the inhibition of 1) inflammasome complex formation, 2) IL-1β production, and 3) pyroptosis. The aim of this work was to characterize the activity of CLM-022 on the priming and activation of NLRP3 activity both in vitro and in vivo.
Method: PBMC were stimulated with LPS, and priming of NLRP3 activity was assessed by measuring gene expression by RT-qPCR. To assess the specificity of CLM-022 inhibition on NLRP3 inflammasome and pyroptosis, WT THP-1 and NLRP3 KO THP-1 macrophages were primed with LPS and stimulated with nigericin; IL-1beta release and pyroptotic cell death were measured by HTRF and LDH release, respectively. For in vivo efficacy studies, CLM-022 was administrated to different acute liver failure and inflammation rodent models. Systemic inflammation, liver functions and inflammation were assessed by measuring circulating levels of IL-1beta, ASAT, ALAT, and hepatic inflammasome gene expression, respectively.
Results: The addition of CLM-022 inhibits IL-1beta & NLRP3 gene expression induced by LPS stimulation of human PBMC. CLM-022 treatment strongly inhibits the NLRP3 inflammasome dependent pyroptotic cell death in THP1 human macrophages (inhibition of IL-1β production, LDH release) but not in the Thp1- NLRP3 KO THP1 cells. In vivo, CLM-022 inhibits circulating IL-1β in the GalN/LPS model and decreases inflammasome pathway priming in the liver, by inhibiting the NF-kB dependent gene expression. CLM-022 administration improves hepatic functions monitored with ASAT and ALAT.
Conclusion: Investigational drug CLM-022 is a dual inhibitor of inflammasome expression and activity with nanomolar activity. It enables disruption of both the priming and activation steps of NLRP3 activity and thus, as a dual inhibitor, demonstrates therapeutic potential for the treatment of acute and chronic inflammatory late-stage liver diseases, including ACLF.

THU-153

Immunometabolism of mononuclear cells from blood and ascites in patients with decompensated cirrhosis: compartment-specific features of metabolic dysfunction

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Background and aims: The development of ascites is a common decompensation event in patients with cirrhosis and is linked to complications such as spontaneous bacterial peritonitis (SBP) and acute-on-chronic liver failure (ACLF). While systemic inflammatory processes in liver disease have been well-studied, the immune and metabolic dynamics within the peritoneal compartment remain less explored. Therefore, this study aims to investigate metabolic characteristics of peritoneal immune cells in advanced liver disease.
Method: Matched blood and ascites samples from patients with acute decompensation (AD) without SBP (n = 20) were analyzed. Mononuclear cells (MNCs) were isolated using density gradient centrifugation and magnetic cell separation. Mitochondrial stress test was performed using the Seahorse Xfe96 Analyzer to assess oxidative phosphorylation (OXPHOS) and glycolysis rates. Immune cell phenotyping in ascites and blood was performed using spectral flow cytometry.
Results: Among all enrolled patients, alcohol-associated liver disease (48%) represented the main cause of liver cirrhosis. The median age of patients was 58 years (range: 29–84), patients were predominantly male (62%) and the median MELD score was 15.5 (range: 6–28). Flow cytometry revealed comparable T-lymphocyte prevalence in blood and ascites (50.6% vs. 56.6%; $p > 0.05$). Monocytes were more abundant in blood (32.6% vs. 5.8%; $p < 0.001$), while NK (6.7% vs. 20.5%; $p < 0.001$) and NKT cells (1.3% vs. 7.3%; $p < 0.001$) were more prevalent in ascites. Furthermore, peritoneal monocytes were predominantly identified as CD14+CD16+ intermediate monocytes with 59.6% compared to 50.6% in blood. Classical monocytes were more frequent in ascites (24.5% vs. < 1%) and nonclassical monocytes were predominantly found in blood (47.5% vs. 15.9%). Peritoneal MNCs demonstrated a metabolically activated phenotype compared to blood MNCs, characterized by significantly higher basal and maximal oxidative respiration ($p < 0.01$) and markedly lower glycolytic activity ($p < 0.001$). Proton leak, a possible indicator of mitochondrial damage, was elevated in peritoneal MNCs ($p < 0.001$). These metabolic changes were accompanied with the presence of activated immune cell subsets. PD1 expression was increased in ascites CD4 T cells (36.7% vs. 11.5%; $p < 0.001$). Moreover, there was a shift in differentiation, with fewer naïve CD45RA+ cells (14.1% vs. 32%; $p < 0.001$) and a higher number of effector/memory CD45RO+ cells in ascites (85.9% vs. 67.8%; $p < 0.001$). Additionally, CD206 expression, a marker for activated macrophages and monocytes, was significantly increased in peritoneal intermediate monocytes (ascites 65.4% vs. blood 21.4%; $p < 0.001$), while expression of CD86 and CD163 showed no significant differences.
Conclusion: Peritoneal immune cells exhibit, in comparison to their blood counterparts, a metabolically active phenotype and show features of immune exhaustion, indicating a distinct role in immune regulation within the peritoneal environment.

THU-154

Downregulation of interleukine-6 receptors on ascitic T cells may shape the immune compartment in the peritoneal cavity

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Background and aims: In patients with advanced liver cirrhosis, high cytokine levels in ascites indicate a dysregulated and excessive immune response within the abdominal cavity. Although it is already known that impaired intestinal permeability and bacterial translocation serve as triggers for this hyperinflammation, the resulting cellular mechanisms remain insufficiently understood. This study aims to analyze the effect of dysregulated interleukin-6 (IL-6) signaling on the T cell compartment in ascites.
Method: Ascitic fluid and peripheral blood samples were collected from patients with liver cirrhosis, and immune cells were isolated. Cytokine and soluble receptor concentrations were measured by ELISA. T cell phenotype and surface receptor expression was analyzed by flow cytometry.
Results: In ascites, the natural IL-6 trans-signaling inhibitor soluble gp130 was found to be 14.4-fold higher than the soluble IL-6 receptor (IL-6R), suggesting a blockade of IL-6 trans-signaling. Further, the surface expression of IL-6R and gp130 was significantly lower among T cells within ascites compared to those circulating in blood ($p = 0.009$ and $p = 0.036$, respectively). gp130+IL-6R+ T cells, that are reactive to IL-6 classical-signaling, were predominantly CD8+ with naïve or effector-phenotype. Overall, gp130+IL-6R+ T cells were significantly decreased in ascites compared to blood ($p = 0.019$). However, CD4+ Th17 cells, whose differentiation is dependent on IL-6, were significantly more enriched in ascites than in blood ($p = 0.0025$).
Conclusion: We suggest that the blockade of trans-signaling and downregulation of IL-6 surface receptors on T cells may represent compensatory mechanisms to mitigate excessive IL-6 signaling driven by high IL-6 levels in ascites. However, IL-6 signaling seems to shape the immune compartment in the peritoneal cavity and may thus contribute to systemic hyperinflammation.

THU-155

Cyclooxygenase-2 promote hepatic microvascular thrombosis and portal hypertension via AKT/mTOR-Thbs1 pathway in partial inferior vena cava ligation mice

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Background and aims: Dysfunction of Liver sinusoidal endothelial cells (LSECs) plays a key role in the formation of hepatic microvascular thrombosis and portal hypertension. Many studies have proven that Cyclooxygenase-2 (COX-2) could regulate chronic liver diseases. However, the role of COX-2 in hepatic microvascular thrombosis and portal hypertension remains unknown and is the focus of this study.
Method: Hepatic microvascular thrombosis and portal hypertension were induced by partial inferior vena cava ligation (pIVCL). We investigated the hepatic differentially expressed genes by RNA sequencing in the sham and pIVCL groups. The role of COX-2 in hepatic microvascular thrombosis and portal hypertension induced by pIVCL was explored in wild-type mice treated with celecoxib and mice with LSEC-specific *Ptgs2* deletion (*Ptgs2*$^{LSEC\Delta/\Delta}$). Human hepatic sinusoidal endothelial cells (HSECs) were used to probe the prothrombotic role of COX-2.
Results: The increase in hepatic microvascular thrombosis was observed in murine liver induced by pIVCL. RNA sequence of liver tissue showed upregulation of *Ptgs2* gene, and pro-inflammatory genes in pIVCL mice compared to sham mice. Hepatic microvascular thrombosis, portal hypertension, and liver inflammation were relieved in *Ptgs2*$^{LSEC\Delta/\Delta}$mice and treated with celecoxib compared to control mice. As revealed by RNA sequence of liver tissue, compared to the pIVCL mice, celecoxib can downregulate the *Thbs1* gene, which plays a vital role in thrombogenesis, and AKT/mTOR pathway. In vitro, upregulation of *PTGS2*, *THBS1*, and AKT/mTOR pathway in HSECs was induced by TNF-α. Treated with celecoxib or the inhibitors of AKT/mTOR pathway reduced the expression of *THBS1* and AKT/mTOR pathway. These results suggested that COX-2

might regulate hepatic microvascular thrombosis by AKT/mTOR-Thbs1 signaling pathway.
Conclusion: In hepatic microvascular thrombosis and portal hypertension mice, the up-regulated COX-2 promotes the expression of the pro-thrombogenesis gene, *Thbs1*, via the AKT/mTOR pathway to contribute to hepatic microvascular thrombosis.

THU-156-YI
An antimicrobial peptide, melittin attenuates gut urease activity and ammonia production in experimental model of cirrhosis
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Background and aims: Antimicrobial peptides (AMPs) are a vital part of innate immune response that play a key role in regulating gut bacteria and protect against infection. Urease expressing bacteria, predominantly gram negative, are increased in cirrhotic gut and contribute significantly to endogenous ammonia production. Here we investigated a novel hypothesis of using AMPs as a therapeutic to target gut urease bacteria and studied the potential of one of the identified AMPs to reduce gut urease activity and ammonia production.
Method: Urease expressing bacteria were screened using BactPepDB database. AMPs were computationally identified and validated through databases (DBAASP.v3, DRAMP, APD) and CAMPR3 predictive models, employing support vector machines, random forests, discriminant analysis to ensure selection of potential AMPs. This led to the selection of a natural AMP derived from bee venom, melittin. Next, in vitro studies with varying concentrations of melittin were performed with a urease expressing bacteria, *Klebsiella pneumoniae* (*kp* 1.5×10^9) for reducing bacterial urease activity and ammonia release. For in vivo studies, ethyl cellulose nanoparticles loaded with melittin using double emulsion method were prepared. Nano-formulated melittin (NM) was administered orally at 10 μg/kg twice weekly in a 10-week thioacetamide induced cirrhosis rat model and compared with a vehicle group with empty ethyl cellulose nanoparticles. Impact of melittin on gut microbiome, bacterial urease activity, ammonia metabolism in organs, plasma ammonia levels and liver disease progression was assessed.
Results: In vitro studies demonstrated that melittin at 390 μg/ml significantly reduced *Kp* urease activity (2fold) and ammonia levels (4.9fold). NM exhibited a spherical morphology, 303 nm size, 76.3% encapsulation efficiency, demonstrating potential for controlled oral delivery with good stability. In animal study, in comparison to controls, NM led to a decrease in portal ammonia by 1.4fold ($p = 0.007$), peripheral ammonia levels by 2.6fold ($p = 0.02$), stool ammonia by 1.3fold ($p = 0.1$), stool and colonic urease activity by 3fold ($p = 0.05$) and 1.4fold ($p = 0.05$) respectively. No significant changes were observed in glutaminase (PAG) gene expression in kidney, colon, duodenum, or glutamine synthetase (GS) expression in muscles and liver. 16S rRNA sequencing revealed reduced species diversity (Shannon index, $p = 0.44$) and significant alterations in gut microbiome composition (87% variance, $p = 0.33$), notable decrease in urease expressing taxa (*Escherichia coli, Streptococcus*) and increased abundance of commensal *Prevotella copri* in NM treated rats vs vehicle. NM treated rats also showed a significant reduction in hepatic fibrosis and immune infiltration as compared to vehicle rats.
Conclusion: Nano-formulated melittin demonstrates a promising therapeutic approach to modulate gut microbiota, ammonia production and also disease progression by targeting urease expressing bacteria in cirrhosis.

THU-157
Novel potential metabolomic mechanisms for albumin-related improvement in cognitive function in patients with patients with hepatic encephalopathy
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Background and aims: Even after recovery from overt hepatic encephalopathy (HE), minimal HE (MHE), which impairs quality of life (QoL), can persist. A double-blind, placebo-controlled randomized clinical trial (HEAL) showed improvement in cognition with albumin infusion versus placebo (normal saline) in patients with prior HE on standard of care (Fagan A., J. Hepatol., 2022). However, the mechanisms of improvement are unclear. Aim: determine differences in serum metabolomics in albumin versus saline in HEAL study.
Method: HEAL included cirrhosis outpatients with prior HE, MHE and hypoalbuminemia already on treatment for HE given 25% IV albumin 1.5 g/kg or saline weekly over 5 weeks. Blood was drawn pre and 1-hour post-infusion at baseline, week 3 (mid) & 5 (study end). Untargeted metabolomics of serum samples was performed using liquid chromatography coupled to high resolution mass spectrometry. Changes in serum metabolites pre vs post-infusion were compared within/between albumin & saline groups for these 3 visits.
Results: Forty-eight (24/group) pts were randomized and balanced (including by HE medication use) at baseline. Adverse events were similar, with MELD and ammonia remaining stable between/within groups. Albumin levels increased and ischemia-modified albumin decreased only in the albumin group at study end vs. baseline. Cognition improved as well as psychosocial QOL. Within group metabolomics: Pre vs post-albumin infusion: There was a significant increase in 2 broad groups tryptophan metabolites & acylcarnitines post-albumin vs pre-albumin, which was only significant at baseline. Tryptophan metabolites were higher (N-acetyl tyrosine, 2.3 fold, $p = 0.003$, Xanthurenic acid 2.7 fold, $p = 0.013$, Kynurenic acid 1.9 fold, $p = 0.02$) as well as acylcarnitines (Decanoylcarnitine 1.8 fold $p = 0.003$, Octanoylcarnitine 1.8 fold, Hexanoylcarnitine 1.5 fold, $p = 0.01$) after albumin compared to pre-albumin. Pre vs post-saline infusion: No change in metabolites vs baseline were found. Between groups: *Visit 1*: post-albumin pts vs placebo had again higher concentrations of tryptophan derivatives and aromatic pathways (N-acetyl tyrosine, 2.6 fold, $p = 0.005$, xanthurenic acid 3.1 fold, $p = 0.013$, kynurenic acid 2.2 fold, $p = 0.005$,L-kyunerine 2.3 fold, $p = 0.007$, hydroxy-kyunerine 2.3 fold, $p = 0.02$ N-acetyl ornithine 2.4 fold $p = 0.007$, o-hydroxyhippuric acid, 5.4 fold, $p = 0.02$), decanoylcarnitine 1.6 fold $p = 0.03$), and lower concentrations of spermidine (0.44, $p = 0.03$). *Subsequent visits*: N-acetyl ornithine remained significantly higher in albumin vs saline (mid 2.5 fold $p = 0.04$, end fold 1.7, $p = 0.006$).
Conclusion: Novel metabolomic pathways related to higher tryptophan metabolites that favorably affect the gut-brain axis & gut barrier, and long-chain acylcarnitines that modulate bio-energetics increase with albumin infusion compared to placebo in an RCT. These changes are maximal after the first albumin infusion and saturate subsequently.

THU-159-YI
Development and validation of dimethylarginines (DAS) as a novel biomarker to identify pre-ACLF and predict outcomes following acute decompensation of cirrhosis in two prospective multicentre european cohorts
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Background and aims: Cirrhosis patients hospitalized with acute decompensation (AD) have a high 90-day mortality. Asymmetric dimethylarginine (ADMA) and its stereoisomer symmetric dimethylarginine (SDMA) reduce nitric oxide generation, cause endothelial cell dysfunction and play a role in driving portal hypertension and liver-related mortality. This study aimed to develop and validate a new scoring system termed DAS, combining these 2 biomarkers, in predicting liver-related events following AD.
Method: The derivation cohort encompassed patients from the DASIMAR study (n = 247), a prospective, observational, UK study recruiting patients admitted non-electively with AD cirrhosis. The validation cohort was from the PREDICT study (n = 409) which was a multicentre European trial with a similar design. ADMA and SDMA analysis were performed by liquid chromatography- tandem mass spectrometry at baseline (T0) and a second time point within 7 days (T1).
Results: Both cohorts exhibited similar baseline characteristics. With regards to inpatient transplant-free mortality in the DASIMAR cohort, T0 DAS was significantly higher in those who died (13%) compared to survivors (6.7 vs 4.1 umol/L, $p < 0.001$). Indeed, T0 DAS remained a predictor of inpatient mortality in multivariate analysis (OR 1.3 [95% CI 1.1–1.5], $p = 0.002$) and was superior to the baseline CLIF-C AD score (OR 1.1 [95% CI 1.0–1.2], $p = 0.003$). When assessing 90-day mortality, T0 DAS was also significantly higher in those who died (n = 56) compared to survivors (5.7 vs 4.1 umol/L, $p < 0.001$). Whilst both T0 and T1 DAS were significant predictors in univariate analysis, only T1 DAS remained significant in multivariate analysis (OR 1.48 [95% CI 1.18–1.86], $p = 0.001$). When assessing 90-day mortality in the PREDICT cohort a similar signal was demonstrated with significantly higher T0 DAS scores in those who died (5.5 vs 4.2 umol/L, $p = 0.033$). Significantly higher T0 DAS scores were noted in the DASIMAR cohort in the pre-ACLF patients (5.3 vs 3.6 umol/L, $p < 0.001$). This was confirmed in the PREDICT cohort where T0 DAS was an independent predictor of ACLF development in multivariate analysis (OR 1.13 [95% CI 1.01–1.25], $p = 0.027$). With respect to renal dysfunction in the DASIMAR population, T0 DAS scores were significantly higher in those who developed an acute kidney injury (AKI) during admission compared to those who did not (5.2 vs 3.5 umol/L, $p < 0.001$). This was shown in multivariate analysis (OR 1.3 (1.1–1.5, $p < 0.001$) and replicated in the PREDICT cohort where T0 DAS also predicted renal failure in multivariate analysis (OR 1.2 [95% CI 1.0–1.3, $p = 0.025$).
Conclusion: This study demonstrates that the novel DAS score can predict liver-related events including mortality, ACLF development and renal dysfunction. With further validation, DAS could be translated for clinical use in identifying patients with pre-ACLF and those at high risk of mortality.

THU-160
Characterization of the muscle-liver axis in a murine model of liver injury
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Background and aims: Loss of muscle mass and function is a common complication of liver cirrhosis associated with poor outcome. Beyond direct effects of liver damage on muscle wasting, skeletal muscle interacts with the liver via myokines, potentially affecting disease progression. Mechanisms underlying the muscle-liver axis remain poorly understood. Therefore, this study aimed to explore skeletal muscle and myokine changes during disease progression in a murine model of liver injury.
Method: Male BALB/c mice (n = 54, aged ≥12 weeks, 25–30 g) received intraperitoneal injections of corn oil (placebo, n = 16) or 25% carbon tetrachloride (CCl_4) in corn oil (0.6 µl/g body weight (bw), n = 33) twice weekly for 4 weeks to induce liver injury, followed by weekly injections for 8 weeks. Untreated mice served as controls (n = 5). Bw was recorded daily, and grip strength (BIO-GS3, Bioseb) was measured weekly. Tissue samples from muscle (M. quadriceps, M. gastrocnemius) and liver, and plasma were collected at 4, 8, and 12 weeks. Fibrosis was assessed by Sirius Red staining. Myokine levels (MILLIPLEX Magnetic Bead Panels), and gene/protein expression in muscle and liver were quantified. Data were analyzed using two-way ANOVA with Tukey's multiple comparison test.
Results: Liver injury ranged from early acute liver failure to mild/moderate fibrosis as shown by Sirius Red staining and increased collagen 1 alpha 1 expression at 4–12 weeks. The liver/bw ratio increased in CCl_4 mice over the study course vs. controls and placebo ($p < 0.05$) reflecting liver injury. Plasma albumin, pseudocholinesterase, cholesterol, triglycerides, and bilirubin levels increased, while alkaline phosphatase decreased during disease progression and vs. placebo ($p < 0.05$). Muscle/bw ratios (at 4, 8, and 12 weeks) and grip strength (at 10–12 weeks) decreased vs. placebo ($p < 0.05$). Follistatin gene expression in M. quadriceps decreased ($p < 0.05$), while myostatin tended to increase ($p = 0.077$). Activin A protein levels marginally increased ($p = 0.0571$) at 12 weeks. Among plasma myokines, only fibroblast growth factor (Fgf) 21, oncostatin M, and osteonectin levels were detectable, but without significant differences between CCl_4 and placebo groups. Acute liver failure was associated with increased muscle myostatin and Fgf21 expression.
Conclusion: CCl_4-induced liver injury was associated with notable reductions in muscle mass and strength, reflecting sarcopenia. While changes in plasma myokines were not detectable, altered myostatin signaling and Fgf21 expression, particularly during acute liver failure, suggest impaired muscle-liver crosstalk. The heterogeneity of liver injury in CCl_4 intoxication is challenging for conducting controlled studies of the muscle-liver axis in chronic liver disease.

THU-161-YI
Proximity extension assay-based proteomics: a reliable tool for prediction of major adverse liver outcomes
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Background and aims: Since liver disease is often clinically unapparent, plasma biomarkers predicting the future development of major adverse liver outcomes (MALO) are urgently needed. Therefore, we assessed the usefulness of a novel, proximity extension assay (PEA)-based high-throughput proteomics to predict MALOs.
Method: Proximity extension assay (PEA)-based plasma proteomic data (>2900 proteins) and clinical information were accessed via the population-based UK biobank (UKB) cohort including >53000 individuals with a median follow-up of >10 years and the subcohorts of obese (>12900) and diabetic (>1600) participants. A validation cohort comprised 287 subjects with severe alpha1-antitrypsin deficiency (Pi*ZZ genotype) with a median follow-up of 3.8 years and fibrosis assessment with transient elastography (21 MALOs). Selected PEA parameters were compared to measurements with routine techniques. Linear models with empirical Bayes moderation (with age and sex as covariates) assessed the differential abundance. Multivariable logistic regression was used to explore the predictive power of identified markers.
Results: Routine measurements of gamma-glutamyl transferase (GGT) and aspartate aminotransferase (AST)) strongly correlated with PEA values (r = 0.91 and r = 0.68, respectively). In the entire UKB PEA cohort with 490 MALOs, >1700 plasma proteins remained significantly different between the groups after adjustment for multiple testing. Most altered proteins were predominantly of liver, intestine, or lymphoid tissue origin and remained significant in the diabetic/obese sub-cohort. Five proteomic biomarkers, ADAMTS-like protein 2, polymeric immunoglobulin receptor, integrin beta like protein 1, thrombospondin 2 (THBS2), and insulin-like growth factor binding protein 7 robustly predicted future MALO at least as good GGT as the best routinely available predictor in all three UKB (sub-) cohorts (AUROCs between 0.80 and 0.86). In the AATD cohort, they all showed gradual increase along fibrosis stages. In AATD cohort, all five markers numerically outperformed routinely measured GGT in the prediction of MALO (AUROCs of 0.88–0.94 vs. 0.78). PEA-based THBS2 strongly correlated with ELISA-based values (r = 0.85).
Conclusion: Our analyses reveal the reproducibility of several PEA-based proteomic biomarkers and demonstrate that they can serve as a promising source of non-invasive MALO predictors.

THU-162-YI
Profiling of intestinal blood vessel-associated macrophages in cirrhosis

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Background and aims: To prevent dissemination of luminal bacteria, the gastro-intestinal tract is equipped with several barriers, including the epithelial layer, pathogen-clearing intestinal macrophages, and the gut-vascular barrier. Failure of these barriers results in bacterial translocation, a major driver of morbidity and mortality in cirrhosis. In this study, we investigated the role played by specialised intestinal macrophages in preserving vascular barrier integrity in an animal model of cirrhosis.
Method: Cirrhosis was induced in animals by subcutaneous injection of CCl_4 for 20 weeks. We performed single-cell transcriptomics of the small intestinal lamina propria macrophage population from cirrhotic and control animals, and from (de-)compensated cirrhosis patients.
Results: In a murine cirrhosis model, intestinal submucosal macrophages from animals at advanced disease stages appeared disorganised and dispersed in the tissue, neither connecting with each other nor the blood vessels, and displaying an ameboid morphology. The disorganised network of these macrophages coincided with increased bacterial translocation in our model. By performing transcriptional profiling of intestinal macrophages, one identified mature macrophage subset showed a reduction of the expression of key chemokines and their receptors (e.g. *Pf4*, *Cxcr4*) and a TGF-beta-related receptor (*Tgfbr1*) in cirrhosis. Moreover, decreased levels of genes involved in heme degradation were observed. Interestingly, transcriptional profiling of duodenal macrophages of cirrhosis patients revealed a similar dysregulation of pathways supporting blood vessels and increased chemokine expression. In our experimental model of cirrhosis, an enrichment in pathways associated to apoptotic cell clearance and scavenging by class B receptors was observed. Functional validation of the latter by performing intravital microscopy experiments, confirmed reduced bacterial clearance by macrophages closely associated to submucosal blood vessels during cirrhosis.
Conclusion: Our findings provide a transcriptional analysis of specialised intestinal lamina propria macrophages, revealing functional impairments in these cells during cirrhosis. These alterations coincide with increased bacterial translocation in our experimental model, underscoring their critical role in maintaining intestinal barrier integrity.

THU-163
Attenuation of inflammatory bystander CD8+ T cell activation in decompensated cirrhosis via non-selective beta-blockers

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Background and aims: Patients with advanced liver cirrhosis display a dysfunctional immune system, leading to immune deficiency on the one hand and systemic inflammation on the other hand. Recently, bystander-activated $CD8^+$ T cells were identified as a key contributor to the inflammatory milieu. Non-selective beta blockers (NSBB) are often used in cirrhosis to reduce portal pressure and subsequently decompensation risk. Moreover, evidence suggests that NSBBs also mediate anti-inflammatory effects, however, the underlying mechanism remains elusive.
Method: In this study, we investigated the impact of NSBBs on $CD8^+$ T cells in patients with decompensated liver cirrhosis (n = 31). Therefore, we performed ex vivo phenotype and in vitro functional analyses of matched blood and ascites $CD8^+$ T cells in patients on NSBB therapy (n = 18) compared to those without (n = 13).
Results: $CD8^+$ T cells from blood and ascites expressed comparable levels of adrenergic beta receptors (ADRB1 and ADRB2). In vitro, propranolol not only reduced the frequency of bystander-activated

($CD69^+CXCR6^+$) $CD8^+$ T cells upon IL12/15/18 stimulation, but also the IFN-gamma production was diminished. In contrast, propranolol did not inhibit antigen-specific $CD8^+$ T cell responses upon CMV pp65 stimulation. *Ex vivo* phenotypic analysis confirmed the *in vitro* data, revealing decreased expression of innate activation markers and lower frequencies of bystander-activated $CD8^+$ T cells in patients on NSBB therapy compared to those without. Of note, plasma and ascites NSBB levels from selected patients negatively correlated with bystander $CD8^+$ T cell frequencies.
Conclusion: These results indicate that propranolol effectively inhibits bystander-activated $CD8^+$ T cells in decompensated cirrhosis while preserving antigen-specific functions. This opens up NSBBs as a promising therapeutic strategy for the targeted inhibition of hyperinflammation and subsequent mitigation of CAID and its associated complications.

THU-164
Mitochondrial transfer from mesenchymal stem cells to hematopoietic stem cells mitigates bone marrow failure and promotes liver regeneration in pre-clinical model of cirrhosis
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Background and aims: Progressive loss of hematopoietic stem cells reserves accounts for regeneration failures in cirrhosis. Metabolic adaptation in HSC plays a critical role in balancing self-renewal and differentiation. Mesenchymal stem cells play a central role in maintaining HSC and functional exhaustion of same has been shown to be associated with poor hematopoietic reserve and osteodystrophy in cirrhosis. In the current study we aim to restoring bone marrow niche in augmenting HSC and their impact on liver repair and regeneration.
Method: Cirrhosis was induced in C57BL/6J mice through intraperitoneal dose of carbon tetrachloride. BM-MSC was infused through either intra-femoral or intravenous route. Animals were randomly divided into 2 groups, one received DiR tagged BM-MSC infusion at the end of 10^{th} week, while the other group received saline. Aged matched healthy controls were used as healthy controls. BM-HSCs was studied using flow cytometry. Mitochondrial biomass and potential were studied using Mito Tracker dyes. Bioenergetics of HSCs was analyzed using Seahorse Extracellular Flux Assay. Mitochondrial transfer from MSCs to HSCs was studied in-vivo and in-vitro co-culture assay.
Results: Intra-femoral MSC infusion showed better recruitment of BM-MSC than Intravenous, enabling a comprehensive evaluation of all parameters through intra-femoral route. Chronic liver injury showed a significant loss of LT-HSCs along with a decrease in maximal respiration, indicating impaired oxidative phosphorylation. Intra-femoral infusion of MSC increase LT-HSC population at 24 h, 72 h and day11 along with increase in the maximal respiration indicating improved oxidative phosphorylation capacity. MSC infused group showed significant increase in mitochondrial biomass (MTG), mitochondrial potential (MTR) in LT-HSCs. The relative expression of TFAM showed no increase at 24 h and 72 h but rises significantly by Day 11, suggesting mitochondrial biogenesis in LT-HSCs initiates later post-therapy. Further In vitro and In vivo study confirmed transfer of mitochondria from MSC to LT-HSC in early time point and HSC account for increase in mitochondrial mass and potential at early time point. Restoring LT-HSC reserve increase F4/80, CD86, CD206, so it augments resolving macrophage number and function, increase regression of fibrosis and regeneration in cirrhotic animal.
Conclusion: MSC-mediated mitochondrial transfer to LT-HSCs restores BM HSC reserve in cirrhosis. Restoring BM HSC reserve augments monocytes number and function, increase regression of fibrosis and regeneration in cirrhosis.

THU-165-YI
Spleen Area affects the predictive performance of the platelet count-based non-invasive tools in MASLD
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Background and aims: Most of the currently available non-invasive tools (NITs) predicting hepatic decompensation (HD) in advanced chronic liver disease (ACLD) include the platelet (PLT) count. However, a non-negligible proportion of Metabolic dysfunction-associated Steatotic Liver Disease (MASLD)-related compensated ACLD patients with clinically significant portal hypertension (CSPH) do not show splenomegaly and hypersplenism-related thrombocytopenia. The present research explored the performance of NITs in predicting a 3-year first HD according to spleen size.
Method: 148 splenic and 27 asplenic (ASP: 25-splenectomized; 2-agenesis) MASLD-cACLD patients receiving an endoscopy evidencing CSPH were enrolled. Ultrasound artificial intelligence (AI)-based tools distinguished splenomegaly-affected (SAP: 91) and normal spleen patients (NSP: 57). Albumin-bilirubin (ALBI) score and PLT count-based NITs (PLNs) [Fibrosis-4 (FIB-4), ALBI-FIB-4 score, red-cell-distribution-width/PLT-ratio (RPR), Liver Stiffness Measurement (LSM)/PLT-ratio (LSM/PLTr), and ANTICIPATE±NASH] were determined. During a 3-year semiannual follow-up, NITs and spleen size were reassessed, as well as the HD occurrence was recorded.
Results: Limitedly to SAP, Spleen Area inversely correlated with PLT count (R: −0.981; $p < 0.0001$), confirming the predominant role of splenomegaly-related hypersplenism in conditioning thrombocytopenia. HD occurred similarly in SAP (20.48%), NSP (21.15%), and ASP (25%) (chi-square, p:0.198). In NSP, PLNs showed a reduced influence on HD [FIB-4 (p: 0.03), ALBI-FIB-4 (p:0.001), RPR (p:0.002), LSM/PLT ratio (p:0.01), and ANTICIPATE ± NASH (p:0.001)] compared to SAP. In NSP, the Spleen Area was inversely associated (aSHR: 0.870) and more significantly ($p < 0.0001$) impacted HD. Consistently, unlike SAP, in NSP and ASP, PLNs showed poor performance, and exclusively ALBI maintained a good accuracy (NSP: AUC 0.651, p: 0.04; ASP: AUC: 0.625, p: 0.03) in predicting 3-year HD.
Conclusion: Spleen size dramatically affects the predictive performance of the PLNs in CSPH-affected MASLD-cACLD patients.

THU-166
NTZ alleviates stress-induced hepatocyte cell death through modulation of oxidative stress and DNA damage signaling pathways in ACLF models
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Background and aims: Acute-on-chronic liver failure (ACLF) is a severe syndrome affecting patients with acutely decompensated cirrhosis, associated with multiple organ failures and high short-term mortality rates. We previously showed that the anti-parasitic drug nitazoxanide (NTZ) directly protects from systemic inflammation and organ damage in preclinical models of ACLF, with a direct effect demonstrated on stress-induced cell death and liver damage (*J Hepatol.* 2022, 2023, 2024). To further characterise the mechanism of

action of NTZ, transcriptomic analyses were performed in stress-induced hepatocytes and liver from a rat model of ACLF.
Method: Immortalized human hepatocytes were stressed with 0.5 mM H_2O_2, a method commonly used to trigger cellular oxidative damage. Tizoxanide (TZ), NTZ active metabolite, was added concomitantly to H_2O_2 for 3 h or 6 h. *In vivo*, ACLF was precipitated through lipopolysaccharide (LPS) injection in rats displaying advanced liver fibrosis induced by carbon tetrachloride (CCl_4). A single dose of NTZ (100 mg/kg) or vehicle was orally administered 1 h before LPS injection. Liver and blood samples were collected 6 h or 24 h post-LPS. Transcriptional changes in hepatocytes and livers were assessed using oligonucleotide microarrays and pairwise comparisons were performed to identify differentially expressed genes.
Results: H_2O_2 treatment of human hepatocytes for 3 h induced a significant transcriptome remodeling, associated with apoptotic cell death. Enrichment analysis revealed that differentially expressed gene sets were mainly related to oxidative stress, DNA damage and cell death pathways. After 6 h, a modulation of genes involved in cell cycle response was also observed. TZ blunted the H_2O_2-induced gene signature at both timepoints by modulating pathways such as NRF2-mediated oxidative stress response, apoptosis, p53 signaling and cell cycle. As an example, expression level of the NRF2-targeted gene HMOX1, was reduced in TZ-treated cells, suggesting that modulation of NRF2 signaling by TZ could explain its protective role on hepatocyte cell death.
In ACLF rats, NTZ treatment reduced LPS-induced serum levels of total bilirubin (−103%, $p < 0.0001$) and bile acids (−130%, $p = 0.02$) and alleviated hepatocellular injury by blunting LPS-induced rise of AST (−100%, $p = 0.003$) and GGT (−99%, $p = 0.014$), in comparison with fibrotic rats. Interestingly, gene expression analysis of ACLF livers revealed that NRF2 response was also modulated by NTZ.
Conclusion: These results suggest that a direct effect of NTZ on oxidative stress response could explain its protective role against hepatocyte cell death and liver damage. Combined with its antibacterial and anti-inflammatory activities, these findings further support the investigation of NTZ treatment as a promising approach to prevent systemic inflammation and organ damage in ACLF patients.

THU-167
Recombinant ADAMTS13 attenuates LPS-induced acute kidney injury and renal microangiopathy in mice with liver cirrhosis by cleaving vWF

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Background and aims: Hepatorenal syndrome (HRS) has a poor prognosis among the complication of liver cirrhosis, yet treatment options are limited. Thrombotic microangiopathy with reduced ADAMTS13 activity and von Willebrand factor (vWF) accumulation has been reported to play a key role in the pathogenesis of acute kidney injury (AKI) in liver cirrhosis. In this study, we aimed to investigate the effect of recombinant ADAMTS13 (rADAMTS13) on acute kidney injury using a mouse model of HRS.
Method: HRS was induced in C57BL/6J mice by intraperitoneal administration of carbon tetrachloride and lipopolysaccharide (AKI-C group). Additionally, a group of mice was treated with rADAMTS13 (10 μg/body) (rAD group). Serological, histological and molecular analyses were performed to assess the effect of rADAMTS13 on liver and kidney injuries in AKI-C group. Tissue blood flow was also measured using a laser Doppler tissue blood flow meter to evaluate differences between the groups.
Results: AKI-C group showed a marked liver dysfunction as well as renal dysfunction with elevated serum level of AKI including KIM-1, osteopontin and NGAL. Plasma ADAMTS13 activity was reduced, and vWF antigen levels were increased. A decrease in blood flow in the liver and kidney tissues was also observed. In the rAD group, compared to the AKI-C group, plasma ADAMTS13 activity was increased, vWF antigen levels were decreased, and liver and kidney blood flow were improved. As a result, liver and kidney injuries were significantly alleviated. Furthermore, in the rAD group, macrophage (F4/80-positive) infiltration and the increased expression of inflammatory cytokines observed in the AKI-C group were suppressed. Accumulation of oxidative stress (4-HNE-positive) was also reduced. In addition, the deposition of CD41a-positive microthrombi in kidney tissues seen in the AKI-C group was significantly suppressed in the rAD group. This group also showed an increased expression of angiogenesis markers (Vegf) and a decreased expression of vascular inflammation markers (Vcam1, Icam1, Sele, Selp).
Conclusion: Administration of rADAMTS13 may improve inflammation, oxidative stress, and reduced blood flow in liver and kidney, thereby mitigating HRS.

THU-170
HBV-specific metabolic footprints and impact on mortality in patients with HBV reactivation and acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is one of the deadliest complications of chronic liver disease and no therapeutic options are available except liver transplantation. HBV is the most common trigger for ACLF in Asia. In a recent study ACLF in HBV patients was associated with distinct changes in the metabolome. Based on this cohort, both pre-ACLF and ACLF patients, triggered by the HBV reactivation were analyzed in more depths for HBV-specific changes.
Method: Clinical data and metabolic profiles of 1024 Chinese patients from the CATCH-LIFE studies with chronic HBV mono-infection who were hospitalized due to an acute hepatic exacerbation were analyzed. ACLF was diagnosed according to the COSSH ACLF criteria. Metabolites of serum samples were quantified using LC-MS and significantly altered footprints were correlated to differing metabolic pathways using the database SMPD via MetaboAnalyst v6. These were then compared between different ACLF and HBV-reactivation statuses in meta-analyses and pathway maps were deduced.
Results: Of the 1024 patients, 357 patients were diagnosed with ACLF at time of admission, 135 with a pre-ACLF and 532 without ACLF. In 30.9% of the ACLF patients and in 10.8% of the pre-ACLF patients, HBV reactivation was observed. HBV reactivation was associated with higher transaminases and CRP in the pre-ACLF patients. 28-day, as well as 90-day and 365-day mortality was increased in pre-ACLF with HBV reactivation in comparison with patients with another ACLF precipitating event (2.1% vs. 25%, 12.5% vs 29.2% and 18.8% vs. 33.3%, respectively). This strong increase in pre-ACLF-linked mortality correlated with a pronounced augmentation of metabolic pathways contributing to the formation of reactive oxygen species (ROS), which prevailed in HBV reactivated ACLF patients. Notably, this was not accompanied by an increase in respective metabolic pathways detoxifying oxidative products. Additionally, metabolites revolving around the urea cycle, thus nitric monoxide (NO) formation, and the polyamine metabolism were highly increased in pre-ACLF and ACLF patients with HBV reactivation. Along these routes, specific metabolites could be identified as putative markers for the differing clinical situations, among which are distinct endogenous amino acid, nucleotide and fatty acid derivatives.

Conclusion: HBV reactivation is accompanied by a high degree of hepatic inflammation, and an early onset and is associated with an increase of mortality in pre-ACLF patients. Importantly, pre-ACLF as well as ACLF are linked to disruptions in distinct metabolic pathways, including the NO, ROS and polyamine pathways in dependency of HBV reactivation. The underlying regulatory mechanisms may present as extremely interesting targets for studies to treat HBV-related development of ACLF as well as decrease its persistence and associated mortality.

THU-171

Statins as an alternative therapy to improve the cardiac chronotropic dysfunction in cirrhotic cardiomyopathy in cirrhotic rats

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Background and aims: Cirrhotic cardiomyopathy (CCM) is a cardiac complication of liver cirrhosis with chronotropic hypo-responsiveness. Statins act as anti-inflammatory, anti-fibrotic, and anti-oxidant agents and decrease the portal pressure in liver cirrhosis. No proper treatment for targeting CCM exists and needs to be developed. Therefore, we evaluated the effect of simvastatin on CCM in cirrhotic rats.
Method: Total of 80 Albino Westar male rats were divided as Sham (control) and bile duct ligation (BDL) (cirrhotic) groups i.e., Sham/Normal saline, BDL/Normal saline, Sham/Simvastatin-15 (15 mg/kg/day), BDL/Simvastatin-15, Sham/Simvastatin-20 (20 mg/kg/day), BDL/Simvastatin-20, Sham/Simvastatin-25 (25 mg/kg/day), BDL/Simvastatin-25, Sham/Lactulose-1.5 (g/kg/day), and BDL/Lactulose-1.5 groups. BDL surgery was conducted to induce cirrhosis while, for control groups, the Sham surgery was performed. After induction of cirrhosis, the animals were gavaged orally the respective drug in normal saline for two weeks. Finally, in-Vivo chronotropic study through electrocardiography, liver function tests i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin through enzyme-linked immunosorbent assay (ELISA), liver histopathology through hematoxylin and eosin staining, and heart malondialdehyde (MDA), brain natriuretic peptide (BNP), and tumor necrosis factor-alpha (TNF-alpha) levels through ELISA were evaluated post-treatment.
Results: Our results indicated that the chronotropic responses decreased in the BDL/Normal saline group and improved in the BDL/Simvastatin-25 group, BDL/Simvastatin-20 group, and BDL/Simvastatin-15 group, dose-dependently, both before and after stimulation with adrenaline (0.5, 1, and 2 mg/kg). The QTc interval was raised in the BDL/Normal saline and declined more in BDL/Simvastatin-25 group than BDL/Simvastatin-20 and BDL/Simvastatin-15 groups. The hepatic fibrosis and inflammation were elevated and graded severe in the BDL/Normal saline group and attenuated and graded minimal in BDL/Simvastatin-25, mild in BDL/Simvastatin-20, and moderate in BDL/Simvastatin-15 group. The spleen weight was increased in BDL/Normal saline group and reduced in BDL/Simvastatin-25 group, BDL/Simvastatin-20 group, and BDL/Simvastatin-15 group in a dose-dependent manner. The heart MDA, BNP, and TNF-alpha and serum ALT, AST, and bilirubin levels were elevated in BDL/Normal saline group and reduced more in BDL/Simvastatin-25 group as compared to BDL/Simvastatin-20 and BDL/Simvastatin-15 groups.
Conclusion: Simvastatin at 25 mg/kg has maximum effect to improve the chronotropic hypo-responsiveness and reduce the QTc interval in cirrhosis-induced CCM in rats. It reduces liver inflammation and fibrosis, serum ALT, AST, and bilirubin levels, and heart inflammation (TNF-alpha), stress marker (BNP), and oxidative stress (MDA) in CCM.

THU-172

A disintegrin and metalloproteinase with a thrombospondin type 1 motif 13 and von Willebrand factor axis regulates acute kidney injury in mice with liver cirrhosis

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Background and aims: Although hepatorenal syndrome-acute kidney injury (HRS-AKI) is one of prognostic risk factors among cirrhosis-related complications in patients with liver cirrhosis, there are still limited established therapeutic options. We have reported that the decreased level of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity and the increase of von Willebrand factor (vWF) involved in hemostatic coagulation were observed along with the development of liver cirrhosis and closely correlates with the level of portal hypertension, suggesting their influences on the circulatory dynamics in chronic liver diseases. In the current study, we investigated the effects of ADAMTS13/vWF axis for the pathogenesis of AKI in a cirrhotic mouse model.
Method: Wild type (WT) and ADAMTS13-deficient (ADKO) mice were used to create an AKI mouse model with liver cirrhosis by combining chronic injury injected by chronic carbon tetrachloride (CCl4) and acute hepatic insult by injection with a double dose of CCl4 followed by administration with lipopolysaccharides to elucidate the effect of ADAMTS13 in AKI in mice with liver cirrhosis. Similarly, WT and vWF-deficient (vWFKO) mice were used to investigate the role of vWF in AKI in cirrhotic mice, as described above. We collected serum, liver, and kidney tissue and compared differences in liver and kidney injury due to ADAMTS13 deficiency.
Results: AKI groups in both WT and ADKO mice increased serum AST/ALT and BUN/Cre levels. These changes in ADKO mice were significantly higher than those in WT mice. Tissue blood flow in liver and kidney were significantly decreased in ADKO group compared to WT group with the increase in vWF level. ADKO mice with AKI showed the elevation of inflammatory markers such as Tnf-α and Il-1β, and the increased number of F4/80-positive cells in kidney tissue. Likewise, the expressions of kidney injury markers including Kim-1, Vim, Hif1α were significantly elevated in ADKO group compared to WT group. In addition, higher elevation of oxidative stress markers such as NOX2/4, HO-1 and eNOS were observed in ADKO mice with AKI compared to WT mice with AKI. On the other hand, vWFKO mice showed the decrease in AST/ALT, BUN/Cre level compared to WT mice. The knockdown of vWF also improve the lowering of tissue blood flow in liver and kidney with the reduction of inflammatory changes and oxidant factors.
Conclusion: ADAMTS13/vWF axis contributes to regulating the induction of inflammation and tissue damage, as well as lowering tissue blood flow in the AKI mouse model. These results suggest that the imbalance of ADAMTS13/vWF axis plays an important role on the progression of AKI in patients with liver cirrhosis, and may be a novel therapeutic target for HRS-AKI.

THU-173

A biliary organoid model to investigate the malignant transformation of primary sclerosing cholangitis to cholangiocarcinoma

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Background and aims: The underlying molecular mechanisms of the progression of primary sclerosing cholangitis (PSC) to cholangiocarcinoma (CCC) are not fully understood. RNA sequencing has revealed that primary human cholangiocytes lose their transcriptional diversity in organoid cultures; however, these organoids retain key cellular properties. Based on this potential, we are developing a robust system to isolate cholangiocyte organoids directly from bile fluid obtained from healthy controls as well as patients with PSC and CCC. This approach aims to enable detailed investigations into the molecular and cellular mechanisms driving the transition from chronic inflammation to tumorigenesis.
Method: Organoids were generated from bile fluid and bile duct biopsies obtained from healthy individuals as well as patients with PSC and CCC. The molecular characterization of the organoids included gene expression analysis, protein expression profiling, morphological assessment, and the evaluation of surface marker protein expression using immunofluorescence. Cholangiocyte-specific markers and hepatocyte-specific markers were analyzed to confirm the cholangiocyte origin of the organoids and to exclude contamination with hepatocytes.
Results: We established organoids from bile fluid and bile duct biopsies, creating a patient-specific repository for PSC, CCC, and control groups. Organoids derived from bile fluid exhibited strong expression of cholangiocyte-specific markers, such as Epcam, Cytokeratin-19, and Sox9, which matched those observed in biopsy/tissue-derived organoids, confirming their cholangiocyte origin. Hepatocyte-specific markers, including Alpha-1-Antitrypsin and Serum Albumin, were not detected, excluding contamination by hepatocytes or other cell populations. This method enables reliable disease modeling. The established organoid model provides an optimal platform for studying molecular changes associated with the progression from PSC to CCC and conducting functional studies.
Conclusion: Our findings confirm that bile-derived organoids represent a reliable and minimally invasive model for investigating PSC and CCC. The cholangiocyte origin of the organoids was validated through specific markers, with no evidence of contamination. This model offers a reliable platform to study molecular changes driving the progression from PSC to CCC and to evaluate potential therapeutic strategies.

THU-174-YI

Activated intestinal fibroblasts induce inflammatory Th17 differentiation in experimental cirrhosis

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Background and aims: Increased intestinal permeability is a central factor in the disruption of the gut-liver axis during cirrhosis. Innovative strategies focused on limiting intestinal inflammation are needed to restore the integrity of the mucosal, endothelial, and epithelial barriers in cirrhosis. Modulating the interaction between intestinal fibroblasts (Fib_{INT}) and cellular immunity in the lamina propria may help to restore intestinal homeostasis in cirrhosis.
Method: A prospective experimental study was conducted using mice with advanced liver injury induced by oral administration of CCl_4 for 12 weeks (n = 5). Control mice received olive oil as vehicle (n = 5). Fib_{INT} activation, chemokine production, and immune recruitment were assesed in ileum samples through gene (RT-qPCR) and protein expression (immunofluorescence). Activation states of primary Fib_{INT} (CD45-CD326-CD90+) isolated from the small intestine and colon of control and cirrhotic mice were evaluated, as well as the expression of molecules involved in T-cell activation (MHC-II, CD40, CD80, CD86, OX-40L, PD-L1) by flow cytometry. Co-cultures of Fib_{INT} (cirrhosis) and T lymphocytes (control), and vice versa, were conducted to determine the modulatory effects of cell-to-cell interactions.
Results: An increase in gene (*COL1A1, FAP, PDPN*) and protein (α-SMA, Pdpn, Vim) expression of stromal cell activation markers was observed in the ileum during experimental cirrhosis. Augmented expression of chemokines (*CCL2, CXCL10*) in the ileum of cirrhotic mice correlated with increased leukocyte (CD45+) infiltration into the villi. Local increases in intestinal lymphocyte (CD3+) and macrophage (F4/80+) populations were detected. In cirrhosis, the percentages of primary Fib_{INT} from the small intestine expressing stromal cell activation markers (Vim and Pdpn) and T-cell stimulation molecules (CD40, CD80, CD86) were elevated compared to control mice. Isolated Fib_{INT} from cirrhotic mice interacted with more CD4+ T lymphocytes *in vitro* and were more effective at inducing their activation (CD25+) and differentiation towards a Th17 profile (IL-17+). Similarly, CD4+ intestinal T lymphocytes from cirrhotic mice could activate Fib_{INT} isolated from control animals (Vim+, CD86+, OX40L).
Conclusion: Fib_{INT} are activated in experimental cirrhosis and acquire the ability to induce an inflammatory Th17 response. These findings suggest that modulating the interaction between intestinal fibroblasts and T lymphocytes may recover intestinal homeostasis in cirrhosis.

THU-175

Characterising renal dysfunction in chronic liver disease rodent models

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Background and aims: Acute kidney injury (AKI) in patients with cirrhosis carries significant morbidity and mortality and accounts for 20% of acute decompensation admissions. However, currently we lack well characterized models to study renal dysfunction in chronic liver disease, necessary to explore targets for new interventions. This study characterises renal dysfunction in known rodent models of chronic liver disease.
Method: 5 rodent models were selected which included 3 models of acute on chronic liver failure (ACLF): bile duct ligation (BDL) rat with addition of lipopolysaccharide (BDL+LPS); carbon tetrachloride (CCL4) mouse model with addition of lipopolysaccharide (CCL4 +LPS); combined western and alcohol diet (WD+ETOH) with alcohol binge (WD+ETOH+Binge). In addition, 2 chronic fatty liver disease models: high fat high cholesterol rat (HFHC) and amylin liver NASH (ALNM) mouse model. All models had a control group. A minimum of 4 animals were assessed in each group. 6 parameters were assessed including Periodic Acid Schiff (PAS) for macrostructural analysis, neutrophil gelatinase-associated lipocalin (NGAL) for tubular damage, macrophage marker CD68, apoptosis marker cleaved caspase 3 (CC3), proliferation marker Ki-67 and Picro Sirius Red (PSR) for collagen deposition. 4 micrometre kidney slices were cut

from paraffin blocks. PAS and PSR stains were performed according to protocol. IHC was performed with CD68, Ki-67, CC3, and NGAL primary antibodies. Tissue was reviewed at x20 microscopic field and analysis performed using Image J, with the analyser blinded to group. Statistical analysis was performed using STATA and GraphPad.
Results: There was a statistically significant increase in NGAL between control and BDL+LPS models (Control vs BDL+LPS p = 0.013,). This was also demonstrated in the WD+ETOH model but was not statistically significant (Control vs WD+ETOH+Binge p = 0.18, WD +ETOH vs WD+ETOH+Binge p = 0.26). The BDL model also demonstrated an increase in CD68 positive cells with increasing severity of model (Control vs BDL+LPS p = 0.043). The majority of models also demonstrated an upward trend between number of glomerular nuclei and increasing model severity suggesting an influx of inflammatory cell types. Ki-67, CC3 and PSR staining did not yield any significant findings across the models.
Conclusion: The results suggest that there are heterogenous structural changes in the kidneys of chronic liver disease models to varying degrees. The BDL model appears to show the most quantifiable changes of severe kidney injury, followed by the ETOH +WD model using the parameters studied. Further work is needed to best exemplify a translational model of renal dysfunction in chronic liver disease, to enable assessment of drug targets and response to intervention, in order to improve clinical outcomes and treatment options in cirrhosis induced kidney injury.

THU-176
Sex-specific differences in preclinical models of advanced chronic liver disease and portal hypertension

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Background and aims: Cirrhosis is a major health concern, but sex-specific differences in its pathophysiology remain unclear. Preclinical studies mainly focused on male animals, limiting translational applicability. This project aimed to comprehensively characterize cirrhotic portal hypertension in male and female rats to understand sex complexities and potential implications. Human relevance was assessed by analyzing two well-defined patient cohorts.
Method: Advanced chronic liver disease (ACLD) was induced in male and female Sprague-Dawley rats by thioacetamide administration (TAA, 250 mg/kg; 12 weeks) or common bile duct ligation (BDL, 28 days). Healthy rats served as controls (n = 15/group). *In vivo* hepatic and systemic hemodynamic (mean arterial pressure; portal pressure, PP; portal flow, intrahepatic vascular resistance), hepatic microvascular function, and general parameters were assessed. Hepatic tissue underwent transcriptomic analysis, including an assessment of sex-specific differences in pathways and cellular composition using gene deconvolution (n = 5/group). Bioinformatic analyses were performed in transcriptomic data from patients' cohorts (GSE: 84044 & 162694).
Results: As expected, animals with ACLD exhibited portal hypertension. TAA males had similar PP to females, whereas BDL males had higher PP than BDL females. There were no differences in other hemodynamic parameters. In the BDL model, females exhibited more fenestrae and porosity, and less fibrosis. Transcriptomic analysis in TAA revealed males had dysregulated pathways in metabolism, while females showed deregulated genes in hormone signaling. In the BDL model, males had higher deregulation in platelet activation, protein degradation regulation, vesicular transport, and disease-related pathways. Gene deconvolution revealed that male rats had a more specialized endothelial phenotype at baseline than females, with greater changes in endothelial and macrophage phenotypes after injury. In MASLD patients, men had dysregulated pathways involved in metabolism, while women showed dysregulated genes in fibrosis, extracellular matrix, and endocrine regulation. In HBV patients, men exhibited more dysregulation in fibrosis, extracellular matrix, inflammation, immune response, cellular alterations, and disease-related pathways. No sex differences in cellular populations were observed in HBV cirrhotic patients. However, female MASLD patients had more activated HSCs and greater loss of healthy endothelial cells compared to men, suggesting these changes could stem from inherent metabolic pathway differences described above.
Conclusion: This study defines the molecular sex differences in the pathophysiology of cirrhosis. Further research in preclinical and human liver disease is essential to accelerate the development of safe and effective treatments for ACLD in both sexes.

THU-177
Albumin as a therapeutic target for endothelial dysfunction in patients with decompensated cirrhosis

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Background and aims: Endothelial cell (EC) dysfunction is a critical driver of disease progression in patients with liver cirrhosis, contributing to acute decompensation (AD) and acute-on-chronic liver failure (ACLF). The administration of human albumin in cirrhotic patients with hypoalbuminemia has been shown to improve EC function. However, the direct effects of albumin on ECs in cirrhosis are unknown. Furthermore, it is unknown which patient category might benefit from albumin treatment. This study investigates *ex vivo* the impact of human albumin administration on ECs exposed to plasma derived from patients with different stages of cirrhosis, in order to explore the mechanisms underlying its protective effects and therapeutic response.
Method: A high-throughput *in vitro* EC model was used to observe EC responses to patient-derived plasma with or without albumin administration. Cultured human umbilical vein ECs were exposed to plasma from patients with decompensated cirrhosis and hypoalbuminemia (serum albumin < 30 g/L, n = 20), patients with compensated cirrhosis (serum albumin >30 g/L, n = 20), or healthy controls (n = 20). Albumin was administered to the plasma samples of patients with decompensated cirrhosis and healthy controls, aiming at physiological levels (~40 g/L) in patients with decompensated cirrhosis and similar doses to samples of healthy controls resulting in supraphysiological levels. The modulatory effects of albumin on EC activation were tested for well-described circulating factors involved in EC dysfunction (lipopolysaccharide (LPS), TNFα and bilirubin). Multiple cellular components were investigated using high-content imaging and multivariate analysis.
Results: Factor analysis identified mitochondrial morphology as a key feature responsible for the discrimination between patients with decompensated cirrhosis from those with compensated cirrhosis and healthy controls. Multivariate analysis revealed that albumin administration shifted EC morphology in plasma of decompensated cirrhosis toward a healthier phenotype, resembling the plasma of patients with compensated cirrhosis and healthy controls. No significant shifts in morphology were observed upon titration of albumin to ECs stimulated by LPS, TNFα or bilirubin.

Conclusion: Plasma from patients with decompensated cirrhosis and hypoalbuminemia induces important morphological changes to ECs, of which changes in mitochondrial morphology are most discriminative. Albumin administration reduces EC activation and dysfunction induced by plasma from patients with decompensated cirrhosis and hypoalbuminemia. These data underline the crucial role of albumin in EC function and point towards a potential therapeutic role of albumin in reducing vascular dysregulation and liver disease progression. Further research is required to explore the potential of this assay in predicting therapeutic responses to albumin.

THU-178

Siglec-5 is a functional biomarker that contributes to poor prognosis in patients with liver cirrhosis

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Background and aims: Patients with liver cirrhosis suffer from immune dysfunction. However, the mechanisms by which cirrhosis-associated immune dysfunction contributes to the difficulty in controlling infections and the progression of liver cancer remain unclear. Sialic acid-binding immunoglobulin-like lectin-5 (Siglec-5), an immunosuppressive molecule expressed on immune cells, has both a membrane-bound form and a soluble form (sSiglec-5) present in the blood. High levels of sSiglec-5 have been reported in sepsis, colorectal cancer, and lung cancer patients, where it is associated with poor prognosis. We aimed to clarify the significance of Siglec-5 as a biomarker and functional molecule in patients with liver cirrhosis.
Method: The expression of membrane-bound Siglec-5 on peripheral blood mononuclear cells (PBMCs) was analyzed using mass cytometry in patients with chronic liver disease and healthy volunteers (HV). Siglec-5 expression on various immune cell subsets was evaluated. The factors inducing Siglec-5 and the functional significance of sSiglec-5 were investigated in vitro. Additionally, the relationship between sSiglec-5 and prognosis was analyzed in 103 patients with cirrhosis and HCC undergoing transarterial chemoembolization (TACE) and 124 patients undergoing living donor liver transplantation (LDLT).
Results: Membrane-bound Siglec-5 on monocytes was significantly elevated in patients with live cirrhosis (F4) as compared with those with chronic hepatitis (F0-3) and HV. Serum sSiglec-5 levels were comparable between F0-3 patients and HV but were markedly elevated in F4 patients. The expression of membrane-bound Siglec-5 on monocytes strongly correlated with serum sSiglec-5 levels. In vitro, monocytes and macrophages stimulated with LPS or TNF-α/IL-1β showed increased expression of Siglec-5, accompanied by elevated sSiglec-5 levels in the culture supernatant. These findings suggest a mechanism underlying the elevated membrane-bound Siglec-5 on monocytes and serum sSiglec-5 observed in cirrhotic patients, potentially driven by gut barrier dysfunction. The addition of sSiglec-5 to PBMC cultures induced upregulation of the immunosuppressive molecule TIM-3 on CD8+ T cells, reduced their proliferation capacity, and impaired their cytotoxic activity. Patients with high serum sSiglec-5 levels demonstrated worse survival rates after TACE for cirrhosis with HCC. Similarly, in LDLT recipients, high sSiglec-5 levels were associated with increased sepsis incidence and reduced survival rates. These results suggest that sSiglec-5 negatively regulates CD8+ T cell activity as a functional molecule.
Conclusion: Siglec-5 derived from monocytes/macrophages impairs T cell function and is associated with poor prognosis in patients with liver cirrhosis.

THU-179-YI

Comparison of hepatocellular carcinoma risk scores in people with cirrhosis: concordance analysis of four prediction tools

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Background and aims: People with liver cirrhosis are at high risk of hepatocellular carcinoma (HCC). Several HCC risk stratification models have been developed, but no single one has yet been sufficiently validated for adoption in clinical practice. The aim of this study was to conduct an analysis of the concordance of HCC scores.
Method: Four HCC risk scores were identified from the literature (aMAP, ADRESS-HCC, THRI, and FASTRAK) and calculated using baseline data from 151 people with cirrhosis participating in local studies. Participants were categorized into low risk (LR), intermediate risk (IR), and high risk (HR) groups according to the HCC risk scores. Available data included age, sex, race, body mass index (BMI; kg/m²), diabetes status, liver disease etiology, platelet count (10^3/L), gamma-glutamyl transferase (GGT; IU/L), alpha-fetoprotein (AFP;ng/mL), and ALBI (Albumin-Bilirubin) score. Visual methods were used to evaluate the distribution of the scores in each risk category, and kappa values were calculated using GraphPad software to assess the agreement between scores.
Results: The cohort had a median age of 60 years (IQR 21–79.9), with 60% male and 99% Caucasian. The median BMI was 29.4 kg/m² (IQR 17.1–43.4), and 36% had diabetes. Metabolic-associated steatotic liver disease (MASLD) was the most common liver disease etiology (31%). Risk categorization according to the HCC scores was as follows: aMAP classified patients into HR (53.6%), IR (29.8%), and LR (16.6%); ADRESS-HCC categorized 24% of patients as HR, 49.7% as IR, and 26.3% as LR; THRI identified 41.7% of patients as HR, 46.4% as IR, and 11.9% as LR; and FASTRAK classified patients as HR (36.4%), IR (27%), and LR (36.6%). Kappa statistics were calculated to assess agreement among aMAP, ADRESS-HCC, THRI, and FASTRAK models. The values were as follows: aMAP vs. ADRESS-HCC: 0.286 (fair agreement), aMAP vs. THRI: 0.497 (moderate agreement), aMAP vs. FASTRAK: 0.327 (fair agreement), ADRESS-HCC vs. THRI: 0.392 (moderate agreement), ADRESS-HCC vs. FASTRAK: 0.201 (fair agreement), and THRI vs. FASTRAK: 0.247 (fair agreement). Among these comparisons, the highest kappa value was between aMAP and THRI (0.497; moderate agreement), indicating the strongest concordance in risk stratification. The lowest kappa value was between ADRESS-HCC and FASTRAK (0.201; fair agreement), reflecting significant differences in their classifications.
Conclusion: Our results indicate considerable variability in risk stratification across models. This highlights a clinical need for prospective studies that follow up people with cirrhosis for HCC development and include validation of existing HCC risk prediction models. Such validation would serve as external corroboration and facilitate clinical adoption of these models.

THU-180-YI

Toll-like receptor 4 inhibition restores cytochrome C oxidase mitigating hyperammonemia-induced hepatocyte mitochondrial dysfunction

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Background and aims: Hyperammonemia has been demonstrated to induce mitochondrial dysfunction in hepatocytes, with a particular impact on oxidative phosphorylation (OXPHOS). While inhibition of Toll-like receptor 4 (TLR4) has shown potential in preserving mitochondrial stability, supporting urea cycle enzyme (UCE) function, and reducing oxidative stress, the underlying mechanisms remain unclear. This study investigates how TLR4 inhibition can restore mitochondrial function under hyperammonemic conditions.
Method: Hyperammonemia was induced in wild-type (WT) and TLR4 knock-out (TLR4KO) mice via a 14-day amino acid (AA) diet. WT-AA mice were treated with either the TLR4 antagonist, TAK-242 (10 mg/kg i.p.) or the ammonia scavenger Ornithine Phenylacetate (OP, 300 mg/kg i.p.) from days 10 to 14. Liver transcriptomic analysis was performed using whole RNA sequencing, with specific focus on OXPHOS genes. Data were analysed with KEGG and Gene Ontology databases. Liver qPCR and western blot were used to confirm related genes and proteins. Quantitative activity of cytochrome C oxidase in isolated hepatocyte mitochondria was assessed using spectrophotometric enzyme assay.
Results: WT-AA mice exhibited significantly elevated ammonia levels compared to controls (333.4 ± 54.5 vs. 47.0 ± 11.9 micromol/L, $p < 0.0001$), which were markedly reduced by both TAK-242 and OP treatment (121.1 ± 51.5 and 131.6 ± 79.8 micromol/L, respectively, $p < 0.0001$). Transcriptomic analysis revealed that, among all five OXPHOS complexes, only complex IV (cytochrome C oxidase) was significantly affected by hyperammonemia, with marked upregulation of cytochrome C oxidase subunit genes (Cox6a2, Cox6b2, Cox7a1, Cox4i2, Cox8b), which normalised following TAK-242 treatment (all $p < 0.001$). These changes were aligned with increased protein expression of cytochrome C oxidase subunits (all $p < 0.05$). Mitochondrial cytochrome C oxidase activity assays further confirmed significantly elevated enzyme activity in WT-AA mice compared to controls (52.6 k/min/mg vs. 33.8 k/min/mg, $p = 0.012$), which was significantly reversed by TAK-242 (39.1 k/min/mg, $p = 0.028$) but remained unchanged with OP treatment (58.5 k/mg/min, $p = 0.906$). Notably, TLR4KO mice showed no changes in cytochrome C oxidase gene or protein expression, nor in enzyme activity, regardless of the AA diet.
Conclusion: Our findings demonstrate for the first time that hyperammonemia drives mitochondrial dysfunction by selectively upregulating cytochrome C oxidase subunits, which are critical for mitochondrial OXPHOS function. TLR4 inhibition effectively mitigates this dysregulation, stabilising mitochondrial bioenergetics and preserving UCE activity. These results suggest that TLR4 antagonist may offer a promising therapeutic approach for hyperammonemia by restoring cytochrome C oxidase regulation.

THU-181

Plasma-induced neutrophil dysfunction is a novel approach to identification of acutely decompensated cirrhosis patients at risk of infection

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Background and aims: Bacterial infection is an important cause of acute decompensation (AD) in cirrhotic patients and further complicates their clinical course and increases mortality. Previous studies have demonstrated significant neutrophil defects in patients with AD and their potential role in identifying the risk of new infection. This study aimed to validate plasma-induced dysfunction of healthy neutrophils (PIND) as a predictor of subsequent infection risk and 90-day mortality.
Method: A total of 160 patients with AD [117 without ACLF (AD-NoACLF) and 43 with ACLF (AD-ACLF)] were prospectively recruited from two tertiary liver units. Plasma samples from 21 healthy controls (HC) and 74 patients with stable compensated cirrhosis were used as controls. Neutrophils isolated from HC were co-incubated with patient plasma and assessed for oxidative burst, reactive oxygen species (ROS) production, and phagocytic capacity. Neutrophils were stimulated with phosphate-buffered saline (constitutive), N-formyl-Met-Leu-Phe (fMLP), opsonised bacteria (*E. coli*), or phorbol 12-myristate 13-acetate (PMA) for 20 minutes prior to flow cytometry analysis. Cell surface expression of CD62L in neutrophils was measured by fluorescence-activated cell sorting (FACS) and reported as geometric mean fluorescent intensities (GMFI).
Results: Neutrophils exposed to plasma from patients in both the AD-NoACLF and AD-ACLF groups showed significantly increased constitutive ROS production (119.4 ± 17.2% in AD-NoACLF and 115.1 ± 23.1% in AD-ACLF, $p < 0.0001$) and fMLP-induced ROS production (128 ± 14.5% in AD-NoACLF and 142.7 ± 35.9% in AD-ACLF, $p < 0.01$) compared to controls, indicating a primed state. However, there was a significant reduction in PMA-induced ROS production (−8.2 ± 4.9% in AD-NoACLF and −25.9 ± 6.9% in AD-ACLF, $p < 0.05$), phagocytic activity (−48.1 ± 4.0% in AD-NoACLF and −54.2 ± 5.4% in AD-ACLF, $p < 0.001$), and CD62L expression [GMFI 449 (95% CI 225–857) in AD-NoACLF and GMFI 423 (95% CI 229–713) in AD-ACLF, $p < 0.0001$). Among AD-NoACLF patients, *E. coli*-induced ROS production was predictive of subsequent infection [AUROC 0.75 (95% CI 0.62–0.87), $p < 0.001$], while PMA-induced ROS production was associated with 90-day mortality ($p = 0.035$). In contrast, none of the other neutrophil function assays were predictive of clinical outcomes in patients with AD-ACLF.
Conclusion: Multiple aspects of normal neutrophil function are impaired by plasma from AD-NoACLF patients, which are associated with an increased risk of subsequent infection and 90-day mortality. The observed phenotype is priming of neutrophil response with a

paradoxically reduced capacity to respond to stimuli and perform phagocytosis. PIND could be further developed as a biomarker to allow identification of patients at risk of new infection and complement existing prognostic scores to enhance identification of those at risk of death.

THU-182

Transcriptomic and metabolic insights into hyperammonemia: the complementary therapeutic roles of toll-like receptor 4 inhibitor and ornithine phenylacetate

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Background and aims: Hyperammonemia is a critical issue in patients with liver disease, where elevated ammonia levels predict mortality and a reduction in ammonia levels is linked to improved survival. Despite this, no effective therapies are available, highlighting an unmet clinical need. Previous studies have identified toll-like receptor 4 (TLR4) as a potential therapeutic target for hyperammonemia by modulating mitochondrial function. This study aims to explore the therapeutic potential of TLR4 inhibition and the ammonia scavenger Ornithine Phenylacetate (OP) through transcriptomic analysis to identify pathways for targeted treatment strategies.
Method: A wild-type (WT) mouse model was studied using a two-week amino acid-enriched diet (AA) to induce hyperammonemia. During the last four days, mice were treated with either the TLR4 antagonist TAK-242 (10 mg/kg, i.p.) or the ammonia scavenger OP (300 mg/kg, i.p.). TLR4 knock-out (TLR4KO) mice, fed the same diet, were included for comparison. Liver transcriptomic analysis was performed using RNA sequencing to investigate key metabolic pathways, including the urea cycle, tricarboxylic acid cycle, oxidative phosphorylation (OXPHOS) complexes, and oxidative stress pathways. Gene expression changes were reported as log2 fold change (FC).
Results: Ammonia levels were significantly elevated in WT-AA mice compared to controls (333.4 ± 54.5 vs. 47.0 ± 11.9 micromol/L, $p < 0.0001$). Both TAK-242 and OP treatments effectively reduced ammonia levels to 121.1 ± 51.5 micromol/L and 131.6 ± 79.8 micromol/L, respectively (both $p < 0.0001$). In contrast, ammonia levels in TLR4KO mice remained low despite the AA diet. Among all metabolic pathways, hyperammonemia in WT-AA mice significantly impacted the OXPHOS complex IV [Cox7a1 (FC 2.19, $p < 0.001$) and Cox6b2 (FC 2.15, $p = 0.006$)] and the urea cycle pathways [Ass1 (FC 1.15, $p = 0.018$), Asl (FC 0.72, $p < 0.001$), and Glul (FC −1.45, $p < 0.001$)]. Both TAK-242 and OP treatment reverted Cox6b2 and Glul expression [*TAK-242*: Cox6b2 (FC −1.64, $p = 0.031$), Glul (FC 1.49, $p < 0.001$); *OP*: Cox6b2 (FC −2.44, $p = 0.001$), Glul (FC 1.51, $p < 0.001$)]. Additionally, Cox7a1 was downregulated in the TAK-242 group (FC −0.76, $p = 0.029$), while Oscp1 was downregulated in the OP group (FC −1.91, $p = 0.021$) indicating distinct mechanisms of action for each treatment. Notably, TLR4KO mice exhibited gene expression changes consistent with a combined effect of TAK-242 and OP treatment.
Conclusion: Transcriptomic analysis revealed that TLR4 plays an important role in mediating metabolic and mitochondrial dysfunction induced by hyperammonemia. The shared and distinct gene expression changes observed with TAK-242 and OP treatments highlight complementary mechanisms, which could be leveraged for more effective therapeutic strategies.

THU-183-YI

Mesenchymal stem cells restore gut-liver axis integrity by targeting intestinal barrier dysfunction and MLN inflammation in cirrhotic mice

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Background and aims: Intestinal and mesenteric lymph nodes (MLNs) inflammation along with loss of intestinal epithelial integrity and gut dysbiosis, accounts for increased enteric bacterial translocation (BT) to liver (a hallmark of cirrhosis that drive liver injury) and systemic inflammation in cirrhosis. Till date there is no available treatment to augment intestinal and MLN inflammation in cirrhosis. This study aims to evaluate the therapeutic potential of mesenchymal stem cells (MSCs) in mitigating intestinal and MLN inflammation, their impact on liver injury/repair in murine model of CCl4 induced cirrhosis.
Method: Cirrhosis was induced in C57BL/6 mice through intraperitoneal (i.p.) injections of carbon tetrachloride (CCl4, 0.1–0.5 ml/kg) 10 weeks. Histological and molecular analyses were used to evaluate intestinal injury, tight junction protein (TJP) expression. Immune cell populations in MLNs were quantified. Gut permeability and BT were assessed via serum endotoxin and IgG+ gut bacteria. Biodistribution of i.p. and intravenously (i.v.) administered MSCs was analyzed in vivo and ex vivo. Therapeutic effects of MSCs on intestinal injury, MLN inflammation and liver function markers were evaluated 7 and 11 days post treatment.
Results: Animals with chronic liver injury exhibited significant increases in intestinal injury [villus blunting, immune infiltration, and reduced TJPs: OCLN (2.8 fold, $p < 0.01$) and Zo-1 (2.6 fold, $p < 0.001$)], MLN inflammation [elevated CD3+ (1.3 fold, $p < 0.01$), CD4+ (1.2 fold, $p < 0.05$), CD8+ (1.2 fold, $p < 0.01$), B cells (1.3 fold, $p < 0.01$)], and reduced enteric BT (IgG^+ gut bacteria, $p < 0.01$), particularly during transition from fibrosis to cirrhosis. Initial assessment of MSC administration routes revealed that i.v. infused MSCs primarily localized to the lungs, liver, and spleen, while i.p. infused MSCs preferentially localized to the MLNs, intestine and liver, persisting for up to 21 days. MSC therapy via the i.p. route significantly alleviated intestinal injury (reduced villus blunting, immune infiltration, and increased TJPs [OCLN (4.2 fold, $p < 0.01$) and Zo-1 (6 fold, $p < 0.01$)], MLN inflammation [reduced CD3+ (0.77 fold, $p < 0.001$), CD8+ (0.86 fold, $p < 0.001$), B cells (0.6 fold, $p < 0.01$)], and reduced enteric bacterial translocation ($p < 0.01$). It also significantly reduced liver fibrosis ($p < 0.001$), liver enzymes AST ($p < 0.001$) and ALT ($p < 0.01$), and restored TJP expression. While i.v.-MSC therapy significantly reduced liver fibrosis and liver enzyme levels compared to i.p.-MSC therapy, it failed to alleviate intestinal injury, MLN inflammation, or enteric bacterial translocation.
Conclusion: Intra peritoneal MSC therapy ameliorates both intestinal and hepatic injury in cirrhotic mice by reducing MLN inflammation, improving intestinal barrier integrity, mitigating bacterial translocation, and restoring liver repair. These findings highlight the potential of MSCs as a therapeutic strategy for management of gut liver axis complications in cirrhosis.

THU-184

Synergy between ornithine phenylacetate and strategies targeting endotoxemia with either a toll-like receptor 4 antagonist (TAK-242) or Yaq-001 for the treatment of hyperammonemia in cirrhosis and ACLF

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Background and aims: Ammonia, accumulates in the blood of patients with cirrhosis, playing a critical role in the development of hepatic encephalopathy (HE). Elevated plasma ammonia levels correlate strongly with disease severity and poor prognosis. Endotoxemia is a feature of decompensated cirrhosis, which worsens hyperammonemia and acts synergistically with it to produce HE. Bacterial infection worsens hyperammonemia and is a common precipitant of HE, Therefore, this study investigated whether targeting ammonia and endotoxin or its signalling would act synergistically to reduce ammonia and prevent HE in rodent models of cirrhosis and acute-on-chronic liver failure (ACLF).
Method: Animal model: Sham or 4-week bile duct ligation (BDL) rat model with or without lipopolysaccharide (LPS) to mimic cirrhosis or ACLF (Total, n = 82; 10-groups). Treatments: 1. Ornithine phenylacetate (oral OP, ammonia scavenger, administered for 5-days prior to sacrifice) or Placebo; 2. OP + Toll-like 4 antagonist (intraperitoneal TAK-242, administered prior to LPS) or Placebo; 3. OP + Yaq-001 (oral, a gut-restricted carbon bead adsorbent, administered for 2 weeks prior to sacrifice) or Placebo. Consciousness was monitored for 6-hours in the ACLF model. Animals were sacrificed after observation, and plasma samples were collected for biochemical analysis.
Results: Ammonia levels were significantly elevated in the BDL group (82.5 ± 14.7 µmol/L) compared to Sham (26.7 ± 3.0 µmol/L, $p < 0.001$) and were markedly higher after LPS injection (280.5 ± 38.7 µmol/L, $p < 0.001$ vs. Sham). OP or TAK-242 monotherapy reduced ammonia levels in BDL (53.1 ± 10.3 and 59.6 ± 7.6 µmol/L, $p = 0.002$ and $p = 0.019$) and BDL+LPS models (145.9 ± 28.4 and 130.5 ± 32.2 µmol/L, $p < 0.001$ for both). Combined OP and TAK-242 therapy further lowered ammonia levels (73.4 ± 11.5 µmol/L, $p < 0.001$) in BDL+LPS model. Clinically, 100% of BDL+LPS rats developed coma within 6 hours. Monotherapy with OP and TAK-242 improved coma-free survival to 62.5% ($p = 0.026$) and 75.0% ($p = 0.007$), while combined therapy achieved 100% coma-free survival ($p < 0.001$ vs. untreated). Yaq-001, reduced ammonia levels in BDL rats (82.5 ± 14.7 µmol/L to 60.8 ± 9.0, $p = 0.004$), which was normalised when combined with OP (35.9 ± 4.9 µmol/L, $p = 0.001$). Blood urea levels increased in BDL+LPS rats treated with TAK-242 alone (8.7 ± 1.5 mmol/L) or combined with OP (8.4 ± 1.9 mmol/L), compared to untreated animals (6.9 ± 1.1 mmol/L, $p = 0.006$ and $p = 0.017$). Besides, compared with untreated models, all the therapies reduced the alanine-aminotransferase (ALT) levels ($p < 0.05$ for all).
Conclusion: Dual targeting of ammonia and endotoxins are synergistic in reducing ammonia levels, enhancing ureagenesis, ameliorating liver injury and preventing coma in ACLF animals. This combined approach should be explored in clinical trials for managing hyperammonemia and HE in ACLF.

THU-185

Neuropathological basis of brain failure in acute-on-chronic liver failure (ACLF): insights into the roles of hyperammonaemia and neuroinflammation

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Background and aims: Brain failure is a component of acute-on-chronic liver failure (ACLF). No treatments are available. Both hyperammonemia and systemic inflammation are pathogenically important and role of 'immunopathology' unknown. Given the heterogeneity of ACLF, clinical manifestations and underlying mechanisms of HE in ACLF are likely to be different. This study aimed to characterize the clinical symptoms and neuropathological features in ACLF rodent models and the role of hyperammonemia.
Method: *Animal models*: ACLF – 4 wk bile duct ligation (BDL) rat model+lipopolysaccharide (LPS); 6-wk carbon tetrachloride (CCl4) mouse+LPS. Hyperammonemia: Administering an amino acid (AA) mixture (1:2 ratio); 14-days. Consciousness was monitored in ACLF models. Three behavioral tests were performed in the hyperammonemic animals. Brains were obtained at sacrifice and neuronal loss and neuroinflammation were evaluated with immunohistochemistry using neuronal nuclei (NeuN), Ionized Calcium-Binding Adapter Molecule 1 (IBA-1, specific for microglia) and Glial Fibrillary Acidic Protein (GFAP, specific for astrocytes).
Results: BDL ACLF animals developed severe coma. Ammonia levels were significantly elevated (Sham: 46.5 [44.1–49.2], BDL: 100.6 [36.9–164.2], BDL+LPS: 340.4 [244.5–532.4] µmol/L, $p = 0.033$). Systemic inflammation markers, including TNF-α, IL-1β, IL-6, IL-10, and IFN-γ increased remarkedly. Histologically, hippocampal microglial loss was noted (percentage of IBA positive areas in hippocampus (%), Sham: 21.15 (18.55–30.84), BDL 14.09 (10.40–22.79), BDL+LPS 12.98 (10.04, 15.68), $p = 0.033$), while astrocyte and neuronal numbers in the hippocampus, cortex, and cerebellum remained unchanged. In the CCl4 ACLF, animals exhibited reduced activity post-LPS injection but did not develop coma, with all surviving to sacrifice at 24-hours. Unlike BDL+LPS animals, microglial activation and increased microglia numbers were observed in the hippocampus (percentage of IBA positive areas in hippocampus (%), vehicle: 8.66 ± 1.92, CCL4+LPS: 15.54 ± 2.44, $p = 0.019$). The expressions of NeuN and GFAP remained similar between vehicle and CCL4+LPS groups. In the pure hyperammonemia models, the ammonia level was significantly increased with AA diet (NP:46 ± 6.33, AA: 86.0 ± 26.7, $p = 0.004$). However, mice on the AA diet showed no behavioral differences, nor any neuroinflammatory or neuronal markers in any brain regions.
Conclusion: The results provide novel insights into the brain immunopathology in ACLF demonstrating distinct clinical manifestations and neuroinflammatory responses attributable partially to hyperammonemia and to neuroinflammation. Hyperammonemia alone was insufficient to induce neurobehavioral or neuroinflammatory changes. Therapeutic approach to brain failure in ACLF will require combinatorial approaches targeting ammonia and inflammation.

THU-186-YI

Endotoxin induced Liver sinusoidal endothelial cell metabolic reprogramming promotes vascular dysfunction and contribute to portal hypertension in experimental cirrhosis

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Background and aims: Liver sinusoidal endothelial cells (LSECs) act hepatic gatekeeper and first to encounter pathogens and xenobiotic due to gut barrier dysfunction in cirrhosis. Sepsis in cirrhosis

aggravates vascular dysfunction and portal hypertension (PHT). Knowledge on LSECs metabolic dysfunction and its contribution to vascular complication in cirrhosis is limited. This study investigated the role of 6-phosphofructo-2-kinase (PFKFB3) via pharmacological modulation of PFKB3 in hepatic microvascular dysfunction during sepsis in cirrhosis and its contribution to PHT.

Method: Experimentally, sepsis was induced by caecum ligation and puncture (CLP) in non-cirrhotic and by exogenous administration of LPS in CCl4 and TAA cirrhotic animals. PFKFB3 targeted inhibition was achieved by 3PO. Controls (Ct1), Ct+ CLP(Ct2), Ct+CLP+3PO(Ct3) were compared with CCl4 cirrhotic rats (Gr1), CCl4+LPS(Gr2), CCl4+LPS +3PO(Gr3) and TAA cirrhotic rats (Tm1), TAA+LPS(Tm2), TAA+LPS +3PO(Tm3). Hepatic hemodynamic were monitored, followed by ex vivo hepatic microvascular function. Cellular, molecular, biochemical, and histological and hematological analysis were performed. Lactate, arterial blood gas, malondialdehyde and nitric oxide (NO), ROS levels were measured. In vitro monocyte adhesion on LSEC was investigated.

Results: Increased Portal pressure (PP) Ct2(+32%), Supra-mesenteric artery blood flow Ct2(+38%), and Portal Blood Flow (PBF) Ct2(+30%) ($p < 0.05$) in vs Ct1 and a marked reduction in Ct3 vs Ct2($p = 0.01$) in non-cirrhotic was observed. Raised PP Gr2(+15%) and Tm2(+18%) vs Gr1 and Tm1($p < 0.05$) and reduction in Gr3(−13%) and Tm3(−15%) ($p = 0.01$) was observed in treated group. Endothelial dysfunction was improved in Ct3, Gr3, Tm3 vs Ct2, Gr2, Tm2 respectively ($p < 0.05$). ROS and lactate levels were increased (+170%) in Gr2, (+140%) Tm2 and was further decreased (−100%Gr3), (−120%Tm3) ($p < 0.01$) upon treatment. Interestingly, increased protein expression of PFKFB3, HK1, LDH1, ICAM1, Claudin5 levels ($p < 0.01$) Gr2, Tm2 & Ct2 vs respective controls confirms metabolic reprograming, further reversal was archived upon treatment. In-vitro increased monocyte adhesion on LSEC was improved upon inhibition of PFKFB3. Periportal inflammation and immune cells infiltration was improved post treatment. Gene expression of IL1-beta, IL-6, HMGB1, DPEP1, ICAM1, TLR4, PFKFB3, HK1, Sem3A and LDH1 were upregulated in Gr2, Tm2 and Ct2 ($p < 0.05$) vs Gr3, Tm3 and Ct3.Serum levels of ALT, AST, ALP and LDH were reduced ($p < 0.05$) in Gr3, Tm3 & Ct3 vs Gr2, Tm2 & Ct2.

Conclusion: The study findings suggest endotoxemia induced metabolic reprograming in LSEC primarily mediated through PFKFB3, a key enzyme participates in energy metabolism. Pharmacological modulation of PFKFB3 restores LSECs function, alleviates vascular dysfunction and PHT, highlighting its therapeutic potential for improving hemodynamic stability and associated vascular complication precisely due sepsis in non-cirrhotic and cirrhotic liver.

THU-187

Efficacy of the apoptosis-signal-regulating kinase 1 (ASK1) inhibitor SRT-015 in in vivo and in vitro pathogen-associated molecular patterns (PAMPs)-induced disease models

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Background and aims: Patients with liver cirrhosis have an increased risk of infections and are at high risk of death from sepsis due to severe immune dysfunction, impaired liver function and altered gut microbiota and permeability. In these patients, immune dysfunction also results into a hyperinflammatory condition in the systemic circulation, as attested by elevation of circulating pro-inflammatory cytokines such as TNFalpha, IL-6 and IL-1beta, which plays a major role in the progression to acute decompensation and acute-on-chronic liver failure (ACLF). Apoptosis-signal-regulating kinase 1 (ASK1) is a key mediator of the inflammatory response, activated by reactive oxygen species produced after recognition of pathogen-associated molecular patterns (PAMPs) by toll-like receptor (TLR) family. Its phosphorylation results in activation of c-Jun N-terminal kinase (JNK) and p38 that regulate cell death and cytokine production. The aim of this study was to investigate the effects of SRT-015, a new investigational drug inhibiting ASK1, on overt activation of human blood immune cells by a variety of PAMPs, and evaluate its efficacy to counteract polymicrobial sepsis in a rodent model.

Method: Fresh whole blood from healthy volunteers was treated 4 h with TLR2 (Pam3CSK4), TLR4 (LPS *E.coli*) and TLR5 (FLA-ST) agonists in presence or not of SRT-015 (2–15 µM). In mice, sepsis was induced through Cecal Ligation and Puncture (CLP) surgery. SRT-015 (10 mg/kg BID) or vehicle was orally administered 30 min before and 5.5 h after CLP, then BID for 6 days.

Results: While cytokines levels were almost not detectable in blood from healthy volunteers, TLR activation greatly induced their secretion reaching 598 pg/ml TNFalpha, 1800 pg/ml IL-6 and 33 pg/ml IL-1beta with TLR2 agonist, 4367 pg/ml TNFalpha, 9667 pg/ml IL-6 and 3300 pg/ml IL-1beta with TLR4 agonist, 3049 pg/ml TNFalpha, 4992 pg/ml and 1148 pg/ml IL-1beta with TLR5 agonist, respectively. SRT-015 (added concomitantly or after TLRs agonists) dose-dependently reduced TNFalpha by 62%***, 30%** and 60%***, IL-6 by 31%**, 33% and 12%, and IL-1beta by 79%***, 59%*** and 91%*** after TLR2, TLR4 and TLR5 activation, respectively (***$p < 0.001$, **$p < 0.01$). In CLP mice, SRT-015 administration significantly improved the survival curves, with 65% surviving mice in SRT-treated mice vs 15% of mice in the control group, 7 days post-CLP ($p = 0.004$).

Conclusion: Although further experiments are needed to fully understand how SRT-015 improved survival in septic mice, it seems to be at least mediated by regulation of the innate immune response. These results further support the development of SRT-015 in advanced liver disease and ACLF.

THU-191-YI

Immunocompetence in outpatients and hospitalized chronic liver disease patients: gene expression profiles and cell-type estimation from stimulated whole blood

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Background and aims: Acute decompensation (AD) of chronic liver disease markedly increases patients' risk of organ failure and mortality. While systemic inflammation and immune cell dysfunction are implicated in adverse outcomes, the underlying mechanisms are incompletely understood. Utilising a combination of ex vivo whole blood lipopolysaccharide (LPS) stimulation, bulk RNA sequencing (RNA-seq), and in silico cell-type deconvolution methods, this study aimed to characterise the immunocompetence of patients hospitalised with AD in comparison to stable outpatients and healthy volunteers (HV).

Method: With NHS ethical approval (IRAS: 170839, REC: 15/LO/0800), venous whole blood samples were taken from healthy non-smoking volunteers aged 18–50 (HV, n = 5), outpatients with refractory ascites attending for day-case paracentesis (ORA, n = 5), and hospitalised AD patients (n = 10). The blood samples were treated with or without 1 ng/mL LPS for 4 hours (Enzo Life Sciences, United States). Next generation sequencing and data pre-processing were done by the Wellcome Sanger Institute. Differential expression and enrichment analyses were conducted utilising DESeq2 (v1.42.0) and clusterProfiler (v4.10.0) in the R environment (v4.3.0). Cell fractions were predicted by CIBERSORTx and differences between groups were

assessed using two-way analysis of variance (ANOVA) followed by Tukey's test.
Results: While HV responded robustly to LPS stimulation, ORA and AD patients showed markedly altered responses. Specifically, 5,404, 2,500 and 3,376 genes were identified significantly altered by LPS in HV, ORA and AD groups, respectively (padj < 0.05, with Benjamini-Hochberg correction). T cell receptor signalling and Th1 and Th2 cell differentiation pathways were enriched in the HV response but not in ORA and AD patients. Notably, only one KEGG pathway was found uniquely dysregulated by LPS in AD patients, namely glycerolipid metabolism (padj = 0.03). In silico deconvolution predictions suggested higher monocytes and far fewer CD4 and CD8 T cells and NK cells in unstimulated samples from ORA and AD patients, who also displayed markedly fewer activated dendritic cells (50.7% decreased, p = 0.001 in AD compared to HV) and far fewer eosinophils (83.0% decreased, p = 0.003 in AD compared to HV) in response to LPS stimulation.
Conclusion: Immunocompetency was impaired in both ORA and AD patients with markedly fewer activated dendritic cells and far fewer eosinophils found in response to LPS stimulation. Unique changes in glycerolipid metabolism were observed in AD patients. Ongoing work includes the validation of cell type deconvolution utilising complete blood count data and determination of cell type-specific gene expression.

THU-192
Ultrasound localization microscopy for diagnosis of clinically significant portal hypertension: a prospective multicenter study
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Background and aims: Currently, hepatic venous pressure gradient (HVPG) remains the gold standard for diagnosing clinically significant portal hypertension (CSPH), but its use is restricted by invasiveness and accessibility. This multicenter study aims to apply ultrasound localization microscopy (ULM) to visualize and quantify hepatic microvasculature in cirrhotic patients, evaluating its potential in non-invasive CSPH diagnosis.
Method: This study enrolled patients aged 17 to 80 with clinical diagnosis of cirrhosis who underwent HVPG measurement between April 2024 and November 2024 based on clinical needs. Exclusion criteria included prior hepatosplenic surgery, TIPS, SonoVue allergy, hypovolemia, and HVPG contraindications. After informed consent, patients underwent ULM, with data acquisition in the portal phase. Real-time imaging was performed, followed by offline quantitative analysis of microvessel functional and morphological parameters. HVPG ≥10 mmHg was considered the gold standard for diagnosing CSPH. The Mann-Whitney U test was used to compare microvessel parameters between the CSPH and non-CSPH groups. Spearman correlation analysis assessed the correlation between microvessel parameters and HVPG values. Simple and multiple linear regression models evaluated independent predictors of HVPG. receiver operating characteristic curve was used to assess the diagnostic performance of microvessel parameters in identifying CSPH.
Results: A total of 11 patients were enrolled, including 8 males, with an average age of 52 (range: 42–54) years. Among them, 7 had alcoholic cirrhosis (including 2 co-infected with hepatitis B), 2 had hepatitis B cirrhosis, 1 had non-alcoholic steatohepatitis, and 1 had primary biliary cirrhosis. Eight patients were diagnosed with CSPH, and 3 were non-CSPH. Compared to the non-CSPH group, the CSPH group exhibited lower vessel density (VD) (62.0 ± 11.2 vs. 43.9 ± 3.3, p = 0.002). There was a strong correlation between VD and HVPG (r = −0.93, p < 0.001), and a moderate correlation between the minimum velocity (r = −0.69, p = 0.02) and HVPG. VD was an independent predictor of HVPG (r^2 = 0.78). The diagnostic performance of VD for CSPH (AUC = 1.0, p = 0.014) was higher than that of the CSPH risk score (AUC = 0.69, p = 0.43).
Conclusion: ULM-based microvessel parameters were proposed with good diagnostic consistency for HVPG measurement.

Cirrhosis and its complications – Other clinical complications except ACLF and critical illness

TOP-219
Effect of exercise based regimen on frailty in children with liver disease-a randomized controlled trial
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Background and aims: Cirrhosis leads to reduced muscle mass and strength, limiting daily activities and impacting quality of life. Resistance training and physical exercise may improve muscle mass and functional capacity in cirrhosis. There is limited available pediatric literature on interventions to improve frailty. We performed a randomized controlled trial to study the effect of exercise-based regimen on frailty in children with cirrhotic liver disease.
Method: Children (9–18 years of age) with cirrhotic liver disease (CLD) with five fried's frailty score more than five were randomly assigned to groups that received exercise training (n = 23) or standard medical treatment (SMT) alone (n = 23). Exercise regimen included aerobic and resistance exercises for a total of at least 50 minutes per day for 3 to 5 days per week for 24 weeks. Frailty assessment was done at baseline, 12 weeks and 24 weeks while myokines, hepatokines levels and body composition analysis was evaluated at baseline and after 12 weeks.
Results: At 12 and 24 weeks, the delta change in frailty scores was significantly greater in the exercise group compared to the SMT group (mean difference (MD) −1.38, 95% CI −2.07, −0.69, p < 0.001) and (MD-2.36, 95% CI −3.3, −1.44, p < 0.001) respectively. By 12 weeks, 60% of patients in the exercise group became non-frail (frailty score less than 5), increasing to 85% by 24 weeks. In the SMT group, 32% and 37% of patients achieved non-frail status at 12 and 24 weeks, respectively. At 12 weeks, the exercise group showed a significant delta reduction in myostatin levels compared to the SMT group (p = 0.02), while no significant differences were noted for follistatin, decorin, or irisin levels. Significant improvements were observed in skeletal muscle mass and phase angle in the exercise group at 12 weeks.
Conclusion: In this pilot trial, exercise regimen significantly improved frailty scores and skeletal muscle mass compared to the SMT. Larger trials are warranted to further evaluate the long-term benefits of exercise in pediatric cirrhotic population.

TOP-220
Prevalence and clinical impact of rectal colonization by multidrug-resistant (MDR) bacteria in patients with acute decompensation of cirrhosis
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Background and aims: Infections by multi-drug resistant organisms (MDRO) are frequent and difficult to treat in patients with cirrhosis. In addition to standard risk factors (epidemiology, antibiotics/health-care exposure), colonization by MDRO may increase the risk of MDRO infections. The screening for rectal colonization by MDRO could be a valuable tool to identify patients with cirrhosis at risk for MDRO infection. This study aimed to assess the prevalence and clinical impact of rectal colonization by difficult-to-treat MDRO (carbapenem resistant [CR] *enterobacteriaceae*, CR *A. baumannii*, CR *P. aeruginosa*, vancomycin-resistant *enterocci*) in hospitalized patients with acute decompensation (AD) of cirrhosis.
Method: Patients admitted for AD underwent rectal swab screening for MDRO colonization at admission and were followed up until death, liver transplant or 90-days. The following clinical endpoints were assessed: development of MDRO infections during hospitalization; transfer to intensive care unit (ICU); development of acute-on-chronic liver failure (ACLF); in-hospital mortality; 28-day mortality; 90-day mortality.
Results: During study period 204 patients underwent rectal swab (mean age 62 ± 12 years old; 64% male, median MELD score 18) and 37 (18%) tested positive for colonization by MDRO (CR *enterobacteriaceae* accounted for 60% of cases). Patients colonized by MDRO had higher incidence of MDRO infections (29 vs 6%; p = 0.006). Almost two third of MDRO infections were sustained by the same pathogen identified in rectal swab. In multivariable analysis (adjusted by age, sex and MELD score), MDRO colonization was associated with higher risk of developing MDRO infections [HR = 5.22; p = 0.003]. Patients colonized by MDRO had higher incidence of ACLF (43 vs 21%; p = 0.009), transfer to ICU (16 vs 8%; p = 0.018) and 90-day mortality (51 vs 14%; p < 0.001). In multivariable analysis, MDRO colonization was associated with an increased risk of developing ACLF (OR = 3.50, p = 0.005), being transferred to the ICU (OR = 3.03; p = 0.016), and mortality during hospitalization (OR = 9.38; p < 0.001), as well as mortality at 28-days (sHR = 5.11; p < 0.001) and 90-days (sHR = 4.89; p < 0.001).
Conclusion: Colonization by MDRO is associated with an increased risk of developing MDRO infections, organ failures and mortality in patients with AD of cirrhosis. Rectal swab could be a valuable screening tool for the clinical management of these patients.

TOP-233-YI

Sustained improvement in minimal hepatic encephalopathy and quality of life in patients with cirrhosis through two-session fresh fecal microbiota transplantation: An open-label pilot randomized controlled trial (The FLAME trial)

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Background and aims: Fecal microbiota transplantation (FMT) is emerging as an effective treatment for hepatic encephalopathy (OHE) in patients with cirrhosis but its role in minimal hepatic encephalopathy (MHE) is unclear. We aimed to assess the efficacy of FMT in comparison to lactulose for improvement in MHE and quality of life.
Method: In this open-label pilot randomized controlled trial patients with cirrhosis and MHE were randomized to receive 2 sessions of freshly prepared FMT 4 weeks apart or daily oral lactulose. The primary outcome was MHE resolution at 12 weeks, defined by Psychometric hepatic Encephalopathy Score (PHES) ≥5. Secondary outcomes included the development of overt HE, changes in the CTP, MELD score, SF-36 score at 12 weeks and PHES scores at 4, 8, and 12 weeks. Between-group and within-group comparisons were performed.
Results: We randomized 130 patients of whom 122 were eligible for analysis (FMT:60; lactulose:62; age:44.3 ± 8.9 years; 118(96.7%) males; Child A/B/C: 54.9%/18.0%/20.5%; median MELDNa: 13 (IQR:10–17)). At 12 weeks, MHE resolution was similar in both groups (FMT:41/60(68.3%) vs lactulose:41/62(66.1%); absolute risk-difference:2.2% (95% CI: −14.4%–18.9%); p = 0.80). Both groups showed significant improvement in all components of PHES and SF-36 scores over 12 weeks. There were no differences in OHE, follow-up CTP and MELD scores. Adverse events [32(53.3%) vs 26(41.9%); p = 0.21], serious adverse events [6(10%) vs 3(4.8%); p = 0.28] and mortality [2(3.3%) vs 1(1.6%); p = 0.62] were similar.
Conclusion: Two sessions of FMT administered four weeks apart were well tolerated and resulted in MHE resolution, improved neuropsychological performance, and quality of life similar to daily oral lactulose.

TOP-234

An optimized diagnostic strategy for MHE in cirrhotic patients based on PHES normalization and Stroop-CN: a prospective multicenter study

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Background and aims: The psychometric hepatic encephalopathy score (PHES) and Stroop are widely used for diagnosing minimal hepatic encephalopathy (MHE). However, PHES requires normalization based on the healthy population, and consumes 20–30 minutes to complete. Additionally, the Stroop has limited diagnostic accuracy. Our study aims to establish an efficient diagnostic strategy that integrates the normalized PHES and adjusted Stroop method (the Stroop-CN) to accurately assess the prevalence of MHE in patients with cirrhosis.
Method: This prospective, multicenter study enrolled 1,428 healthy controls and 1,442 patients with cirrhosis from 40 hospitals. The PHES norms and Stroop-CN model were established based on healthy controls and then applied to diagnose MHE in patients with cirrhosis. The diagnostic efficacy of the combination diagnostic strategies was calculated by constructing the crosstabulation.
Results: Using the PHES norms derived from healthy controls, 24.2% (349/1442) of patients with cirrhosis were diagnosed with MHE (PHES score ≤4). In further analysis, 757 patients with available Stroop test results were divided into the test and validation cohorts. The 2-step diagnostic strategy, which integrated the Stroop-CN with a subtest from the PHES, demonstrated high discriminatory efficiency, achieving an accuracy of 0.825, sensitivity of 0.830, specificity of 0.824, positive predictive value (PPV) of 0.512, and negative predictive value (NPV) of 0.952. These results were consistent across both test and validation groups. According to this 2-step strategy, 59.6% of patients were able to avoid the full PHES assessment, resulting in a significant reduction in testing time by approximately 20–70%.
Conclusion: Our study revealed a notably significant prevalence of MHE among patients with cirrhosis based on the PHES norms

established using a large sample of healthy people. Furthermore, the optimized two-step diagnostic strategy significantly enhances diagnostic efficiency and substantially reduces testing time.

TOP-235-YI

Impact of growth hormone therapy on complications, disease severity, and frailty in decompensated cirrhosis: a randomized controlled trial

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Background and aims: Disruptions in the growth hormone (GH) and insulin-like growth factor 1 (IGF-1) axis are associated with complications and mortality in decompensated cirrhosis. This trial evaluates the effects of long-term GH therapy on IGF-1 levels, complications, and survival in patients with decompensated cirrhosis.
Method: In a single-center, parallel-group, randomized open-label randomized trial, 96 patients with decompensated cirrhosis (excluding those with HCC, PVT, AD, or ACLF) were randomized to standard medical therapy (SMT) alone (control, n = 48) or SMT plus GH (GH group, n = 48). GH was administered subcutaneously at 2 IU/day for 12 months, with dosing adjusted based on IGF-1 levels. Patients were followed monthly for one year to monitor complications (new/worsening/refractory ascites, gastrointestinal bleeding, grade ≥2 hepatic encephalopathy [HE], bacterial infections, acute kidney injury [AKI] stage ≥1B, ACLF), liver transplantation, and mortality. The primary endpoint was 12-month complication-free survival, with secondary endpoints including individual complication rates, changes in MELD and CTP scores, liver frailty index (LFI), GH, and IGF-1 levels.
Results: Median age was 47 years (IQR: 42–46.3), with 96.9% male participants. The median MELD score was 14.8 (SD: 3.76), and baseline characteristics were similar across groups. Complication-free survival was significantly higher in the GH group (59.5%) compared to controls (34.9%, p = 0.034). The GH group showed lower cumulative incidences of ascites (27.6% vs. 50.2%, p = 0.028), ACLF (2.5% vs. 22.3%, p = 0.004), and hospitalization (17.3% vs. 47.0%, p = 0.005). No significant differences were observed for HE, gastrointestinal bleeding, bacterial infections, or AKI. A trend toward better survival was noted in the GH group (86.1% vs. 70.9%, p = 0.068). No patients underwent liver transplantation.
Significant improvements in MELD and CTP scores were observed in the GH group (delta-MELD: −10.9% [−25.2 to 7.97], p = 0.007; delta-CTP: −14.3% [-28.6 to 12.5], p = 0.003), whereas no meaningful changes occurred in the control group (delta-MELD: −3.32% [-21 to 27.8], p = 0.729; delta-CTP: 0% [−16.7 to 12.5], p = 0.356). Liver frailty (LFI) improved significantly in the GH group (delta-LFI: −2.24% [−6.72 to 2.46], p < 0.001), as did IGF-1 levels (delta-IGF-1: 78.8% [12.6 to 160], p < 0.001). These improvements were significantly different from the control group for both LFI (p = 0.004) and IGF-1 (p < 0.001). GH levels showed a trend toward reduction in the GH group (p = 0.059), with no change in controls.
Conclusion: GH therapy significantly improved complication-free survival, liver frailty, disease severity, and IGF-1 levels in patients with decompensated cirrhosis. These findings highlight the potential of GH as a therapeutic strategy, warranting further exploration into its molecular mechanisms and implications for transplant outcomes.

TOP-236-YI

Neurofilament light chains and glial fibrillary acidic protein in serum for predicting post-TIPS hepatic encephalopathy

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Background and aims: Predicting the development of hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic shunt (TIPS)-insertion is challenging in routine clinical practice, and biomarkers would be desirable to identify patients at risk. This study evaluated the value of neurofilament light chains (NfL) and glial fibrillary acidic protein (GFAP) measured in serum prior to TIPS insertion for predicting post-TIPS HE.
Method: A total of 144 patients with cirrhosis from three tertiary care centers in Germany (Mainz, Hannover, Lübeck) were prospectively recruited. Patients were followed for post-TIPS HE, death and liver transplantation. NfL and GFAP levels were measured using the single molecule array technology. In a subgroup of patients from Mainz, NfL and GFAP levels were also measured longitudinally on day 30 and 180 after TIPS.
Results: Median age was 61 years (interquartile range (IQR) 53, 67), median MELD was 12 (IQR 9, 14) and Child-Pugh stages were A: 21 (15%), B: 108 (75%), C: 15 (10%). The main indications for TIPS-insertion were ascites (72%) and secondary prophylaxis after bleeding (24%). In total, 55 (38%) patients developed post-TIPS HE during follow-up, and 43 (30%) died or underwent liver transplantation. Cumulative incidence of post-TIPS HE 3 months after TIPS-insertion was 42% in patients with NfL levels above the median vs 23% in patients with NfL levels below the median (p = 0.018). In contrast, cumulative incidence of patients dichotomized by median GFAP did not differ significantly (30% vs 35%, p = 0.7). In Fine and Gray competing risk regression analyses, higher NfL levels (sHR 1.01, 95% CI 1.00–1.01, p = 0.028) were independently associated with post-TIPS HE after adjusting for relative portosystemic gradient reduction, MELD, history of HE, platelets, and age. In contrast, GFAP levels were not (sHR 1.00, 95% CI 1.00–1.00, p = 0.2). In addition, higher NfL levels were associated with a higher risk of death/ transplantation in multivariable Cox regression analyses after adjusting for MELD and age (HR 1.01, 95% CI 1.00–1.01, p = 0.027), while GFAP levels were not. In a subgroup of patients with sera available 30 and 180 days after TIPS-insertion, NfL levels were stable at day 30 and decreased at day 180, while GFAP levels did not change significantly.
Conclusion: NfL serum levels measured prior to TIPS-insertion are associated with both post-TIPS HE and prognosis. Thus, NfL may be a valuable biomarker to identify patients at high risk for poorer outcome.

SATURDAY 10 MAY

SAT-119-YI

Detection of Candida species via shotgun sequencing in patients with decompensated cirrhosis is associated with impaired survival and higher risk of acute-on-chronic liver failure

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Background and aims: Patients with decompensated liver cirrhosis exhibit alterations in the gut and oral microbiome, leading to mucosal barrier dysfunction resulting in an increased risk of infections. Dysbiosis is closely linked to an overall lower number of bacteria compared to healthy controls. This shift creates an environment where fungal organisms, particularly those of the *Candida* genus, become more abundant and are more likely to be detected, especially when highly sensitive diagnostic methods are employed. To date, the clinical relevance of the detection of fungal species in body fluids is poorly investigated. This study aims to compare the clinical outcome of cirrhotic patients with positive *Candida* detection versus those without.
Method: A number of 155 patients were enrolled in this prospective study that is part of the INFEKTA trial. Urine and ascites samples were collected from all patients when available. *Candida* detection was performed using shotgun metagenomics sequencing utilizing rapid, long-read technology for DNA analysis. Clinical data were analyzed utilizing binary logistic regression and competing risk regression analysis, considering death and liver transplantation (LTx) as competing events. All parameters demonstrating a significant association with the outcome of interest were included in the multivariable models. The study endpoints were mortality, acute kidney injury (AKI), acute-on-chronic liver failure (ACLF) and infections within 365 days after urine and ascites sample collection.
Results: Out of the 155 patients, 60 (39%) had positive *Candida* detection (Cand +) in either ascites or urine, while 95 (61%) had no *Candida* detection (Cand -) in both specimens. The overall frequency of positive *Candida* results was similar in urine (31%) and ascites (31%) samples. At timepoint of sampling, patients had comparable MELD scores (Cand +: 16 [12–21] vs. Cand -: 15 [11–21], p = 0.71) and CRP levels (Cand +: 18 [9–34] vs. 15 [7–28] mg/dL, p = 0.41). Binary logistic regression identified alkaline phosphatase as the sole variable significantly associated with *Candida* detection (OR 1.004, 95% CI 1.001–1.007, p = 0.01). However, Cand + patients demonstrated a significantly higher risk of mortality (HR 2.28, 95% CI 1.11–4.68, p = 0.03) and ACLF (HR 1.97, 95% CI 1.02–3.80, p = 0.04) compared to Cand – patients. Detection of *Candida* was not associated with the risk of AKI (HR 1.82, 95% CI 0.99–3.32, p = 0.053) or infections (HR 1.59, 95% CI 0.88–2.88, p = 0.13).
Conclusion: *Candida* species are frequently detected in the urine and ascites of patients with decompensated cirrhosis when modern, highly sensitive techniques are employed. Although its presence is not associated with the risk of infections or AKI, it is linked to an impaired survival and higher incidence of ACLF. Thus, it may serve as an indicator of inferior clinical outcome.

SAT-120
DOACs offer superior safety and survival over traditional agents in anticoagulant therapy for cirrhosis

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Background and aims: Liver cirrhosis presents a complex hemostatic balance, increasing risks of both thrombosis and bleeding. Anticoagulants like warfarin, LMWH and DOACs have been used to manage these risks, but their safety and efficacy in cirrhotic patients remain unclear. This study aims to compare the clinical outcomes of these anticoagulants in cirrhotic patients using a large-scale, real-world dataset.
Method: This retrospective cohort study utilized claim data from the Korean National Health Insurance System, encompassing 38,770 patients newly diagnosed with liver cirrhosis between 2015 and 2022. Patients were categorized based on the anticoagulant therapy they received: warfarin (n = 2,644), DOAC (n = 15,297) or LMWH (n = 20,829). Inverse Probability of Treatment Weighting (IPTW) was utilized to adjust for confounders, and survival outcomes were analyzed using Kaplan-Meier methods.
Results: Major bleeding events were more frequent in warfarin (34.93%) than in DOAC (26.33%) and LMWH (25.15%) (P < 0.001). Variceal bleeding occurred in 9.82% of warfarin users, significantly higher than in DOAC (4.75%) and LMWH (4.08%) users. Other gastrointestinal bleeding was also the most prevalent in the warfarin group (32.29%), followed by DOAC (23.67%) and LMWH (25.91%) groups. The DOAC group also had the lowest rates of liver-related complications, with hepatic encephalopathy at 2.76% and refractory ascites at 12.71%, compared to respective rates of 4.98% and 20.09% in the warfarin group. DOAC showed better 3-year (75.49% vs 67.15% or 66.37%) and 5-year survival rates (65.56% vs 57.59% or 56.64%) than LMWH or warfarin.
Conclusion: DOACs offer lower bleeding risks and better survival than warfarin, suggesting DOAC may be a safer alternative for cirrhotic patients.

SAT-121-YI
Hybrid care models in liver disease management: lessons from telemedicine during the COVID-19 pandemic

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Background and aims: COVID-19 necessitated rapid adoption of telemedicine, highlighting its role in hybrid care models for liver disease management. Patients with cirrhosis, viral hepatitis, and post-liver transplantation (LTX) care require frequent monitoring, making continuity of care essential. This study evaluated telemedicine's effectiveness and safety during the pandemic at a German tertiary center and explored its integration into future hybrid care models.
Method: In a retrospective study, we analyzed 2,557 appointments (1,963 Hepatology, 594 LTX) between March–June 2020 at University Hospital Frankfurt. Outcomes included appointment modality, adherence rates, and safety parameters. Patient characteristics and predictors of successful telemedicine implementation were assessed using multivariate analysis.
Results: Overall, 35.3% of appointments were conducted via telemedicine (40.4% Hepatology, 32.8% LTX). LTX patients were older (median 58 vs 51 years) and had more comorbidities. Among hepatology patients, chronic HBV (29.9%), MASLD (18.6%), and cirrhosis (19.3%) were most common. Routine check-ups and stable patients were managed remotely, while complex cases requiring diagnostics were scheduled in person. MASLD patients were predominantly managed remotely (46.7%), while HBV/HDV co-infected patients required in-person visits (81.8%). Telemedical adherence rates were higher than in-person visits (91.8% vs 89.4%). In LTX patients, telemedical adherence was significantly higher than in-person visits (97.9% vs 89.5%, p < 0.001). In multivariate analysis, older age (OR 1.018, p < 0.01) predicted better adherence. Hospitalization rates were low and comparable across modalities, confirming telemedicine's safety. Importantly, appointment modalities were determined by physicians based on clinical urgency, ensuring patient-centered and safe care delivery.
Conclusion: Telemedicine proved effective and safe for managing selected hepatology and LTX patients during the pandemic. Higher

adherence rates and stable clinical outcomes support its integration into routine care. A hybrid model combining remote monitoring for stable patients with in-person visits for complex cases or procedures optimizes resource utilization while maintaining quality of care.

SAT-122-YI

Acute kidney disease in acutely decompensated cirrhosis: impact on clinical outcomes

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Background and aims: Patients with cirrhosis are prone to developing kidney dysfunction, with acute kidney injury (AKI) being common and significantly affecting prognosis. In this context, the impact of acute kidney disease (AKD), whether occurring after an AKI episode (AKI-AKD) or independently (NAKI-AKD), remains poorly understood.
Method: Patients hospitalized for acute decompensation (AD) between July 2022 and November 2024 were prospectively enrolled. AKI and AKD were defined as per 2024 International Club of Ascites criteria. Follow-up ended at liver transplantation (LT) or death.
Results: A total of 307 patients were prospectively enrolled. Median age was 60 years (IQR 53–68); 71% were male. Alcohol was the most common etiology (45%) and the primary reason for hospitalization was ascites (60%). Patients were categorized as follows: no kidney disease (NKD) 111 (36%), AKI 53 (17%), AKD 81 (26%), with AKI-AKD 31 (10%) and NAKI-AKD 50 (16%), chronic kidney disease (CKD) 37 (12%), and acute-on-chronic kidney disease 25 (8%). NKD patients were significantly younger compared to all the other groups ($p < 0.05$), while median age was similar between NAKI-AKD, AKI-AKD and AKI ($p > 0.6$ for all comparisons). The proportion of patients in Child class C was higher in AKI compared to NKD and NAKI-AKD (62% *vs* 41% *vs* 38%, $p = 0.015$ and $p = 0.024$), while it was not significantly different compared to AKI-AKD (48%, $p = 0.31$). After a median follow-up of 5.8 (IQR 1.7–13.4) months, 87 (28%) patients received LT and 79 (26%) died. Following discharge from index hospitalization (282 patients), the 3-month probability of rehospitalization was 23% for NKD and NAKI-AKD, 24% for AKI-AKD and 34% for AKI (overall log-rank $p = 0.51$). The risk of new-onset CKD at 3-month after inclusion was 2/65 (3%) for NKD, 3/15 (20%) for AKI, 6/21 (29%) for NAKI-AKD and 8/15 (53%) for AKI-AKD (all groups *vs* NKD, $p < 0.05$; AKI *vs* AKI-AKD $p = 0.13$, AKI *vs* NAKI-AKD, $p = 0.71$; AKI-AKD *vs* NAKI-AKD, $p = 0.18$). The 1- and 6-month LT-free survival were: 98% and 96% in NKD, 96% and 82% in NAKI-AKD, 86% and 66% in AKI-AKD, 74% and 59% in AKI. The 6-month LT-free survival was significantly higher for NKD (log-rank $p < 0.01$ for all comparisons), not significantly different between NAKI-AKD and AKI-AKD ($p = 0.12$), significantly worse in AKI compared to NAKI-AKD (log-rank $p = 0.007$), while no significant difference was observed between AKI and AKI-AKD (log-rank $p = 0.35$).
Conclusion: AKD is common among patients hospitalized for decompensated cirrhosis, particularly the NAKI-AKD form. While AKD seems not to influence the risk of short-term rehospitalization, our data show: 1) a clear trend towards an increased risk of new-onset CKD, in particular for AKI-AKD; 2) significantly worse LT-free survival with respect to NKD; 3) similar LT-free survival rates between AKI-AKD and AKI. Overall, our preliminary findings suggest that AKD, and specifically AKI-AKD, is clinically relevant in these patients as it entails a negative impact on prognosis.

SAT-123-YI

5-year outcomes of a dedicated, multidisciplinary clinic for decompensated cirrhosis

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Background and aims: Decompensated cirrhosis is a complex multi-system condition associated with high rates of healthcare utilisation, morbidity and mortality. Multidisciplinary chronic disease collaboration is standard of care in conditions such as heart failure where it has been proven to reduce hospitalisation and mortality. There is limited evidence regarding the potential efficacy of extending such models of care to patients with decompensated cirrhosis outside of liver transplant settings. This study aims to conduct a prospective, non-randomised, single arm feasibility study to assess the impact of a multidisciplinary and multifaceted liver clinic on admission rates, liver disease severity, and survival.
Method: The Complex Liver Care Clinic (CLCC) is a multidisciplinary ambulatory care service co-designed with clinicians, researchers and patients based at a tertiary hospital in Melbourne, Australia servicing a population of 1.5 million people. The CLCC integrates clinicians (Pharmacists, Nurses, Hepatologists, Dietitians and Addiction Medicine) and day procedures (large volume abdominal paracentesis and albumin infusion). Between January 2019 and June 2024, 282 adult patients with decompensated cirrhosis were recruited following their index hospital admission to receive care through CLCC. Patients were excluded if they did not attend at least one appointment. Outcomes assessed included 12-month liver-related readmission, time to readmission, transplant free survival, and liver disease severity.
Results: A total of 282 CLCC patients were analysed: mean age 57 (±13.32 SD) years and predominantly male (61%). The median baseline Model for End-Stage Liver Disease (MELD) was 14.6 (Interquartile range (IQR): 11–18.9) and median Child-Pugh 8 (IQR: 6–9). By 3 months, there was a statistically significant reduction in median MELD to 12.8 (IQR: 9.8–16.5, $p = 0.003$) and median Child-Pugh score to 7 (IQR: 6–8, $p = 0.01$). A total of 93 patients (33%) had at least one liver related readmission within 12 months, of which 21% were due to ascites, at a median time of 88 days (IQR: 31–189) from index appointment. Child-Pugh score was identified as a statistically significant marker of 12-month re-admission (HR 1.203, $p < 0.001$). A total of 27 referrals were made for liver transplant assessment, with 9 patients progressing to transplantation at a median of 313 days (IQR: 234–733). There were 101 (36%) deaths over the follow up period at a median 388 days (IQR: 125–668). The median transplant-free survival time was 641 days (IQR: 304–1061).
Conclusion: Our 5-year study demonstrated improved clinical outcomes for patients who participated in a novel model of care for decompensated cirrhosis. There was significant reduction in liver prognostic scores by 3 months and no liver-related admission in two-thirds of patients by 12 months. We plan to conduct a larger controlled study to evaluate overall cost effectiveness of this novel model, which integrates care and the infrastructure to deliver whole of person care.

SAT-131

Physical frailty is associated with myosteatosis and physical frailty assessment tools may predict the presence of myosteatosis in liver cirrhosis

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Background and aims: Myosteatosis (MyoS) is considered a prodromal phase of sarcopenia, signaling the onset of muscle loss. Nutritional and lifestyle interventions during the MyoS stage may help prevent the progression to sarcopenia. Physical frailty (PF) is a syndrome characterized by diminished physical function and reserves, making it difficult for patients to manage stressors. This study aimed to investigate the association between PF and MyoS and evaluate whether PF assessment tools can serve as cost-effective and simple alternatives to imaging for MyoS evaluation.
Method: Skeletal muscle index (SMI) and MyoS were assessed via computed tomography (CT) at third lumbar vertebra (L3). MyoS was defined by muscle radiodensity values of < 41 Hounsfield Units (HU) for body mass index (BMI) < 24.9 kg/m² and < 33 HU for BMI ≥25 kg/m². The Liver Frailty Index (LFI) and the Short Physical Performance Battery (SPPB) were used as PF assessment tools in patients with liver cirrhosis (LC).
Results: The study included 199 consecutive patients with LC (67.3% male; median age: 61 years, IQR 52–68; MELD score: 10.5, IQR 8–16; 38.7% with compensated LC). MyoS was identified in 144 (72.4%) patients. Among those with MyoS, 52 patients (36.1%) were classified as frail using LFI (≥4.5), and 53 (36.8%) were frail according to SPPB (≤8), compared to 4 (7.3%) and 5 (9.1%), respectively, in the non-MyoS group ($p < 0.001$). LFI scores were significantly higher in patients with MyoS than in those without [median 4.195 (IQR 3.82–4.86) vs. 3.86 (IQR 3.45–4.20), $p < 0.001$]. Similar differences were observed with SPPB scores ($p < 0.001$). In multivariate analyses adjusted for age, gender, and MELD scores, LFI [HR 1.933 (95% CI 1.091–3.426), $p = 0.024$] or SPPB [HR 0.771 (95% CI 0.635–0.937), $p = 0.009$] were significantly associated with MyoS. SPPB values demonstrated the strongest correlation with HU values (correlation coefficient $r = 0.453$, $p < 0.001$), followed by LFI ($r = 0.388$, $p < 0.001$). When patients were categorized into three groups (no muscle changes, MyoS alone, and MyoS with muscle loss), PF scores worsened progressively as muscle quality and quantity declined ($p < 0.001$ for both LFI and SPPB). In receiver operating characteristic (ROC) curve analysis, SPPB exhibited adequate diagnostic accuracy for detecting MyoS (AUROC 0.701). An SPPB cut-off value of 9 yielded a sensitivity of 80.1%, specificity of 45.1%, positive predictive value (PPV) of 79.3%, and negative predictive value (NPV) of 46.3%.
Conclusion: Physical frailty was more prevalent in patients with MyoS compared to those without. PF assessed using SPPB or LFI independently predicted the presence of MyoS after adjusting for multiple covariates. PF scores worsened proportionally with declines in muscle quality and quantity. The SPPB test may serve as a surrogate marker for evaluating muscle quality.

SAT-132

Loculated ascites in the setting of spontaneous bacterial peritonitis is associated with increased morbidity and mortality

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Background and aims: Loculated ascites generally refers to ascitic fluid that is compartmentalized within the peritoneal cavity, often due to adhesions or inflammatory processes, such as infections. The presence of loculated ascites can complicate the management of cirrhotic patients by limiting paracentesis. This study sought to analyze the clinical outcomes of patients with spontaneous bacterial peritonitis (SBP) and loculated ascites at a large metropolitan area hepatology transplant center.
Method: The International Classification of Disease-10 codes for cirrhosis, SBP, and ascites were used to identify patients hospitalized from 1/1/2010–9/10/2024. Chart review via the electronic medical record was then performed using the following inclusion criteria: 1) clinical and radiographic evidence of cirrhosis with or without histology, 2) SBP confirmed with ascitic fluid polymorphonuclear cell count >250/mm³, and 3) evidence of complex loculated ascites on CT or MRI imaging. Patients with secondary bacterial peritonitis, prior liver transplant, and/or non-hepatobiliary malignancy were excluded. Descriptive statistics were used to analyze the primary endpoints of survival and major adverse liver outcome (MALO) events, along with the following secondary endpoints: length of stay (LOS), ICU admission, and escalation of antibiotic therapy.
Results: Initial database screening identified 1447 patients, of whom 28 met inclusion criteria. Average MELD score on admission and at time of SBP diagnosis was 27.5 and 30, respectively. The etiology of liver disease was highly variable, with the most common being alcohol (29%) followed by metabolic-dysfunction associated steatohepatitis (21%). The overall mortality rate for these 28 patients was 75% (21/28), with 80.9% (17/21) dying during or within 6 months of hospitalization. 50% (14/28) developed hepatic encephalopathy (HE) during admission while 64% (18/28) developed renal impairment, of whom 33% (6/18) required renal replacement therapy. Response to antibiotic therapy was limited; 93% (26/28) did not show any improvement in ascitic fluid PMN count upon follow up paracentesis. 70% (21/28) had persistent neutrocytic ascites despite antibiotic escalation in all but one patient, of which 62% (13/21) received empiric anti-fungal treatment. 46% (13/28) underwent intraperitoneal drain placement or surgical washout. The median LOS was 30 days, with 43% (12/28) requiring ICU stay.
Conclusion: Patients with decompensated cirrhosis who develop loculated ascites in the setting of SBP have a high risk of developing adverse outcomes, including renal impairment and HE. Such patients also have high mortality, which may be driven in part by infection that is refractory to antibiotic therapy. Prevention of loculation formation via earlier diagnosis of SBP followed by prompt guideline-directed antimicrobial therapy may improve outcomes.

SAT-133

Adherence to a remote monitoring platform for the liver cirrhosis population, a multicenter feasibility study

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Background and aims: Remote monitoring (RM) for liver cirrhosis patients may improve clinical outcomes through patient education, tight control and efficient communication. We designed a multicenter cohort study aimed to develop an RM platform with and for patients with (de)compensated liver cirrhosis to assess its feasibility regarding satisfaction and adherence.
Method: A stakeholder committee iteratively defined the project's goals, scope, design and content. We adapted generic content from myIBDcoach for Dutch Inflammatory Bowel Disease patients. We created an RM platform for smartphone, tablet and computer with a liver-specific monitoring module incorporating LDSI 2.0, CLDQ, QuickStroop and weight tracking together with e-learnings. Monitoring frequency was tailored to disease stage: (recent) decompensation vs. compensated state. Healthcare providers responded to alerts of exceeded thresholds within 48 hours. We conducted a prospective feasibility study in a secondary and tertiary Dutch center. Adult liver cirrhosis patients were eligible. We excluded patients with hepatocellular carcinoma, post liver transplantation or insufficient Dutch proficiency. Participants were followed for 6 months, with post-follow-up evaluations including disease outcomes, adherence, a questionnaire and interviews until data saturation. We performed subgroup analyses using Pearson Chi-Square or Fisher's Exact Tests.
Results: Of 139 screened patients, 89 were excluded due to: no consent (28%), no interest (24%), digital illiteracy (17%), language barriers (11%) or other reasons (20%). We included fifty patients, with a median age 64.0 years (IQR 57.75–67.0), the majority was male and treated in the tertiary center (both n = 32; 64%). Predominant etiologies were steatotic liver diseases (SLD, n = 27, 54%) and autoimmune diseases (n = 10; 20%). At baseline, 50% (n = 25) was decompensated, and 40 patients completed follow-up (80%). Liver-related complications occurred in 17 patients (34%), with 5 admissions, 2 liver-related deaths and 3 liver transplants. Thirty-six patients had one or more unfinished modules during follow-up (72%). Of 24 evaluation respondents, 18 patients thought the idea of RM was valuable, 5 were neutral, 1 disagreed (75%, 20.8% and 4.2%). More SLD patients had unfinished modules compared to patients with other etiologies ($p < 0.05$), although the two groups did not significantly differ in their perceived RM value ($p = 0.142$).
Conclusion: This multicenter feasibility study demonstrates moderate adherence and satisfaction to an integrative RM platform in a representative liver cirrhosis population. Patients with SLD were more likely to have one or more incomplete modules. Future research should elaborate on the patients' barriers and adherence markers through larger prospective studies to improve RM effectiveness and complication prevention.

SAT-134
Impact of parenteral nutrition on the risk of infections and the disease course of malnourished patients with decompensated liver cirrhosis

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Background and aims: Malnutrition is a common problem in patients with advanced liver disease and associated with an increase of mortality and complications of cirrhosis. Guidelines consequently recommend the early and intensive implementation of nutritional interventions, for example the initiation of (home) parenteral nutrition (HPN). However, there is a lack of evidence regarding the safety and prognostic impact of HPN on disease progression in patients with decompensated liver cirrhosis (dLC). Therefore, we aimed to investigate the impact of HPN on relevant cirrhosis-specific complications and its safety among patients with end-stage liver disease.
Method: We analyzed a number of 96 prospectively collected, consecutive patients with dLC and malnutrition who were treated at our center between 2013 and 2018. Of these, 32 patients received HPN and were compared with those patients who remained without intervention using 1: 2 propensity score matching. The primary endpoint was mortality, secondary endpoints were the incidence of infections, bloodstream infections, overt hepatic encephalopathy (oHE) and non-elective rehospitalization within 90-days of follow-up.
Results: The investigated patients had a median MELD score of 16 points at baseline. The median age was 54 years in the intervention group and 58 years in the control group. The predominant etiology of liver cirrhosis was alcohol-associated in both groups (43.7% and 57.8%).
In the competing risk analysis, no differences in mortality (HR = 1.44; $p = 0.48$) or rehospitalization rate (HR = 1.28; $p = 0.47$) were found between the groups. Patients with HPN had a significantly higher incidence (28.1%; n = 9 vs. 1.6%; n = 1) and a significantly higher risk (HR = 21.3; $p = 0.004$) of bloodstream infections compared to the control group. However, the incidence of total bacterial infections was high in both the intervention and control group (59.4%; n = 19 vs. 65.6%; n = 42), with no significant differences (HR = 0.82; $p = 0.45$) in the competing risk model. Of note, a significantly ameliorated risk for oHE was detected in the HPN group compared to the controls (HR = 0.28; $p = 0.03$) after adjusting for rifaximin treatment in the multivariable competing risk model.
Conclusion: The implementation of HPN in patients with advanced liver cirrhosis is not associated with an increased risk for overall infectious complications, although a linkage with a higher risk for bloodstream infections was detected. Furthermore, HPN may reduce the likelihood for oHE in malnourished patients with decompensated cirrhosis.

SAT-135-YI
SHiNE-UK: a national evaluation of hepatocellular carcinoma surveillance and treatment pathways

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Background and aims: Hepatocellular carcinoma (HCC) is a rapidly growing cause of cancer mortality despite advancing treatment strategies, with the mounting burden of chronic liver disease a major concern. Earlier diagnosis and improved access to curative treatments are key, with concerted efforts to achieve 'precision surveillance' via risk-prediction modelling and better diagnostics. However, low adherence to surveillance standards is widely reported, though measurement fraught with heterogeneity and limitations, fuelling the debate over its effectiveness. This study aims to evaluate the performance of current UK HCC pathways.
Method: A pan-UK multi-centre retrospective cohort study was conducted. Eligible cases were identified and local audit performed with follow up 1/1/22–30/1/24. REDCap facilitated data collection and query resolution. Analysis was performed in RStudio. Surveillance adherence was measured using a modified proportion of time covered (mPTC) method, assuming 6-months cover per test. Regression analysis was performed to identify factors associated with adherence and Barcelona Clinic Liver Cancer (BCLC) stage.
Results: A total of 68 UK hospitals participated including specialist and non-specialist liver centres. Surveillance pathways included a dedicated imaging procedure code (26%), pathway navigators (21%), interventional programmes (15%) and automated recall (9%). LI-RADS was used for ultrasound (11%) and CT/MRI (64%). Patients in surveillance (n = 1,674) had median mPTC rates of 27.5% for alpha-fetoprotein testing, 68.4% for surveillance scans, and 72.9% for all abdominal imaging. Over two years, HCC incidence in surveillance was 2.5%, with 41% at early stage (BCLC 0-A). Cumulative incidence by aMAP risk—low (0%), medium (1.1%), high (5.2%)—was significant ($p < 0.001$), with no events in the low-risk group. Among patients with incident HCC (n = 723), the rates of early-stage diagnosis (BCLC 0-A) were 44% and curative first-line treatment 27%. Only 48% had known cirrhosis and 42% were enrolled in surveillance prior to diagnosis. Presentation occurred through incidental findings (38%), surveillance (37%), and symptomatic channels (24%). The rate of first-line treatment utilisation was 79%, with frailty and HCC progression the most common reasons for non-utilisation. Absence of surveillance was significantly associated with late-stage diagnosis (BCLC B-D; $p = 0.025$).
Conclusion: This national evaluation assessed the current performance of HCC surveillance and treatment pathways in the UK. Underperformance appears to stem from a combination of failures in identifying cirrhosis and ineffective surveillance, compromising early-stage diagnosis and access to curative treatment. Future efforts should harness both service improvement and emerging innovations to improve equitable access to curative treatment.

SAT-136-YI
Identification of prognosis determining risk factors in outpatients with cirrhosis

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Background and aims: Cirrhosis is one of the leading causes of liver transplantation (LT) and mortality worldwide, so it is essential to improve prognostic assessment for better disease management and patient outcomes. Ascites, a common complication, is a sign of disease progression and poorer outcome. However, the impact of ascites volume changes over time on long-term outcomes remains underexplored. This study investigates the influence of ascites development and volume changes on transplant-free survival, with the aim of providing refined and specific thresholds.
Method: This prospective observational cohort study includes adult outpatients with cirrhosis at the LT outpatient clinic at the University Hospital Essen. Patients underwent blood analysis and detailed sonographic ascites measurements. Follow-ups at three and 12 months tracked disease progression and endpoints (death or LT). Baseline measurements and disease progression were analyzed using univariable logistic regression, repeated with delta values representing changes from baseline to follow-up. Multivariable logistic regression incorporated delta scores as independent variables, with baseline measurements, age, sex, and MELD scores as covariates. Predictive performance was assessed using AUROC, sensitivity, specificity, PPV, and NPV. Thresholds for score changes were based on ≥90% sensitivity or specificity. Nonlinear associations were visualized with spline plots using restricted cubic splines.
Results: The study includes 342 patients, 58% male patients with an overall mean MELD-Score of 12. ROC analysis showed a high predictive accuracy (AUC: 94%) for measurements in the lower abdomen. A 21 mm increase in ascites, measured in the lower abdomen, was linked to high risk (90% specificity) and increases up to 10 mm were not associated with adverse outcomes (91% sensitivity). Baseline measurements were statistically significant in predicting outcomes ($p < 0.01$). Correlations with the ICA classification suggest the following thresholds: grade 1 (≤10 mm), grade 2 (11–43 mm), and grade 3 (>43 mm), improving precision and reducing observer bias.
Conclusion: These findings highlight the prognostic significance of lower abdominal ascites measurements, underscoring the need for an objective classification of ascites volume and measurement, emphasizing the importance of documenting longitudinal changes in ascitic volumes systematically and more detailed.

SAT-137
Community-acquired infections requiring hospitalization in patients with alcohol-related cirrhosis

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Background and aims: Liver cirrhosis is associated with increased risk of bacterial infections, which also worsen the prognosis of their disease. However, there is a lack of reliable population-based data to quantify the incidence and mortality of these infections, which is crucial to contemplate future preventative measures. Therefore, we examined the incidence of community-acquired bacterial infections leading to hospitalization.
Method: In this population-based observational study, we identified all patients in the Central Denmark Region who were diagnosed with alcohol-related cirrhosis (ALD cirrhosis) between 2013–2022. We followed them from diagnosis of ALD cirrhosis until death or the end of follow-up on 31 August 2023. We computed the cumulative incidence of culture-positive bacteremia considering death a competing risk event. Further, we used the Kaplan-Meier method to compute survival from the date of positive blood culture.
Results: We included 2,525 patients with median age 61 (IQR: 54–68), 69% male. During 7,225 person-years of follow-up, 282 patients were hospitalized with a culture-positive bacteremia. 34 of these patients had more than one type bacteria in their blood, according to the positive cultures, with a maximum of 7 different bacterial agents in one patient. Of the bacteria identified, 74 (26%) were infections with Staphylococcus Aureus, 58 (21%) were Escherichia coli, 31 (11%)

were Enterococcus species, 25 (9%) were Klebsiella species, whilst 6 (2%) of the infections were with Streptococcus Pneumoniae. The risk of bacteremia was 6% after 1 year (95% CI: 5–7), 10% after 3 years (95% CI: 9–11), and 12% after 5 years (95% CI: 10–13). Following a positive culture for bacteremia the 7-day mortality in the cohort was 21% (95% CI: 17–27), whilst the 30-day mortality was 35% (95% CI: 30–41).
Conclusion: Patients with ALD cirrhosis have a 10% risk of being hospitalized with bacteriemia within 3 years after being diagnosed with cirrhosis. Patients with a bacteremia have a very high short-term mortality. By mapping out this risk more precisely, our hope is that future interventions to prevent bacteremia, such as vaccination programs or prophylactic antibiotics, could reduce mortality among patients with ALD cirrhosis.

SAT-138

Functional and structural evaluation of patients with cirrhosis to consider recompensation

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Background and aims: Decompensated cirrhosis is defined as the appearance of events such as ascites, variceal hemorrhage and/or overt hepatic encephalopathy. Nowadays, there is evidence that, eliminating or controlling the etiological factor, not only slows down its progression but can induce recompensation. The Baveno VII consensus proposes the concept of rewarding the partial structural and functional regression of cirrhosis, implying the disappearance of decompensations. Objectives: To evaluate the recompensation stage in patients whose etiological factor of liver disease was eliminated.
Method: Longitudinal, observational and analytical study, patients with liver disease related to alcohol consumption (OH) and hepatitis C virus (HCV) were included, patients who were confirmed by the patient and the primary caregiver abstinent from alcohol for more than 12 months were evaluated, and determination of decreasing gamma-glutamyl transferase (GGT). And those who were cured of hepatitis C (using DAAs) with sustained viral response for 12 months were evaluated by viral load. Transitional elastography was performed at baseline and 12 months (Fibroscan touch 502 equipment), evaluation of laboratory studies and absence of any decompensation with the withdrawal of diuretics, anti-ammonium measures and non-selective beta-blockers to consider compensation. The protocol was approved by the ethics and research committees; it was ensured that the personal data of the patients were not published. Statistical analysis: Qualitative variables were expressed in frequencies and percentages, and numerical variables in means and standard deviation. We used X2, Fisher's exact, Student's t, and Mann-Whitney U to compare groups. A logistic regression model was built to analyze favorable factors. The value of $p < 0.05$ was considered statistically significant.
Results: In a period of 6 years and evaluation of 1187 patients seen in the liver clinic consultation, 300 patients with decompensated cirrhosis were included, 208 due to OH consumption who completed abstinence and 92 HCV treated with DAAs who achieved SVR, only 41 (13.66%) had recompensation criteria, 32 patients (78%) men with age 54.84 ± 10.58 years old, who previously presented ascites, hepatic encephalopathy and variceal hemorrhage. As a follow-up, it was documented that they ascended one stage on the Child Pugh scale (from C to B and from B to A), and a decrease in the MELD score from 16.3 to 8.42 ± 1.47 points, with withdrawal of medications (diuretic, measures antiammonia and beta blocker), liver stiffness decreased from a baseline average of 35.04 ± 16.93 kpas versus 21.13 ± 10.89 kpas in the recompensation stage, a decrease of 13.91 kpas, which represents 39.69%. Male gender ($p = 0.025$) and the absence of previous ascites ($p = 0.014$) favored the recompensation.
Conclusion: The concept of recompensation is real, with >20% reduction in liver stiffness and functional improvement; Male sex and the absence of previous ascites favor the recompensation.

SAT-139

Prevalence and determinants of reduced muscle status among adults with cirrhosis attending liver clinics

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Background and aims: Cirrhosis, particularly decompensated disease, is characterised by reduced skeletal muscle mass and function that is associated with increased mortality, morbidity, and healthcare utilisation. Mechanisms implicated in impaired muscle status: alterations in sex steroids, altered ammonia and glycogen metabolism, and malnutrition. The Sarcopenia in Cirrhosis study is an ongoing prospective observational study of adults with cirrhosis who attend out-patient hepatology services in Adelaide, Australia. Study aims are to (i) investigate the prevalence and determinants of impaired skeletal muscle quality in an outpatient population of adults with cirrhosis. (ii) determine the trajectory of change in muscle quality over time, and (iii) assess relationships of muscle quality and its trajectory of change to clinical outcomes. Baseline cohort data are presented here.
Method: Adults aged 18–70 years who attend liver outpatient services in Adelaide, Australia. Cirrhosis diagnosed based on liver transient elastography >20 kPa, or >15 kPa with supporting histology, radiology, or clinical findings. Patients were excluded if unable to provide informed consent, diagnosis of hepatocellular carcinoma or other malignancy, pregnant or breastfeeding, or where the treating clinician believes the patient's prognosis is terminal. Consenting eligible subjects undergo study assessments at baseline and at 12 months. Assessments include upper arm circumference, DXA height-adjusted appendicular lean mass, handgrip strength and liver frailty index. End of study data to be collected include incident clinical events, hospital admissions and mortality.
Results: 97 eligible, consenting participants. Females 36 (37.1%). Age range 32–71 years, median age 57 years (IQR 52.1–63.8). Median MELD 11 (IQR 7–13). Median liver stiffness 38 kPa (IQR 23.3–65.9). 59.2% of subjects have had previous decompensation. Aetiologies of liver disease: alcohol-related cirrhosis 36 (37.1%), MASH 21 (21.6%), Met ALD 19 (19.6%), hepatitis C (± alcohol/ MASH) 7 (7.2%), cholestatic liver disease 8 (8.2%), others 6 (6.2%). Mean dominant handgrip strength 29.3 kg (sd 12.7). Prevalence reduced muscle strength (defined as handgrip strength < 15 kg female, < 30 kg male): 19 of 86 subjects assessed (22.1%). Prevalence frailty (defined as Liver Frailty Index score >4,5): 12 of 82 subjects assessed (14.6%).
On univariate analysis, reduced muscle strength is associated with low zinc status (OR 0.61, p 0.009). On univariate analysis, frailty is associated with reduced mid arm circumference (OR 0.86, p 0.014).
Conclusion: In a cohort of adults with cirrhosis who attend out-patient liver services the prevalence of reduced muscle strength is 22.1%. Prevalence of frailty is 14.6%. Factors associated with impaired muscle status include zinc status.

SAT-140

Predictive value of systemic inflammation biomarkers towards recompensation versus progression to further decompensation in patients with decompensated cirrhosis

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Background and aims: The clinical course of patients with decompensated cirrhosis is heterogenous, since while many progress to further decompensation and experience liver-related death, some may recover and achieve recompensation with cure/control of the primary etiologic factor. Given the gradual increase of systemic inflammation (SI) with clinical cirrhosis stages, we investigate a broad panel of SI biomarkers and their dynamics across the course of decompensated cirrhosis patients.
Method: A two-center, prospective cohort of cirrhosis outpatients evaluated between 01/2017 and 12/2023 were stratified at baseline (BL) as compensated (CC), decompensated (DC) and recompensated (ReC) cirrhosis. At baseline and follow-up (FU: after a minimum of ≤ 6-months), surrogates of portal hypertension (PH) and multiple markers of SI were evaluated by a bead-based immunoassay using a flow cytometer. The cirrhosis stage at FU and further clinical outcomes were recorded. Patients were censored upon occlusive portal vein thrombosis, liver transplantation, hepatocellular carcinoma or death.
Results: A total of 152 cirrhosis patients were included with a median follow-up of 19.2 months (median age: 59.8 years; 68.4% men; n = 92 ALD as the main etiology). At BL, 39 (25.7%) showed CC, 23 (15.1%) ReC, and 90 (59.2%) DC. MELD was significantly higher in DC (10 v 9.5 v 12, p < 0.001) as well as SI markers such as IL6 (11.6 v 11.1 v 22.5, p < 0.001), IL8 (33 v 43.9 v 89.3, p = 0.005) and IL10 (6.9 v 3.5 v 10.5; p = 0.001), and PH surrogates such as VWF (264 v 203 v 306, p < 0.001). HVPG was significantly lower in recompensated patients (18 v 13 v 19 mmHg, 0.030) in comparison to CC and DC. There were no significant differences within other SI markers. DC showing progression to further decompensation (n = 23, 25,6% of DC) revealed significantly higher levels of multiple cytokines (IL10, Il1b, IL12p70, IL17A, IL8, IP10) vs. BL (all p < 0.05). In turn, DC patients achieving recompensation (n = 25, 27,8% of DC) showed significantly decreasing MELD (13 v 10, p = 0.05) and PH (HVPG (18 v 13mmHg, p = 0.001) and VWF (285 v 210, p = 0.001), but also of SI biomarkers (IL6, IL8, IL10, IL23, IP10, all p < 0.05) vs. BL.
Conclusion: Patients with DC show not only impaired liver function and PH but also a pro-inflammatory state. Importantly, with progression to further decompensation or regression to recompensation, we found significant dynamics in SI biomarkers paralleling liver disease surrogates (MELD, HVPG).

SAT-141
Chronic Liver Disease and Autoimmune Haemolytic Anaemia: A Case Series

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Background and aims: Chronic anaemia is common in patients with chronic liver disease (CLD), often due to multifactorial causes and causes increased morbidity and mortality rates. Autoimmune haemolytic anaemia (AIHA) is a rare autoimmune disorder that can complicate CLD. AIHA is characterised by autoantibody-mediated red blood cell destruction, and its coexistence with CLD, presents diagnostic and management challenges. This study aims to explore the clinical characteristics, management, and outcomes of patients with AIHA and CLD at King's College Hospital over a 21-year period.
Method: This retrospective case series involved adult patients (≥18 years) with a diagnosis of both CLD and AIHA at King's College Hospital from 2002 to 2022. Data on demographics, liver disease aetiology, AIHA treatment, and outcomes were collected from electronic health records. The patients were identified using search criteria for various CLD combined with AIHA diagnosis. AIHA diagnosis was based on laboratory parameters, including a positive direct anti-globulin.
Results: Ten patients (70% female) with concurrent AIHA and CLD were identified. The median age at time of diagnosis for CLD and AIHA was 34 years and 43 years, respectively. The most common liver disease was autoimmune hepatitis (40%), followed by alcohol-related liver disease (30%). 80% of the patients presented with chronic liver disease before the onset of AIHA. Seven patients (70%) had cirrhosis, and five (50%) received liver transplantation. In three cases, AIHA occurred post-liver transplantation. Treatments included corticosteroids (90%), IVIG (40%), and rituximab (40%). Rituximab was particularly used in treatment-refractory cases or post-liver transplant patients. Treatment-refractory AIHA occurred in four patients (40%), 2 of which developed treatment-refractory AIHA after their liver transplantation. Possible cofactors that were identified that might influence the development of AIHA in patients with CLD were COVID-19 infection in 3 patients (30%), cytomegalovirus (CMV) infection in 1 patient (10%), and Crohn's disease in 1 patient (10%).
Conclusion: This study highlights the complex pathophysiology and treatment landscape for AIHA in patients with chronic liver disease, particularly those who have undergone liver transplantation. Our findings underscore the necessity for further research to better understand the role of chronic liver disease as an immunological trigger for AIHA. Investigating the pathways linking liver inflammation and immune dysregulation could provide valuable insights into the pathogenesis of AIHA in patients with CLD as well as patients developing AIHA post-liver transplantation.

SAT-142-YI
Liver frailty index: a prognostic tool for predicting mortality in cirrhotic patients

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Background and aims: Liver frailty represents a critical prognostic indicator in cirrhosis, reflecting the intricate relationship between chronic liver disease and systemic physiological deterioration. The Liver Frailty Index (LFI) quantifies functional decline through objective physical performance measures, including handgrip strength, standing balance, and repeated chair rise tests. Emerging research suggests LFI provides a measurable score correlating with adverse clinical outcomes. This study aims to evaluate the LFI's utility in assessing functional status and predicting mortality among patients with cirrhosis.
Methods: This prospective cohort study included 75 patients diagnosed with cirrhosis during their outpatient control visits between April 2023 and September 2024. Patients with physical disabilities precluding performance of LFI assessment were systematically excluded. Standardized evaluations of handgrip strength, standing balance, and repeated chair rises were systematically applied to all participants. Patients with an LFI score ≥4.5 are categorized as frail. Clinical evaluations included MELD 3.0 scores, Charlson comorbidity scale and mortality were documented during the study period. Cirrhosis etiology was primarily MASH (32%). Viral hepatitis represented the second common cause of cirrhosis (22%).
Results: Of the 75 cirrhosis patients studied, 11 patients died during the median follow-up period of 18 months. Comparative analysis

revealed statistically significant differences between deceased and surviving patients. Specifically, the initial LFI and MELD 3.0 scores were significantly higher in the mortality group, while albumin levels were lower (4.6 ± 0.5 vs. 4.1 ± 0.5; p:0.003, 14 ± 4 vs. 10.6 ± 3.3; p:0.02 and 3.15 ± 0.4 vs. 3.67 ± 0.6; p:0.01) Notably, age, gender, bilirubin, creatinine, and Charlson Comorbidity Index (CCI) scores showed no significant difference. Stratification by the predefined LFI cut-off value (≥4.5) demonstrated mortality patterns: 6 of 17 frail patients and 5 of 58 non-frail patients died during the study period. Multivariate analysis identified frailty [hazard ratio: 6.41 (95% CI: 1.42–28.5); p = 0.016] and MELD 3.0 score [hazard ratio: 1.29 (95% CI: 1.07–1.55); p = 0.007] as independent mortality predictors. Kaplan-Meier survival analysis revealed cumulative mortality rates at 6, 12, and 18 months were 26.1%, 33%, and 40.2% in the frail group, compared to 2%, 3.4%, and 10% in the non-frail group (p = 0.002), underscoring the prognostic significance of the LFI.

Conclusion: Frailty, measured by LFI during outpatient examinations, serves as an independent predictor of mortality in cirrhotic patients. The index represents a convenient non-invasive method for comprehensively assessing patient fragility and predicting survival in clinical hepatological practice.

SAT-143

Cirrhotic cardiomyopathy: diagnostic challenges and debating role in mortality prediction in cirrhosis

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Background and aims: Cirrhotic cardiomyopathy (CCM) is a complex and underrecognized condition in chronic liver cirrhosis, characterized by impaired systolic and diastolic function, electrophysiological abnormalities, and/or chronotropic incompetence. Initially defined by the 2005 World Gastroenterology Congress Montreal Criteria, CCM was subsequently refined by the 2020 Cirrhotic Cardiomyopathy Consortium (CCC) Criteria. This study aimed to evaluate CCM in cirrhosis patients according to these two diagnostic criteria and to assess its prognostic significance.

Method: Between September 2022 and June 2023, a total of 75 patients with liver cirrhosis were prospectively enrolled in the study. Patients younger than 18 years and those with a history of cardiac revascularization, coronary artery disease, congenital heart disease, valvular heart disease, or severe pulmonary disease were excluded. Individuals presenting for routine gastroenterological evaluation were referred to the cardiology department, where cardiac assessments, including electrocardiography (ECG) and transthoracic echocardiography (TTE), were performed. Data on hospitalizations, episodes of decompensation, and mortality were documented during and after the study period. The median patient follow-up was 18 months (1–29 months).

Results: Of 75 patients, CCM was identified in 29 patients (38.7%) according to the 2005 Criteria, with 2 patients meeting systolic dysfunction and 27 meeting diastolic dysfunction criteria. The median Child-Pugh score for these patients was 6 (5–12), the median MELD-Na score was 10 (7–26), and the median MELD 3.0 score was 12 (7–26). Among these patients, 14 (48.3%) were in the decompensated group, while 15 (51.7%) were in the compensated. When the 2020 (CCC) Criteria were applied, 3 patients (4%) were diagnosed with CCM, 1 had systolic and 2 had diastolic dysfunction. Of these, 2 patients (%66.7) were decompensated and 1 patient (% 33.7) was compensated. When the 2005 Criteria were applied, the cumulative mortality rate in patients diagnosed with CCM was 14% at 12-month follow-up and 20% at 24-month follow-up. When the 2020 criteria were applied, mortality occured only 1 in 3 patients diagnosed with CCM during the 24-month follow-up. The mortality rate did not differ significantly in patients with and without CCM detected for both 2005 and 2020 criteria (p:0.94; p:0.90).

Conclusion: Although CCM has traditionally been associated with poor outcomes in cirrhosis, emerging evidence indicates that its direct role in predicting mortality is limited. Further research is required to elucidate the pathogenesis, refine diagnostic criteria, and better understand the clinical relevance of CCM in cirrhosis, ultimately informing potential therapeutic strategies. This study presents a thorough review of the current understanding of CCM, highlighting its diagnostic challenges, clinical implications, and the ongoing debate regarding its influence on the progression of cirrhosis and patient survival.

SAT-144-YI

FastPHES offers a rapid but valid alternative for the detection of cognitive impairment in patients with liver cirrhosis

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Background and aims: Guidelines recommend screening for cognitive impairment (CI) in patients with liver cirrhosis. The PSE-Syndrome test yielding the Psychometric Hepatic Encephalopathy Score (PHES) is considered "gold standard," but is often criticized as time consuming. Recently, the Animal Naming Test (ANT) and the QuickStroop have been proposed as time-saving alternatives. However, the lack of age- and education-adjusted norms for these tests impede a valid diagnosis. Considering the fact that the PHES in patients with cirrhosis results predominantly from the digit symbol (DS) and serial dotting (SD) test scores, we aimed to establish German norm values for a significantly shortened PHES (fastPHES) test consisting only of DS and SD. We aimed to compare the easier fastPHES with the PHES, ANT and QuickStroop in patients with cirrhosis. In addition, the predictive value of the fastPHES for the development of overt hepatic encephalopathy (oHE) episodes within a year after assessment was evaluated.

Method: The test results of the German cohort of healthy subjects (n = 217) assessed for the re-evaluation of PHES norms in 2020, was used for the calculation of fastPHES norms. Then the new fastPHES was compared to PHES and ANT in a prospectively recruited cohort of patients with cirrhosis (n = 271). In a part of these patients (n = 155), a comparison with QuickStroop was also possible. For each test, sensitivity and specificity analyses were performed in relation to abnormal PHES or the presence of HE grade 1–2. Additionally, receiver operating characteristics (ROC) analyses with abnormal PHES as reference value were performed. Finally, the predictive value of the different tests in forecasting oHE during one year follow-up was estimated using Fine and Gray's competing risk analyses. Here, death and liver transplantation were competing events.

Results: The analysis of the norm cohort's test results revealed an appropriate cut-off of ≤2 for an abnormal fastPHES. In 92.5% of the patients with HE grade 1–2 the fastPHES was abnormal. Compared to an abnormal PHES as reference, the fastPHES showed a sensitivity of 82.1% and a specificity of 90.9%. In comparison, the ANT and Quickstroop showed a sensitivity of 66.7% and 83.3% and a specificity of 59.6% and 59% respectively. Area under ROC was 0.92, 0.67 and 0.79 for fastPHES, ANT and QuickStroop, accordingly. Regarding the predictive value for the development of oHE in one year of follow-up, the abnormal PHES revealed a subdistribution hazard ratio (sHR)

of 3.24 (p < 0.001) while the fastPHES showed a sHR of 2.1 (p = 0.006). ANT and QuickStroop showed an sHR of 1.8 (p = 0.035) and 1.05 (p = 0.89) in this respect.
Conclusion: The here proposed fastPHES offers a rapid but still valid diagnosis of CI in patients with cirrhosis when there is a lack of time to determine the PHES and is, in this respect, superior to other time-saving test procedures.

SAT-145-YI
Clinical trajectories of patients with cirrhosis and ascites receiving long-term albumin. A proposal for a personalized management based on real-world experience
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Background and aims: Long-term albumin (LTA) is widely used in Italy in patients with cirrhosis and ascites. This study aims to analyse the clinical course and outcomes of patients receiving LTA to provide tools for personalizing their management.
Method: Patients with cirrhosis and ascites included in an Italian multicentre, retrospective, real-world study (Real-ANSWER) were followed during LTA treatment until death, liver transplantation, or end of follow-up. Based on the response at 3 months of LTA, patients were classified as 'responders' (resolution of ascites to grade 0–1), 'partial responders' (persistent ascites but no need for further paracentesis) and 'non-responders' (still receiving paracentesis).
Results: Of the 312 patients enrolled (median Child-Pugh 8, MELD 15, MELD-Na 18), 34% were responders, 33% partial responders and 33% non-responders. At baseline, non-responders had more severe ascites, higher White Blood Cells (WBC) count (6.0 vs 4.80 vs 4.90 10^9/L, p = 0.001) and creatinine (1.1 vs 0.9 vs 0.9 mg/dl, p = 0.003) compared to other groups, while no differences were found in aetiology of cirrhosis, serum albumin, MELD and Child-Pugh scores. Effective etiological treatment was higher (but not statistically significant) in responders than partial and non-responders (44% vs 35% vs 30%, p = 0.09). Among responders, 40% discontinued LTA due to improvement (median: 7 months; IQR 4–12), 26% received a transplant, 15% died. Among non-responders, 18% received TIPS (median: 5 months; IQR 3–12), 33% died, 11% received a transplant. Interestingly, among non-responders, 15% discontinued LTA due to subsequent improvement (median: 14 months; IQR 10–22), half of whom received etiological treatments. Among partial responders, 16% discontinued LTA due to improvement (median: 10 months; IQR 5–22), 21% underwent transplantation and 42% died. The cumulative incidence of 18-month mortality was lower in responders, while no differences were seen between partial responders and non-responders (18% vs 46% vs 42%, p < 0.001).
Conclusion: Based on the ascites response after 3 months of LTA, three categories with different clinical courses can be identified, thus helping the decision-making process. Non-responders should be assessed for TIPS placement, except those undergoing effective aetiological treatment who can be re-evaluated later. Responders should continue with LTA as they have the highest chance of survival, resolution of ascites and possibly recompensation. A case-by-case decision should be instead performed in partial responders.

SAT-146
A novel non-invasive diagnostic model for high-risk varices in cirrhosis: a multicenter retrospective and prospective study
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Background and aims: The non-invasive diagnostic method recommended by the Baveno VI and Baveno VII consensus for the diagnosis of high-risk varicose veins (HRV) have limited endoscopy sparing rates or require additional diagnostic equipment. This study aims to develop a novel diagnostic model to improve the diagnostic efficiency of HRV without requiring extra equipment.
Method: A multicenter retrospective cohort and a prospective cohort were established. Data including endoscopy findings, abdominal ultrasound results, liver stiffness measurements (LSM) using iLivTouch, and laboratory test parameters were collected from cirrhotic patients aged 18–65 years. Univariate and multivariate logistic regression analyses were conducted to identify influential variables. The area under the receiver operating characteristic curve (AUC) was calculated. A new diagnostic model was developed in the retrospective cohort and validated in the prospective cohort.
Results: As of June 19, 2024, the study included 3,405 patients from 22 centers, comprising 2,862 patients in the retrospective cohort and 543 patients in the prospective cohort. In the retrospective cohort, the Baveno VI (BV6) and Expanded Baveno VI (E-BV6) criteria spared 17.68% and 29.00% of endoscopies, respectively. The HRV missing rates were 2.53% for BV6 and 7.59% for E-BV6. After adjusting the cutoff values for LSM and platelet count (PLT), we established a Modified Baveno VI (M-BV6) criteria with an endoscopy sparing rate of 22.68%, higher than BV6, with an equivalent HRV missing rates of 2.53%. In the prospective cohort, the endoscopy sparing rates for BV6 and M-BV6 were 26.34% and 32.04%, respectively, with HRV missing rates of 1.83% for both. Univariate and multivariate logistic regression analyses revealed that spleen area (SA) was an independent predictor for HRV diagnosis. The AUCs for PLT, LSM, and SA for diagnosing HRV were 0.833, 0.715, and 0.794, respectively. Then BV6-SA diagnostic model was developed by incorporating SA into the BV6 criteria. Using this model, the endoscopy sparing rates were 64.35% in the retrospective cohort and 74.68% in the prospective cohort, with HRV missing rates of 4.26% and 4.81%, respectively. The MBV6-SA model, which integrated SA into the M-BV6 criteria, demonstrated endoscopy-sparing rates of 65.33% and 74.94%, and HRV missing rates of 4.26% and 4.81% in the retrospective and prospective cohorts, respectively.
Conclusion: This study is the first to validate the applicability of LSM measured by iLivTouch in diagnosing HRV with the BV6 criteria, and M-BV6 further improved the endoscopy sparing rates compared to BV-6. Most importantly, the BV6-SA model and MBV6-SA model we established substantially increased the endoscopy sparing rates with acceptable HRV missing rates.

SAT-149-YI
Hospital acquired infection is associated with higher mortality in patients hospitalised with acute decompensation of liver cirrhosis and infection
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Background and aims: Infection is a common decompensating event in patients hospitalised with complications of liver cirrhosis. The impact and significance of recurrent and nosocomial infections in these patients is not as well described.

Method: We performed a post-hoc analysis of antibiotic usage and outcomes for patients diagnosed with hospital acquired infection (HAI) during the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial. A total of 777 patients were randomized to daily 20% human albumin infusions or standard of care during hospitalisation due to an acute decompensation of cirrhosis across 35 different UK hospitals between 2016–2019. Data on type of infection for those who developed HAI after being treated empirically for infection on trial entry was available from 15/17 patients that survived to 90 days and 16/19 patients that died by 90 days.
Results: HAI was diagnosed in a higher proportion of patients who did not survive to 90 days (27.5% vs 12.4%, p = 0.007). Median time to HAI in those that went on to die (n = 16) within 90 days was 6 days compared to 8 days in those that went on to survive 90 days (n = 15 (p = 0.029, HR log rank ratio 0.53, 95% CI 0.25–1.11). Overall, 90-day mortality in infected patients at hospitalisation that developed subsequent HAI was 53%. The most frequently diagnosed site of HAI in survivors and non-survivors was the lower respiratory tract (5/17 and 5/19), then spontaneous bacterial peritonitis (2/17 and 3/19). Most patients in both groups did not have a causative pathogen identified (n = 5 in survivors, n = 2 in non-survivors) and there was no antimicrobial resistance reported.
Conclusion: 90-day mortality was high in patients admitted with decompensated liver cirrhosis who developed additional HAI after being treated for infection at presentation and did not appear influenced by site of infection, specific pathogens or antimicrobial resistance in this cohort. Non-survivors developed HAI earlier in their admission and may reflect that intrinsic patient factors are likely to be more important to survival than choice of empirical antibiotics. The high mortality in the HAI group may also be related to clinicians being less vigilant for infection in patients already empirically treated with antibiotics, resulting in delayed diagnosis.

SAT-150
Highly variable antibiotic prescribing practices in a real world cohort of patients in the United Kingdom with decompensated cirrhosis

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Background and aims: Increasing antimicrobial resistance is described in hospitalised patients with liver cirrhosis, encouraging rationalising empirical antibiotic prescribing where infection is suspected. Yet liver care bundles promote early broad spectrum use because of the harm associated with infection. In view of these potentially contrasting messages, we examined real world antibiotic usage and outcomes in hospitals in the United Kingdom (UK).
Method: This was a post-hoc analysis of antibiotic prescribing in the first 48 hours in patients diagnosed with infection at entry to the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial, from a total of 777 patients randomized to daily 20% human albumin infusions or standard of care during hospitalisation due to an acute decompensation of cirrhosis across 35 UK hospitals (2016–2019). We performed a descriptive analysis of empirical antibiotic choices, and assessed baseline characteristics and outcome data for patients treated empirically with single versus multiple agents to detect any significant differences between the groups using Mann-Whitney U test.
Results: 211 patients were diagnosed with infection and prescribed antibiotics at trial entry, with antibiotic prescribing data available for 205. The total number of empirical antibiotics prescribed was 279 for 205 patients, of which the most frequently occurring were piperacillin-tazobactam (74) and co-amoxiclav (46). 149 patients received a single agent and 56 received multiple agents, with 38 different combinations of antibiotics identified. Overall, 91/205 (44%) patients had their antibiotics changed from 1st line empirical choice during their hospitalisation, with 72/91 (79%) switched to agents of equal or broader spectrum antimicrobial activity. Baseline characteristics were similar between the multiple and single agent groups, with the only significant difference being the median admission CRP, which was higher in the multiple agent group (61 versus 39.5, p = 0.03). There was no significant difference in 28-day mortality but mortality in the multiple antibiotic group was higher at 90 days (p = 0.03). In patients who received gentamicin, 4/16 (25%) developed renal dysfunction and 9/16 (56%) died by 90 days.
Conclusion: Highly variable prescribing practices for cirrhosis patients admitted to UK hospitals were evident from the number of antibiotics in varying combinations used empirically in this study. We have not identified a specific cause for a higher 90-day mortality in patients who received multiple agents empirically, as the groups were similar in respect to baseline characteristics. It is possible that the patients in the multiple antibiotic group had more severe disease not accounted for by our data, but may also reflect that use of multiple agents such as aminoglycoside antibiotics carries a risk of iatrogenic harm.

SAT-151
Mortality in patients hospitalised with decompensated cirrhosis and infection is associated with higher baseline measures of infection and organ dysfunction

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Background and aims: Infection is frequently diagnosed in patients presenting to hospital with decompensated liver cirrhosis, with systemic inflammation and immune dysfunction described in patients who develop organ failures and death. We examined characteristics and serum biomarkers of a large cohort of these patients admitted to hospitals across the United Kingdom (UK) to assess whether these findings held true in this cohort.
Method: We performed a post-hoc analysis of baseline characteristics, outcome data and serum biomarkers for patients diagnosed with infection at entry to the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial. 211 patients with infection were identified from a total of 777 patients randomized to daily 20% human albumin infusions or standard of care during hospitalisation due to an acute decompensation of cirrhosis across 35 different UK hospitals between 2016–2019. Baseline demographics, admission medications and admission laboratory values were available for 206 patients and are presented as medians and 95% confidence intervals with the Mann-Whitney U test to detect differences between survivors and non-survivors at 90 days. Results of other serum biomarkers for infection, inflammation and cardiorenal function were available for a subcohort of 36 patients.
Results: 69/206 (33.5%) of patients diagnosed with infection at trial entry did not survive to 90 days. These patients were older (median age 58.9 vs 53.2, p = 0.0002), had higher baseline creatinine values (93 vs 67, p = 0.0003) and higher Model for End-stage Liver Disease scores (21.94 vs 18.87, p = 0.0003) than survivors. Non-survivors were more likely to have alcohol-related hepatitis (p = 0.007) and hepatic encephalopathy (p = 0.025), and to develop hospital acquired infections (p = 0.007) and renal dysfunction (p = 0.00073). 90-day mortality was not associated with prophylactic antibiotics or rifaximin, proton pump inhibitors or beta-blockers at trial entry. Baseline white cell count (WCC) (8.1 vs 11.3, p = 0.0005) and C-reactive protein (CRP) (38 vs 55, p = 0.037) were significantly higher in non-survivors. In a subcohort of 36 patients, there was no significant association between mortality at 90 days and other serum biomarkers of infection and inflammation, including procalcitonin (PCT). Serum syndecan-1 was significantly higher at trial entry (p = 0.0063) and day 5 (p = 0.004) in non-survivors.

Conclusion: Our data show that disease severity and organ dysfunction are significantly associated with 90-day mortality in this cohort of patients hospitalised with decompensated cirrhosis and infection. Conventional markers for infection (WCC and CRP) appear to be the most useful predictive laboratory tests for infection severity. The significant association between 90-day mortality, baseline creatinine and syndecan-1 levels suggests there is a role for further studies examining the cardiorenal axis in decompensated cirrhosis.

SAT-152

Optimising management of patients discharged from hospital following an acute decompensation of cirrhosis – a multicentre UK perspective

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Background and aims: Following hospitalisation with acute decompensation (AD) of cirrhosis, patients experience significant morbidity with 90-day mortality rates reported over 50% in the sickest cohort. Significant variation in care exists with the British Association for the Study of Liver Disease (BASL) endorsing a discharge bundle to help standardise management. The aim of this study was to assess management and outcomes following hospitalisation with AD against these standards, and to elicit variations in care.
Method: A UK based multi-centre prospective study was conducted up to 90 days following discharge with AD as defined by Baveno VII criteria. Adult patients who were admitted with AD from 01/01/2024–31/03/2024 were identified at each site by a nominated site lead via electronic handover sheets and checked against their discharge letter. Patients who had died during the admission were excluded. Anonymised excel password-protected data sheets were used.
Results: A total of 48 patients across 3 sites were recruited with the median age being 63 (IQR 19). Aetiology of those included were alcohol-related (75.0%), MASLD (12.5%), cryptogenic (6.3%), PBC (2.2%), Hepatitis C (2.1%), and MetALD (2.1%). 54.2% of patients were admitted with ascites without spontaneous bacterial peritonitis (SBP), 14.6% with hepatic encephalopathy, 14.6% with variceal bleeding, 12.5% with SBP and 4.2% with hepatorenal syndrome -acute kidney injury. 7 patients (14.6%) were re-admitted to hospital during follow-up (5 due to further decompensation) with 13 (27.1%) patients dying within 90 days of discharge. No significant difference was noted in readmissions and mortality between specialist and non-specialist centres. With regards to decompensation management, 7 patients (100.0%) who were admitted with a variceal bleed were prescribed a beta blocker, but only 1 out of 7 patients had a repeat gastroscopy performed within the recommended 4-week period. Of the 6 patients that were diagnosed with SBP, 5 patients (83.3%) were prescribed secondary prophylaxis. Of the 36 patients with alcohol-related liver disease, only 17 (47.2%) were reviewed by the alcohol-care team as an inpatient. 15 (31.2%) patients were identified as not being future transplant candidates. Only 7 (46.6%) of these had appropriate treatment escalation plans documented in their discharge letter.
Conclusion: Despite the limited sample size of this pilot study, we highlight the parameters in post discharge care following AD that require urgent improvement with regards to optimising prescriptions, clinical reviews, interventions as well as advanced care planning. We will explore these concepts as well as variations in care more in the next phase of this program, which is a nation-wide based study through the UK hepatology trainee consortium (ToRcH-UK).

SAT-153

COVID-19 pandemic significantly increased anxiety and depression in patients with cirrhosis, but not in patients without liver disease

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Background and aims: The Coronavirus Disease 2019 (COVID-19) pandemic caused a significant increase of anxiety and depression, particularly in patients with chronic diseases like diabetes or hypertension. However, little is known about the prevalence of both disorders in patients with liver cirrhosis hospitalized during the pandemic. Furthermore, it's unclear if the prevalence of both diseases has changed in the post-COVID area or if there is a lasting effect of the pandemic.
Method: Retrospective analysis of three cohorts including patients with liver cirrhosis (LC) and without any liver disease who had been treated at the University Medical Center of Hamburg-Eppendorf at three different time periods: April to June 2019 (pre-COVID, cohort 1), April to June 2020 (COVID pandemic, cohort 2) and from April to June 2024 (post COVID, cohort 3). Patient Health Questionnaire-4 (PHQ-4) was used to diagnose depression and anxiety on admission. Demographic characteristics were extracted from patients electronical medical file. Patients with a history of mental disorders were excluded from the study.
Results: A total of n = 603 patients were analyzed, n = 294 with LC (cohort1/2/3: n = 110/129/55), n = 309 without any liver disease (non-LD; cohort 1/2/3: n = 104/101/104), n = 238 (40%) were female, median age 61 years (range: 18–94). In cohort 1, the prevalence of depression was 3.6% in LC patients and 2.8% in non-LD patients (p = 0.75), in cohort 2 it was 19% vs. 3.9% (p > 0.005), and in cohort 3 it was 3.5% vs. 2.8% (p = 0.81). The rate of anxiety was 4.5% in LC patients vs. 1% in non-LD patients (p = 0.11) in cohort 1, 21% vs. 3.9% (p > 0.0002) in cohort 2, and 1.8% vs. 1.9% (p = 0.9) in cohort 3. In a multivariate analysis that included age, gender, presence of LC, liver function, and exposure during the pandemic, only exposure was a significant risk factor for depression (OR: 4.6, 95% CI: 1.6–17.2; p = 0.03). For anxiety, higher age (OR: 1.05, 95% CI: 1.0–1.1; p = 0.04) and exposure to COVID (OR: 6.4, 95% CI: 1.8–29.3; p = 0.006) were significant risk factors.
Conclusion: In the pre-COVID era, the prevalence of depression and anxiety was comparable in LC and non-LD patients, but the COVID pandemic significantly increased the prevalence of both disorders only in LC patients, underlining the vulnerability of these patients to external stressors. Although the prevalence decreased in the post-pandemic period, these findings highlight the need for early psychological screening and targeted mental health interventions for patients with end-stage liver disease during future pandemics or other global health crises.

SAT-154

A metagenomics approach to frailty in patients with cirrhosis undergoing a multifactorial intervention

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Background and aims: Frailty is a relevant prognostic factor in patients with cirrhosis, independently of the degree of liver failure. In a previous study, we observed an improvement in frailty and a decrease in emergency room consultation and falls in patients with cirrhosis during a multifactorial programme consisting of home-exercise, branched-chain amino acids and a multistrain probiotic. The aim was to study the fecal microbiota composition associated with frailty and its improvement in patients with cirrhosis.
Method: We analyzed fecal samples of 24 outpatients with cirrhosis included in a previous study (Román, Hepatol Commun 2024). Frailty was assessed by the Liver Frailty Index (LFI). Frail and prefrail patients (n = 22) were randomized to the multifactorial intervention (home-exercise, branched-chain amino acids and a multistrain probiotic) or control for 12 months. At baseline and at 12 months, we determined LFI, gait speed, fecal microbiota composition by metagenomic shotgun sequencing, and a battery of biomarkers in serum samples. A group of 15 age and gender-matched healthy controls was also included.
Results: Patients with cirrhosis showed a lower alpha diversity than controls. At baseline, the main differences between patients with cirrhosis and controls were increases in the abundance of Anaerotruncus massiliensis, Enterocloster bolteae, Streptococcus parasanguinis, Dialister invisus, Ruminococcus gnavus, Clostridium scindens, and 3 different Veillonella species in cirrhosis samples. In patients with cirrhosis, there was a positive correlation between the abundance of Rothia dentocariosa and LFI, and between Bacteroides faecis and gait speed. Streptococcus thermophilus showed a negative correlation with IL-6 and Lactobacillus acidophilus a positive correlation with mtDNA. Veillonella parvula and Veillonella dispar abundances positively correlated with ccK18. After the multifactorial intervention, LFI and gait speed improved, and the main changes in the microbiota composition were a decrease in the abundance of Akkermansia muciniphila, and an increase in Streptococcus thermophilus, Lactobacillus acidophilus and several species of Bifidobacterium.
Conclusion: Frailty in patients with cirrhosis was associated with a distinct microbiome signature that correlated with biomarkers of inflammation, mitochondrial dysfunction and liver damage. After a long-term multifactorial intervention, frailty improved in parallel with changes in microbiome composition. These results provide information useful to identify new therapeutic targets to improve frailty and its consequences in patients with cirrhosis.

SAT-155
Reduced COVID-19 vaccination effectiveness and clinical outcomes for decompensated cirrhosis: a nationwide population-based study

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Background and aims: This study investigated the effectiveness of coronavirus disease 2019 (COVID-19) vaccination in decompensated cirrhosis.
Method: This study comprised a population-based cohort of 1,583,777 patients with chronic liver disease (CLD) including decompensated cirrhosis, from the National Health Insurance Service data in the Republic of Korea. The primary outcome was the risk of COVID-19 infection within 6 months after vaccination between 26 February 2021 and 31 December 2021. Hospitalisation and all-cause mortality rates were also investigated. Target trial specifications with propensity score matching were used to minimise the bias between the unvaccinated and vaccinated groups.
Results: The mean age of patients was 54.2 years and 54.5% of them were men. In total, 61,765 patients (3.9%) had decompensated cirrhosis. Compared to the unvaccinated group, the vaccinated group exhibited a lower risk of COVID-19 infection (hazard ratio [HR] = 0.94; 95% confidence interval [CI] = 0.91–0.97), hospitalisation (HR = 0.86; 95% CI = 0.83–0.89), and all-cause mortality (HR = 0.27; 95% CI = 0.20–0.36). However, there was no beneficial effect of the COVID-19 vaccination on the clinical outcomes of patients with decompensated cirrhosis. The multivariable analysis determined that COVID-19 vaccination reduced all-cause mortality (HR = 0.39; 95% CI = 0.32–49) in CLD and decompensated cirrhosis increased all-cause mortality in patients with COVID-19 infection (HR = 2.94; 95% CI = 2.15–4.02). These results were consistent during the pre-Delta and Delta-variant periods.
Conclusion: COVID-19 vaccination reduced the risk of COVID-19 infection, hospitalisation, and mortality in patients with CLD. However, patients with decompensated cirrhosis had a poor prognosis and diminished vaccination effectiveness. Early detection and antiviral treatment are warranted to manage COVID-19 infection effectively in patients with decompensated cirrhosis.

SAT-156
Role of renal biomarkers on sarcopenia and frailty in patients with cirrhosis

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Background and aims: Sarcopenia and frailty are the risk factors for poor prognosis in patients with liver cirrhosis. This study was to investigate the role of renal biomarkers on sarcopenia and frailty in patients with cirrhosis.
Method: A total of 78 cirrhotic patients with serum creatinine < 1.5 mg/dL were analyzed with serum renal biomarkers (creatinine-to-cystatin C ratio, IL-18, KIM-1, and NGAL), sarcopenia, and liver frailty index (LFI). Sarcopenia was defined as a skeletal muscle index less than 36.54 cm^2/m^2 (male) and 30.21 cm^2/m^2 (female), respectively. LFI composed 3 performance-based tests (grip strength, chair stands, and balance). Frailty was categorized as frail (LFI >4.5), prefrail (LFI 3.2–4.5), or robust (LFI < 3.2). We analyzed the risk of sarcopenia and frailty according to a variety of renal biomarkers in patients with cirrhosis.
Results: The mean age was 59.2 years and females was 32%. Child-Pugh class A and B were 82% and 18%, respectively. Sarcopenia, prefrail, and frail were observed in 43 patients (55.1%). There was no significant difference in serum IL-18 (205.8 vs. 236.7 pg/mL, p = 0.285), NGAL (110.8 vs. 104.3 ng/mL, p = 0.537), and KIM-1 (224.6 vs. 250.5 pg/mL, p = 0.482) according to sarcopenia and frailty. However, serum creatinine-to-cystatin C ratio was significantly lower in

patients with sarcopenia and frailty compared to no sarcopenia and frailty (0.73 vs. 0.83, p = 0.002). A univariable analysis showed that sarcopenia and frailty were associated with age ≥60 years [odds ratio (OR) 2.42, p = 0.06], female (OR 2.88, p = 0.043), Child-Pugh class B (OR 14.73, p = 0.012), and creatinine-to-cystatin C ratio < 0.8 (OR 5.59, p = 0.001). A multivariable analysis indicated that the risk factors for sarcopenia and frailty were Child-Pugh class B (OR 9.04, p = 0.044), and creatinine-to-cystatin C ratio < 0.8 (OR 4.03, p = 0.008). Serum IL-18, NGAL, and KIM-1 were not associated with sarcopenia and frailty.
Conclusion: Serum creatinine-to-cystatin C ratio is associated with an increased risk of sarcopenia and frailty in cirrhotic patients with favorable renal function.

SAT-157

Identification of sarcopenia in patients with liver cirrhosis by combining anthropometry and ultrasound of thigh and psoas

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Background and aims: The gold standard for the diagnosis of sarcopenia in patients with cirrhosis is the evaluation of the skeletal muscle index (SMI) at the level of the third lumbar vertebra. We aimed at evaluating the usefulness of other techniques other than SMI for the diagnosis of sarcopenia in patients with cirrhosis.
Method: Unicentric prospective study. Patients with cirrhosis who underwent an abdominal computed tomography (CT) for any reason (June/2020–April/2024) were included. Sarcopenia was defined as SMI<39 cm^2/m^2 in women and < 50 cm^2/m^2 in men. Sarcopenia was evaluated by means of anthropometry, bioimpedance (BIA) and ultrasonography of thigh and psoas muscle. Thigh muscle thickness index (TMTI) and psoas muscle thickness index (PMTI) were measured. Thigh elastography was also measured. Biochemical markers were evaluated.
Results: 250 cirrhotics were included (74.4% men), median age 62 years. Pugh Child (A: 44.2%; B: 42.4%, C: 13.3); 43% with ascites. Sarcopenia was present in 95 (38%) patients (42% men vs. 27% women, P = 0.03). Median TMTI was lower in sarcopenic patients 0.89 cm/m^2 (IQR, 0.72–1.06) vs. 1.13 cm/m^2 (IQR, 0.95–1.33), P < 0.001. Median PMTI was lower in sarcopenic patients 1.16 cm/m^2 (IQR, 1.04–1.27) vs. 1.38 cm/m^2 (IQR, 1.17–1.51), P < 0.001. Regarding anthropometric evaluation, all measures were lower in sarcopenic patients (P < 0.05). Skeletal appendicular mass, body cell mass, body protein mass and muscle compartment evaluated by BIA were lower in sarcopenic patients (P < 0.05). Phase angle (PhA) was lower in sarcopenic patients, without statistical significance (P = 0.06). In the PhA segmental analysis, the right arm (P < 0.001) and the right leg (P = 0.002) were different in patients with sarcopenia. In patients with ascites only the PhA segmental analysis of the right leg was different (P = 0.03). The prevalence of myosteatosis by CT was higher in sarcopenic patients (55% vs. 41%. P = 0.03) and thigh elastography was not different (P = 0.52). In the univariate analysis, the significant measures for identifying sarcopenia for the entire cohort and by sex and with an AUROC >0.700 were: body mass index (BMI), calf and thigh circumferences, TMTI and PMTI. These were included in the multivariate analysis and a model was generated, which showed an AUROC of 0.839 (95% CI, 0.789–0.890). Other simpler models were designed, with 3 variables (BMI, calf circumference and TMTI or PMTI) with AUROC values of 0.819 and 0.812, respectively. There were no differences between both (P = 0.43). Nomograms were developed with the models of 3 variables. TMTI and PMTI cutoff points were evaluated for the diagnosis of sarcopenia.
Conclusion: Thigh and psoas muscle ultrasound combined with anthropometry are excellent alternatives for the evaluation of sarcopenia in patients with cirrhosis and could be an alternative to SMI for the identification of sarcopenia in those patients.

SAT-158

Factors predicting response to long-term albumin administration and impact on survival in patients with decompensated cirrhosis. A single-centre real-world experience

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Background and aims: Although controversial, long-term albumin administration in patients with decompensated cirrhosis is very common. However, its efficacy in real clinical practice is not fully elucidated. We aimed at evaluating the efficacy of chronic albumin infusion and predictors of clinical response in this outpatient setting population.
Method: The cohort was comprised of all consecutive patients with decompensated cirrhosis under chronic albumin infusion [n = 69; (84% men); age 62 (9.9) years; etiology: (alcohol 33%, MASLD 8.7%, MetALD 15.9%, viral 14.5%, mixed 11.6%, other 15.9%); Median MELD: 16 (IQR:12–20)]. The indications were ascites [grade 2 or 3 (63.2%), refractory (23.5%)], hyponatremia (2.9%), and type 2 hepatorenal syndrome (2.9%). Twenty-eight patients (39.1%) had prior history of hepatocellular carcinoma (HCC) and nearly 64% had tumoral progression at baseline or throughout follow-up. Median treatment duration and albumin dose were 12 weeks (IQR: 6–27) and 30 g/week (IQR: 20–40), respectively. Clinical response (CR) was defined as i) decrease of number of paracentesis/thoracentesis, ii) natremia correction, iii) improvement in renal function. CR was achieved in 35 patients (50. 7%).
Results: Age, etiology, prior HCC and serum albumin >3.4 g/dl during treatment were associated with CR in univariate analysis. In multivariate analysis, only the absence of progressive HCC [OR: 25.35 (CI 95% 2.99–215.05)] and albumin >3.4 g/dl after one month of treatment [OR: 4.13 (CI 95% 1.27–13.46)] were associated with CR. Transplant or TIPS-free survival was significantly higher in responders compared with non-responders, regardless of the history of HCC (p-value log-rank test < 0.05). Heart failure occurred in 6 patients (8.7%), all with HCC (21.4% vs 0%; p = 0.008).
Conclusion: Clinical response to albumin administration in patients with decompensated cirrhosis is associated with significantly higher survival. Serum albumin concentration after 30-days is an early predictor of response allowing for therapy adjustment and resources optimization. The presence of HCC, especially if progressive, is associated with lower clinical response and higher risk of complications.

SAT-159

Increasing 'Liver Frailty Index' scores are associated with increased mortality and unplanned hospital admission in patients with cirrhosis: a retrospective cohort study

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Background and aims: The Liver Frailty Index (LFI) aims to identify cirrhosis-related sarcopenia and functional decline: increased LFI has

been associated with excess mortality in those patients awaiting transplant. It has also been shown to predict decompensation and admissions. At present, the evidence for its use is predominantly for transplant waitlist patients and further studies are required to validate the LFI for use in a 'non-transplant' cohort of patients with cirrhosis.
Method: LFI scores were routinely calculated in the outpatient liver clinic by a Hepatology nurse specialist. Hospital admissions in both the year before and after the point in time the LFI score was calculated were reviewed as was all-cause mortality rates from time of LFI to notes review.
Results: In total, LFI scores were calculated for 259 patients. Scores were 'frail' in 16% (n = 42), 'pre-frail' in 62% (n = 161) and 'robust' in just 22% (n = 56). Average number of unplanned hospital admissions in the 12 months prior to the LFI being obtained for frail, pre-frail and robust patients was 1.29 (0–10), 0.37 (0–4) and 0.14 (0–2) respectively. For the 12 months following the LFI, these figures were 1.09 (0–8), 0.64 (0–6) and 0.18 (0–3) respectively. At up to 36 months, all-cause mortality was 19% (n = 49) being 40% (n = 17) of frail patients, 16% (n = 25) in pre-frail patients and 13% (n = 7) among robust patients. Average number of months until death was 13 (3–34) in the frail cohort, 20 (4–39) in pre frail patients and 18 (4–38) in robust patients.
Conclusion: Higher LFI scores are associated with increased mortality and increased hospital admissions in the pre frail cohort. This data demonstrates the utility of LFI to predict adverse outcomes in a predominantly non-transplant listed cirrhosis cohort.

SAT-160
Phase angle as a predictive factor for mortality in hospitalized patients with cirrhosis
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Background and aims: Phase angle (PA) measured by bioelectrical impedance analysis (BIA) is a valuable tool for assessing body composition, frailty, and prognosis in patients with chronic diseases, including cirrhosis. Most studies on PA in cirrhosis have focused on outpatient populations, with limited data available on hospitalized patients. The objective of this study was to assess the usefulness of PA in predicting adverse events (mortality, readmissions, and falls) in hospitalized patients with cirrhosis.
Method: Consecutive patients admitted with decompensated cirrhosis to the hepatology ward of two hospitals were included. PA was measured by BIA at admission, and patients were followed prospectively for one year to monitor the occurrence of death, readmissions, and falls.
Results: A total of 109 patients were included, with a mean age of 62 ± 11 years, 77% were male, and 69% with alcohol-related liver disease as the cause of cirrhosis. The mean MELD score was 15.7 ± 5.3. Ascites was the most common reason for hospitalization (58%). During a follow-up period of 265 ± 122 days, 33/109 (30.3%) patients died, 61/109 (56%) required at least one readmission, and 25/109 (23%) experienced one or more falls. Patients with a PA ≤4 (n = 47) had a significantly higher risk of mortality (adjusted for liver transplantation as a competing risk) during follow-up than patients with PA>4 (47% vs. 21%, p = 0.005). PA and the Charlson comorbidity index were identified as the independent predictive factors of mortality in the multivariable analysis (sHR 2.18, 95% CI 1.10–4.34, p = 0.026; and sHR 1.30, 95% CI 1.14–1.47, p < 0.001, respectively). However, PA did not show statistical significance in predicting readmissions or falls.
Conclusion: PA measured by BIA and the Charlson comorbidity index were the independent predictive factors of mortality during follow-up in patients with cirrhosis hospitalized in a hepatology ward. PA could serve as a useful tool for estimating prognosis in these patients.

SAT-161
Prevalence and prognosis of cirrhotic cardiomyopathy in hospitalized patients with decompensated cirrhosis
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Background and aims: Cirrhotic cardiomyopathy (CCM) is defined as cardiac dysfunction in patients with cirrhosis in the absence of pre-existing heart disease. Its prevalence and clinical implications remain controversial. This study aims to assess the prevalence of CCM, including both systolic and diastolic dysfunction, in patients with decompensated cirrhosis, and to investigate its correlation with prognosis.
Method: Retrospective analysis of a prospective cohort of hospitalized patients with decompensated cirrhosis from Parc Taulí Hospital (Barcelona) between October 2017 and January 2020. Clinical and laboratory data were collected at admission, and mortality, complications, and cardiac events within one year. Echocardiographic parameters obtained 3 months before or after inclusion were collected and reviewed by cardiologists.
Results: A total of 125 patients, predominantly male (77%), with alcohol-related cirrhosis (78%) were included. The median Child-Pugh and MELD score was 9 (7–10) and 15 (11–20), respectively. Among the entire cohort, 38 patients (30%) had an echocardiogram; six of these patients had pre-existing heart disease and were excluded from the analysis. No significant differences were found between those with and without an echocardiogram, except that the former had a higher incidence of acute kidney injury and hepatocellular carcinoma compared to the latter. The main indication for performing an echocardiogram was anasarca. Interestingly, no patient showed systolic dysfunction, either by LVEF (left ventricular ejection fraction) or GLS (global longitudinal strain). Nevertheless, 72% showed at least one parameter of diastolic dysfunction. Specifically, 9% had an E/e' ratio ≥15, 16% had a septal e' velocity < 7 cm/s or lateral e' velocity < 10 cm/s, 28% had a tricuspid regurgitation velocity (TRvel) >2.8 m/s, and 63% had a left atrial volume index (LAVI) >34 mL/m². A total of 16% met the criteria for CCM, although some echocardiographic data were lacking in 53% of patients. CCM was not associated with mortality, decompensation, or cardiovascular events. However, TRvel was associated with higher mortality, and LAVI >34 mL/m² with a higher risk of decompensation.
Conclusion: CCM is an underrecognized entity in clinical practice, with an estimated prevalence of 16% in decompensated cirrhosis. While no patients presented systolic dysfunction, 72% had at least one parameter of diastolic dysfunction, some of which were correlated with prognosis. Further studies are needed to better evaluate the clinical relevance of this condition.

SAT-162

Epidemiology and Risk factors for development of AKI-HRS based on the new consensus definition

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Background and aims: A new definition of AKI-HRS has recently been proposed by Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) for AKI. The main difference is addition of urine output and presence of pre-existing chronic kidney disease (CKD). The knowledge on epidemiology and risk factors for developing AKI-HRS based on the updated definition is limited. We aim to describe the epidemiology and risks factors for developing AKI-HRS.
Method: 288 inpatient admissions from Jan 2022 to March 2024 were included from an ongoing prospective study (REDUCE and SOLIDARITY-DAM). Retrospective data collection was carried out. Patients were categorized into those who developed AKI-HRS and those who did not (AKI-HRS (n = 57) Vs No AKI-HRS (n = 231)). Risks factors for the development of AKI-HRS was interrogated by standard statistical tests.
Results: The cohort mean age was 63.2 ± 10.1 years, BMI 25.6 ± 4.6 kg/m^2, majority were male (71.2%). MASLD/MASH was the most prevalent etiology of cirrhosis (39.2%) followed by alcohol (36.8%), viral (16.4%), and others (7.6%). AKI occurred in 83 (29%) of which 57 (19.7%) were classified as having AKI-HRS based on the updated definition. The updated definition allowed for an additional 16 (5.6%) patients to be classified as AKI-HRS. In patients who developed AKI-HRS, a higher proportion of MAFLD/MASH and lower of viral etiology was seen ($p = 0.043$). Patients with past decompensating events (hepatic encephalopathy, ascites), ischemic heart disease (IHD) and CKD developed AKI-HRS more frequently ($p < 0.05$). The use of diuretics and higher Child's-Pugh (CTP) score was associated with development of AKI-HRS. The use of non-selective betablockers was not associated with development of AKI-HRS. Patients with sepsis as a decompensating event developed AKI-HRS more often than variceal and non-variceal bleeding, alcoholic hepatitis, or HBV flare. No difference was observed in the preadmission creatinine, GFR, bilirubin, white cell count, markers of inflammation like neutrophil to lymphocyte ratio or platelet to lymphocyte ratio (p = NS for all). In the univariate analysis male gender ($p = 0.010$), decompensated cirrhosis ($p = 0.005$) (HE < 0.001) and Ascites ($p < 0.001$)), IHD ($p = 0.046$), use of diuretics ($p < 0.001$) and preadmission CTP score ($p < 0.001$) were significant predictors of development of AKI-HRS whereas CKD or current decompensating events were not (p = NS for both). In the multi-variate model, CTP score and IHD were significant predictors for the development AKI-HRS.
Conclusion: Preadmission CTP score and IHD independently predicts the development of AKI-HRS whereas markers of systemic inflammation and sarcopenia did not in this cohort.

SAT-163

Factors associated with AKI development and external validation of the AKI prediction score

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Background and aims: Acute kidney injury (AKI) portends a worse prognosis in cirrhotics, and is associated with an higher morbidity, mortality and progression to chronic kidney disease. Early identification of patients who may develop AKI is important to mitigate the risk of development of AKI and improve outcomes. Higher MELD and Child Pugh score, low serum albumin and higher bilirubin levels are risk factors for development of AKI. The AKI prediction score was developed to predict AKI in cirrhotic patients, but it has not been externally validated, limiting its broader applicability. The aim of this study is to find out the predictors of AKI development in patients with cirrhosis and to examine the "AKI prediction score" by Patidar et al for external validation and wider applicability. Our other goal was to obtain a cut off score for MELD and MELD-Na to predict the risk of developing AKI.
Method: Patients for this study were recruited from our ongoing multicenter prospective study of "predictors of decompensation, ACLF and mortality in cirrhosis" (SoLiDaRity-DAM). A total of 294 inpatient admissions from Jan 2022 to March 2024 were included in the analysis. Cirrhosis was defined based on histology, biochemical or radiological investigations. AKI was defined as an increase in serum creatinine (SCr) ≥0.3 mg/dL within 48 hours or a percentage increase in SCr ≥50% from baseline as per KDIGO definition. Standard statistical tests were applied for group comparison and predictors of AKI was analyzed using cox-proportional hazard regression. ROC curves were analysed for statistical differences with Delong's test. Optimal cut off values were identified by maximization of Youden's index.
Results: The mean age of cohort was 63.2 ± 10.1 years, majority being male (71.0%). Alcohol was the most common etiology for cirrhosis (32.2%) followed by Metabolic dysfunction-associated liver disease (27.4%), viral hepatitis (22.6%) and other causes. The published AKI prediction score had an AUC of 0.7368 (95% CI: 0.6429–0.8307), while MELD had an AUC of 0.7265 (95% CI: 0.6342–0.8189), and MELD-Na had an AUC of 0.7066 (95% CI: 0.6105–0.8027). Although the AKI prediction score had the numerically highest AUROC, there was no statistically significant difference between the 3 ROC curves. DeLong's test for the two correlated ROC curves for the AKI prediction score, MELD, and MELD-Na showed a Z value of 0.56441 and a p-value of 0.5725. In our cohort, the optimal cutoff values for predicting AKI were determined as follows: an AKI prediction score of −2.01 (specificity 0.745, sensitivity 0.649), MELD of 18 (specificity 0.700, sensitivity 0.702), and MELD-Na of 23 (specificity 0.721, sensitivity 0.649).
Conclusion: A MELD cutoff of 18 and MELD-Na of 23 predict patients with decompensated cirrhosis at risk for AKI. The AKI prediction score had an AUROC of 0.7368 in our population. Utilization of the MELD, MELD-Na, and AKI prediction scores can aid in the early identification of patients at risk for AKI, helping to reduce the likelihood of its development.

SAT-164

Periodontal diseases in cirrhosis: prevalence, microbiome profile and dental assessment safety and tolerability

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Background and aims: Social determinants of health and healthcare practitioners' concerns about risk of cirrhosis represent major barriers to dental care access for liver patients. We compared prevalence of periodontal disease and microbiome profiles between cirrhotic patients (PTs) and healthy volunteers (HVs). Safety of oral assessments, perception of oral health and barriers to receiving dental care were also investigated.
Method: Adults with liver cirrhosis attending the Royal Free Hepatology Clinic were invited to participate. HVs were either patients' relatives or medical staff. Subgingival dental plaque samples were collected from 27 PTs and 24 HVs. DNA was extracted and processed with high-throughput sequencing technology (Illumina). Alpha and Beta diversity tests were performed to ascertain

similarities across samples and bacteria communities. Linear discriminant analysis effect size (LEfSe) was used to identify most prevalent taxa between the groups. A qualitative questionnaire was administered to all participants pre and post dental screening and answers were compared (Fisher). PTs received telephone follow-up at 1 week.
Results: 25/27 PTs had never experienced previous barriers to dental care, 1 did not answer and 1 found obstruction due to bleeding risk. Mean age differed significantly between the groups (57 PTs vs 35 HVs, $p < 0.0001$). On microbiome analysis, PTs exhibited a reduced presence of microbial species on alpha-diversity indices, with higher abundance of Lactobacillus and Limosilactobacillus and lower abundance of Cardiobacterium, Neisseria, Lautropia and Corynebacterium at phylum level ($p < 0.001$).
There were no differences between groups in time since last dental visit or deep clean, number of alcohol units per week, smoking history and frequency of flossing and mouthwash. PTs more frequently perceived to suffer from gum disease (40.7% vs 12.5%, $p = 0.01$), to have a "tooth that doesn't look right" (66.7% vs 20.8%, $p = 0.002$), and were more often diagnosed with periodontitis at our assessment (74% vs 17%, $p < 0.0001$). After the assessment, there was no substantial difference in occurrence of gum bleeding, infection and reported experience, compared to controls. 1 week later, 1 PT reported gum bleeding after leaving the hospital and 1 reported persistent gum discomfort.
Conclusion: Our cohort of cirrhotic patients had higher prevalence of periodontitis and lower microbial diversity than healthy controls, with distinct differences in subgingival microbiome, which may reflect a link between periodontal and liver health. There were no major immediate complications and no significant difference in reported experiences when cirrhosis patients were compared to HVs. Further studies evaluating the long-term safety and impact of periodontitis management are required to confirm our findings.

SAT-165

Oral health and microbiome: do they influence cirrhosis outcomes? A comparison of cirrhotic patients with periodontitis versus those with good oral health

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Background and aims: The role of gut translocation of bacteria in triggering systemic inflammation and predisposing to infective episodes in patients with liver disease is increasingly acknowledged. However, little is known about the relationship between periodontal health and risks of complications from cirrhosis. We assessed oral microbiomes and clinical outcomes of a cohort of cirrhotic patients undergoing a dental screening for periodontal disease.
Method: Adults with cirrhosis attending the Royal Free Hepatology Clinic who were able to travel, with no severe bleeding disorder, not pregnant and >10 teeth were invited to participate if able to consent. 27 participants underwent a 30-minute periodontal screening, followed by orthopantomogram and baseline biochemistry. DNA was extracted from subgingival samples and processed with high-throughput sequencing technology (Illumina). Alpha and Beta diversity tests were performed to ascertain similarities across samples and bacteria communities. Linear discriminant analysis effect size (LEfSe) was used to identify most prevalent taxa. Follow-up by case note review was performed at 1, 3 and 6 months and compared with Fisher exact test.
Results: 20 (74%) patients were diagnosed with periodontitis (P) at assessment, while 7(26%) were healthy (H). Patients with cirrhosis and periodontitis had significantly higher MELD (median MELD 12 vs 8, $p = 0.009$). Within the microbiome, there was no difference in alpha-diversity, but the P group had higher Beta-diversity on Unweighted UniFrac method and significantly lower abundance of Fusobacterium (genus level) on LEfSe. At 1 and 3-months follow-up, some patients from P group were admitted to hospital (5, 25% at 1-month; 1, 5% at 3-months), developed HE (2, 10% at 1- and 3-months) and variceal bleed (1, 5% at 1- and 3-months), compared to none in the H group. In the P group, new infection was seen in 6 (30%) patients at 1-month, 3 (15%) at 3-months, and 1 (5%) at 6. At 6 months, 2 (10%) Ps were inpatients and 2 (10%) had died, while all 7 (100%) Hs were outpatients.
Conclusion: Our study showed that most cirrhotic patients had periodontitis and that compared to those with no periodontitis their clinical outcomes were overall poorer, though numbers were too small to reach statistical significance. The severity of liver disease was also worse in those with periodontitis, which may explain more unfavourable outcomes. The periodontitis group had higher microbiome diversity and lower abundance of Fusobacteria. Further analysis is needed to elicit the prevalence of pathogenic species in each group. Main limitations to the interpretation of these results were sample selection bias, single-arm design, and small sample size. Further studies with larger randomised cohorts are required to confirm our conclusions.

SAT-166

Use of light-EEG to rule out covert hepatic encephalopathy in advanced chronic liver disease

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Background and aims: Hepatic encephalopathy (HE) is a common and severe complication of advanced chronic liver disease (ACLD), adversely affecting patient morbidity, mortality and quality of life. Early detection of minimal HE (MHE) is crucial for overall prognosis. Current diagnostic methods, including neuropsychometric tests and standard electroencephalography (EEG), are limited by accessibility, patient compliance, and resource constraints. This study aimed to evaluate the diagnostic accuracy of a low-cost, portable, and user-friendly light EEG system for ruling out MHE in patients with ACLD.
Method: A total of 97 patients with ACLD (60% alcohol-associated liver disease; 40% other etiology) or non-cirrhotic portal hypertension were prospectively included. Light-EEG recordings were performed, and spectral analysis identified parameters such as mean dominant frequency and power across δ, θ, α, and β bands. MHE diagnosis was based on neuropsychometric tests, including Number Connection Test and Critical Flicker Frequency. Receiver operating characteristics (ROC) were analyzed to determine ß-activity cut-offs for ruling in and ruling out MHE.
Results: A history of overt HE was present in 18% (n = 17) of the cohort and 64% (n = 62) presented with decompensated ACLD (21% variceal bleeding and 43% ascites). Patients with HE demonstrated significantly reduced β-activity in the temporo-occipital (10.0% vs. 14.8%) and parietal regions (10.4% vs. 16.9%) compared to those without HE ($p < 0.01$). A β-activity cut-off of < 6.1% was highly specific (100%) for ruling in MHE, while a cut-off of >22.9% was highly sensitive (100%) for ruling it out.
Conclusion: Light-EEG is a simple, reliable, and cost-effective alternative to standard EEG, enabling effective MHE exclusion in ACLD patients. Notably, the light EEG system achieved these results without requiring extensive training or patient cooperation, highlighting its practicality for clinical use.

SAT-167

Obesity decreases liver-related death in patients with cirrhosis: a retrospective, propensity score-matched study

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Background and aims: The association between obesity and mortality in patients with cirrhosis remains controversial, probably due to the obscure criteria for obesity.
Method: This retrospective observational study enrolled 499 patients without hepatocellular carcinoma (HCC). The patients were evaluated for obesity during the subsequent 8-year follow-up period. Obesity was defined as a body fat percentage of ≥25.8% for men and ≥36.5% for women, as measured using a bioelectrical impedance analysis. After propensity score matching (PSM) was adjusted for age, sex, etiology, and severity of liver disease, 197 patients were assigned to either the obese or non-obese group. The prognostic impact of obesity in patients with cirrhosis was evaluated by differentiating between liver-related and non-liver-related deaths. All subsequent analyses used post-PSM data.
Results: The median observation period was 4.1 years. In both the obese and non-obese groups, there were 110 males (55.8%) with a median age of 68 years old. Sarcopenia was more common in the non-obese group than in the obese group (P < 0.01). A total of 113 patients died, and 3 patients underwent liver transplantation during the follow-up period. Of the 113 deceased patients, 66 died of liver-related events, and the remaining 47 died of non-liver-related events. The cumulative incidence of liver-related deaths was significantly higher in the non-obese group than in the obese group (P = 0.02), while there was no significant difference in the cumulative incidence of non-liver-related deaths between the obese and non-obese groups (P = 0.73). Multivariate competing risk analyses revealed that a non-viral etiology (hazard ratio [HR] 8.29; 95% confidence interval [CI], 2.99–22.9), decompensated cirrhosis (HR 6.12; 95% CI, 3.36–11.2), sarcopenia (HR 2.47; 95% CI, 1.21–5.04) and obesity (HR 0.49; 95% CI, 0.26–0.94) were independently associated with liver-related death. Among patients with a non-viral etiology, female patients, and patients with decompensated cirrhosis, the cumulative incidence of liver-related death was significantly higher in non-obese patients than in obese patients (P < 0.01, 0.03, and < 0.01, respectively).
Conclusion: Obesity decreased liver-related death in patients with cirrhosis, particularly in female patients, patients with a non-viral etiology, and patients with decompensated cirrhosis.

SAT-170-YI

Variables associated with postoperative mortality in advanced chronic liver disease patients undergoing urgent or elective surgery. a multicentre spanish cohort

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Background and aims: Postoperative mortality risk is higher in patients with advanced chronic liver disease (ACLD). However, the most recent score (VOCAL-Penn) seems to have lower accuracy in European patients [Canillas L. et al.; JCM2023]. The aim was to assess variables related to 90-day postoperative mortality in elective and emergent surgeries.
Method: Multicentric study including major surgeries (2010–2023) from 5 Spanish Hospitals in patients with ACLD according to 1) transient elastography >15 kPa, 2) thrombocytopenia and splenomegaly, 3) nodular liver surface, and 4) esophageal varices. Cox regression analyses were performed to identify predictors of mortality based on the type and urgency of surgery, comorbidities, liver function, and radiological or endoscopic signs of portal hypertension.
Results: We show the preliminary data (N = 2,031). The median age was 69, and 68.4% (n = 1,390) were men. Most of etiologies were alcohol (48.3%) and viral (32.6%). Emergent surgery was performed in 760 (37.4%) patients. Surgeries were abdominal (39.7%), orthopedic (21.8%), and abdominal wall (20.2%). Mortality at 90 days was 10.2% (n = 208) (18.4% in emergent and 5.4% in elective, p < 0.01). Surgeries were grouped by mortality in group 1 [abdominal wall (6.1%), abdominal-laparoscopic (5.8%) and vascular (7%) surgeries], group 2 [major orthopedic (10.2%) and cardiothoracic (11.2%)], and group 3 [abdominal-open (19.1%) and others (13.8%)]. In elective surgeries, mortality was significantly related to type of surgery (2.6% in group 1, 7.2% in group 2, and 9% in group 3), age (73 vs. 69 years), ASA-IV (42.6% vs. 10.6%), diabetes (47.1% vs. 31.8%), atrial fibrillation (20.9% vs. 9.6%), ascites (25.4 vs. 8.2%), and values of bilirubin (1.2 vs. 0.8 mg/dl), albumin (4.4 vs 4.2 g/dl), sodium (137 vs. 140 mmol/L) and platelets (96 vs. $131 \cdot 10^9$/L). Variables independently associated with mortality [HR (95% CI)] were surgery [group 1 (ref.), group 2: 2.1 (1.1–4.1), group 3: 4.0 (2.0–7.7)], age [1.0 (1.0–1.1)], bilirubin [1.1 (1.0–1.2)], ASA-IV [9.3 (2.1–40.7)], and ascites [2.4 (1.2–4.9)]. In emergent surgeries, mortality was significantly related to type of surgery (12.6% in group 1, 16.4% in group 2, and 29.3% in group 3), ASA-IV (56.5% vs. 27%), ascites (41.7% vs. 23.5%) and values of bilirubin (1.9 vs. 1.0 mg/dl), INR (1.4 vs 1.2), and platelets (110 vs. 125 10^9/L). Variables independently associated with mortality [HR (95% CI)] were the surgery [group 1 (ref.), group 2: 1.9 (1.2–3.0), group 3: 2.9 (1.9–4.5)], bilirubin [1.1 (1.1–1.1)], and ascites [1.8 (1.2–2.8)].
Conclusion: Our multicenter Spanish cohort of patients with ACLD has shown different variables associated with mortality in elective and emergent major surgeries. A new combined score could improve diagnostic accuracy for predicting surgical risk in European patients.

SAT-171

The novel classification as acute vs. non-acute decompensation provides prognostic value in cirrhosis patients developing ascites

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Background and aims: Hepatic decompensation indicates a surge in morbidity and mortality in patients with cirrhosis. Baveno VII defined first and further decompensation and. Moreover, in an attempt to provide a more granular understanding of the path to/presentation of hepatic decompensation, a differentiation into acute decompensation (AD) and non-acute decompensation (NAD) has been proposed. We aimed to assess differences in the clinical course of AD vs. NAD in patients with ascites as first decompensation event.
Method: 543 cirrhosis patients developing ascites as first decompensation were included in this single-center longitudinal cohort study, and followed until further decompensation, liver transplantation (LT) or death. AD was defined as grade 3 ascites or ascites complicated by spontaneous bacterial peritonitis [SBP] or acute-kidney injury (AKI), while NAD was defined as grade 2 ascites. Hospitalization status was recorded.
Results: Mean age was 56.6 years, the majority of the patients (65%) were male with the most common etiology being alcohol-related liver disease (59.5%). 15% of patients had a cured etiology at baseline. 304 (56.0%) met the criteria for AD (20 [6.6%] with SBP, 19 [6.3%] with AKI), of which 218 (71.7%) were hospitalized while 86 (28.3%) were not hospitalized. Similarly, 234 (44.0%) were classified as NAD, of which 114 (48.7%) were hospitalized and 125 (51.3%) were not hospitalized. During a median follow-up of 4.1 years, further decompensation was observed in 348 patients (64.1%), ACLF occurred in 150 patients (27.6%), 33 (13.8%) underwent LT, and 125 patients (23.0%) died including 105 (19.3%) liver-related deaths. AD was associated with a significantly higher risk of subsequent further decompensation (subdistribution hazard ratio [SHR]: 2.02 [95% CI: 1.64–2.49], $p < 0.001$) and mortality (SHR: 1.37 [95% CI: 1.08–1.74], $p = 0.010$) vs. NAD. However, after stratifying according to hospitalization status, AD conferred only an increased risk when requiring hospitalization (SHR [all vs. non-hospitalized NAD] for hospitalized NAD: 1.23 [95% CI: 0.86–1.78], $p = 0.260$; non-hospitalized AD: 1.13 [95% CI: 0.74–1.72], $p = 0.570$; hospitalized AD: 1.69 [95% CI: 1.22–2.33], $p = 0.001$]. Of note, inflammation as assessed by C-reactive protein (CRP) was not associated with transplant-free mortality in NAD patients while it showed an independent association adjusting for age, sex, MELD, albumin and etiological cure at baseline in AD patients (adjusted SHR per log-change: 1.28 [95% CI: 1.08–1.51], $p = 0.005$).
Conclusion: Classifying patients according to AD vs. NAD identified subgroups of distinct risk for further decompensation and transplant-free mortality. Inflammation was an independent risk factor of mortality only in patients with AD.

SAT-172-YI

Branched-chain amino acids in liver cirrhosis and hepatic encephalopathy: a meta-analysis of clinical evidence

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Background and aims: Hepatic encephalopathy (HE) is a brain dysfunction characterized by neurological and psychiatric changes associated with liver insufficiency or portal-systemic shunting, ranging from minor symptoms to coma. Nutrition plays a vital role in managing cirrhosis and HE, with branched-chain amino acid (BCAA) supplementation gaining attention for its potential to improve muscle protein synthesis, remove ammonia in muscle and reduce the risk of malnutrition and HE symptoms. The aim was to evaluate the beneficial and harmful effects of BCAA compared to any control intervention in individuals with HE and cirrhosis.
Method: We conducted a systematic search across multiple databases (April 2024). Randomized clinical trials (RCTs) comparing BCAA to any control intervention were included, irrespective of bias control, language, or publication status. Outcomes included all-cause mortality, improvement in HE, adverse events, quality of life, and nutritional status. Risk of bias was evaluated using the Risk of Bias 2 tool, and evidence quality was assessed using the GRADE approach. Meta-analyses (random-effects and fixed-effects) were performed, with subgroup and sensitivity analyses to explore heterogeneity and robustness of results.
Results: This meta-analysis included 18 RCTs (934 participants) with overt (13 trials) or minimal HE (5 trials). Nine trials assessed oral BCAA, and eight evaluated intravenous BCAA. Control interventions included no treatment/placebo, diets, lactulose, or neomycin. BCAA had no significant effect on mortality compared with controls (risk ratio (RR) 0.85, 95% CI 0.70 to 1.04; 867 participants; 17 trials; moderate quality). However, BCAA significantly reduced HE manifestations (RR 0.78, 95% CI 0.65 to 0.93; 934 participants; 18 trials; high quality). Sensitivity analyses confirmed this benefit in trials with a low risk of bias (RR 0.62, 95% CI 0.50 to 0.77). BCAA showed no notable effects on adverse events, quality of life, or nutritional parameters. Excluding trials with lactulose or neomycin as controls, BCAA maintained its beneficial effect on HE (RR 0.79, 95% CI 0.65 to 0.96), with no differences when compared directly to lactulose or neomycin (RR 0.81, 95% CI 0.46 to 1.42).
Conclusion: BCAA supplementation improves HE symptoms. We found no effect on mortality. Few trials reported adverse events, quality of life, or nutritional status. The interplay between BCAA supplementation, nutritional status, and newer established treatments like rifaximin for managing HE remains a subject of ongoing debate.

SAT-173-YI

History of overt hepatic encephalopathy is associated with worsen cognitive tests and cerebral atrophy in a prospective cohort of outpatients with cirrhosis with multimodal evaluation and brain magnetic resonance imaging with diffusion tensor imaging

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Background and aims: Hepatic encephalopathy (HE) is a severe complication of liver cirrhosis. It can take a range of forms according to its severity: Covert HE (CHE) is defined by subtle neurocognitive impairments (NI) whereas Overt HE (OHE) includes confusion, motor manifestations and can lead to coma and death. The consequences of OHE on human brain and cognitive function remains unclear but evidences of brain alterations have been identified in animal models. The aim of this study was to compare patients with liver cirrhosis

with history of OHE episodes and to identify its impact of brain function and morphology.
Method: Retrospective study of a prospective cohort of outpatients with cirrhosis (March 2018–June 2024) referred for cognitive complaints. Multimodal evaluation was conducted: neuropsychological evaluation (including HE detection tests: PHES, ANT), Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI) with spectroscopy and Diffusion Tensor Imaging (DTI). The diagnosis of CHE was made based on an adjudication committee including a neurologist, a hepatologist and a neuropsychologist. OHE history was identified by the track on the medical file.
Results: 164 patients were included, the median age was 62 (55–67), 72% of males, aetiology of cirrhosis was alcohol/MASH/Viral/mixed for 65.2/52.4/14/39.6% of them. Median MELD was 12 (9–15) and Child Pugh index 8 (6–9). Overall, 75% had a history of OHE (HOHE) and 65.9% were diagnosed with CHE. In the HOHE group, Child Pugh, MELD score and ammonia were greater ($p = 0.01$, $p = 0.002$, $p = 0.003$) and cognitive tests were worse (MoCA, PHES, ANT, respectively $p = 0.042$, $p = 0.007$, $p = 0.007$). Memory evaluation (FCSRT, Rey's Figure) was worse ($p = 0.042$, $p = 0.174$) and was not influenced by CHE status. EEG tracks were slower ($p < 0.001$) and patients had more brain atrophy and T1 hypersignals of grey central nuclei at MRI ($p = 0.015$, $p = 0.043$). No differences were found for triphasic waves at EEG, vascular leukopathy or MRI spectroscopy ($p = 0.226$, $p = 0.565$, $p = 0.165$). Differences were found in DTI Fractional Anisotropy (FA) and Radial diffusivity (RD) ($p = 0.005$, $p = 0.028$) and this was not depending on CHE status. In the HOHE group, more patients were diagnosed with CHE ($p < 0.001$). Among patients diagnosed with CHE, HOHE was associated with brain atrophy and slower EEG tracks ($p = 0.016$, $p = 0.017$). DTI FA was also significantly different ($p = 0.027$) in CHE patients with HOHE.
Conclusion: History of OHE seem to have structural and functional long-term consequences on the brain independently from CHE. HOHE patients had more NI, brain atrophy, slower EEG background rhythm and markers of brain diffusivity. Cognitive tests evaluating memory were worse in these patients, and did not depend on CHE. Furthermore, in patients diagnosed with CHE, history of OHE was associated to morphological alteration on brain MRI and diffusivity variables. The occurrence of OHE episodes should be considered for the prognosis of neurological evolution in patients with liver cirrhosis.

SAT-174-YI

The impact of anticoagulant therapy on safety of variceal ligation in cirrhotic patients: a systematic review and meta-analysis

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Background and aims: Banding ligation is a commonly used intervention for managing oesophageal varices. However, anticoagulant therapy is frequently prescribed in patients with cirrhosis for various reasons. The interaction between anticoagulant therapy and the safety of variceal banding in cirrhotic patients remains poorly understood. This systematic review and meta-analysis aims to evaluate whether anticoagulant therapy affects the outcome of variceal ligation in people with cirrhosis.
Method: Four databases (PubMed, Scopus, Embase and Web of Science) were searched for articles published until October 2024. Articles with data on non-cirrhotic patients were excluded. Major study variables included mortality, length of hospital stay, number of banding sessions, technical success rate of banding, type of anticoagulant, and risk of bleeding. The overall risk of bleeding and number of banding sessions was determined using a fixed-effect model for eligible studies.
Results: Out of 402 studies identified using our search strategy, eight underwent full-text review, with four records included in the systematic review and meta-analysis. Studies originated from France, USA, Switzerland, and Italy. A total of 388 patients were included. Warfarin and LMWH were the anticoagulants used, with portal vein thrombosis being the most common indication for anticoagulation. No significant difference was observed in MELD scores between groups ($p = 0.241$). One study reported band ligation success rates of 83% and 84% for patients with or without anticoagulation, respectively, with no statistically significant difference. Another study found mortality rates of 2 (2.5%) and 4 (2.2%) in the anticoagulant and non-anticoagulant groups, respectively, which were not significantly different. Hospital stay duration was statistically similar between groups (7.3 ± 2 vs 11.6 ± 6.4). Fixed-effect model analysis revealed no significant difference in the number of banding sessions between anticoagulant and non-anticoagulant groups ($p = 0.561$, p-heterogeneity = 0.678, $I^2 < 0.01$). The fixed-effect model demonstrated that continuing anticoagulants during oesophageal variceal ligation (EVL) was not associated with a higher pooled risk of bleeding (OR = 1.72 (CI: 0.59–5.02), $p = 0.319$; $I^2 < 0.01$).
Conclusion: Our meta-analysis shows anticoagulant therapy during banding of oesophageal varices in cirrhosis does not significantly increase adverse outcomes. Variables such as technical success rates, mortality, hospital stay, and banding sessions showed no statistically significant differences between patients on and off anticoagulants. These findings suggest that carefully monitored anticoagulant therapy can be safely maintained during EVL procedures. However, larger prospective studies are needed to establish these preliminary results and develop more precise treatment protocols.

SAT-175-YI

Natural history of overt hepatic encephalopathy defining factors associated with progression, resolution and mortality

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Background and aims: Overt hepatic encephalopathy (OHE) is an important cause of hospitalization of patients with cirrhosis. OHE is potentially reversible but factors influencing progression, resolution and mortality of patients with OHE is not known particularly with confounders such as the presence or absence of acute on chronic liver failure (ACLF), use of specific therapies and lack of accurate follow up

data. Therefore, the aims of the study were to evaluate the natural history of an acute episode of OHE and to determine factors of progression, resolution and mortality.
Method: The data for this study were from the PREDICT study, which was a prospective, observational cohort study of patients with cirrhosis hospitalized for an acute decompensation or ACLF. Progression was defined as development of OHE (grade 2 or higher) or transition from grade 2 to grades 3 or 4 at week 1. Resolution was defined as the absence of OHE at week 1 in patients with OHE at admission. Univariable and multivariable logistic regression analyses were performed. Survival was evaluated with Kaplan Meier curves and the log-rank test. Post-hoc analysis of the interaction was adjusted for multiple comparisons using the Tukey method.
Results: 1273 cirrhosis patients were included [68% males; 59 (51–67) years; alcohol (56%)], 16% were admitted with OHE and 16% with ACLF. In multivariable analysis older age, MASLD etiology, previous history of OHE, treatment with lactulose at admission and Child-Pugh score were associated with OHE ($p < 0.05$). 3% (n = 31/913) had progression of OHE, which was associated with older age, alcohol consumption and Child-Pugh score at baseline ($p < 0.05$), with a significantly shorter time-to-death ($p < 0.001$, log-rank 18.7). 79% (n = 88/112) resolved OHE with significantly longer time-to-death ($p = 0.040$, log-rank 4.7). Interaction between OHE and ACLF to predict mortality at 28 days was significant ($p = 0.003$), with higher differences across all ACLF grades compared with HE grades.
Conclusion: Presence of ACLF and non-recovery from OHE are associated with higher short-term mortality rates, while resolution of OHE is associated with significantly better prognosis. Understanding the natural history of patients with an acute episode of OHE and the factors defining prognosis and response to therapy will have profound implications on the development of novel approaches to the management of this debilitating illness.
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SAT-176-YI
Minimal serum creatinine fluctuations impact on prognosis in acutely decompensated cirrhosis
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Background and aims: Renal dysfunction is common in cirrhosis, affecting prognosis. The impact of subtle increases in serum creatinine (sCr) on major clinical outcomes of patients hospitalized for acute decompensation (AD) remains unclear.
Method: Patients with cirrhosis hospitalized for AD from July 2022 to October 2024 were prospectively evaluated. Stable renal function (SRF) was defined as sCr equal or below patients' baseline value defined as per International Club of Ascites (ICA); minimal renal dysfunction (MRD) was defined as any sCr level exceeding the baseline without fulfilling acute kidney injury (AKI) or acute kidney disease criteria as per ICA definitions. Follow-up ended at liver transplantation (LT) or death.
Results: 304 patients were enrolled. Median age was 60 years. Ascites and alcohol-related liver disease were the most frequent cause of hospitalization (60%) and etiology (45%). Patients were classified as follows: 13% SRF, 39% MRD, 28% AKI, 12% chronic kidney disease (CKD) and 8% acute-on-chronic kidney disease. Median follow-up was 5.7 months (1.7–13.2). Median sCr values were: 0.79, 0.98, 1.68, 1.81 and 3.13 mg/dL, respectively. Median follow-up was 5.7 months [1.7–13.2]. Overall, 87 (29%) patients underwent LT and 79 (25%) died. Among the 105 patients with follow-up ≥3 months, 14 (13%) developed new-onset CKD. The incidence was 0/31 for SRF, 7/47 (15%) for MRD and 7/27 (26%) for AKI (MRD *vs* SRF, $p = 0.038$; MRD *vs* AKI, $p = 0.36$). 104/278 (37%) patients discharged from index hospitalization were re-hospitalized. The 3-month cumulative incidence of rehospitalization was comparable across groups (42%, 32%, and 39%; log-rank $p = 0.73$). The 6- and 12-month LT-free survival were respectively 97% and 94% in SRF, 88% and 78% in MRD, 64% and 52% in AKI (MRD *vs* SRF, $p = 0.028$; MRD *vs* AKI, $p < 0.001$).
Conclusion: MRD is very common among patients hospitalized for decompensated cirrhosis. Our preliminary results suggest that MRD is clinically meaningful as it entails intermediate prognosis between SRF and AKI, thus confirming the few data available in the literature so far. These patients may then need careful monitoring to prevent unfavorable clinical outcomes.

SAT-177
Specialist palliative care is under-utilized at end of life in chronic liver disease, especially in patients without liver cancer
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Background and aims: The burden of liver disease in Finland is high and increasing. Traditionally, cancer patients have better access to palliative care services than patients with non-malignant diseases, although symptom burden is high in both groups. Thus, we aimed to examine the use of health care services and access to specialist palliative care (SPC) services among patients who died of either non-malignant liver disease or liver cancer.
Method: From the nationwide causes of death register, we identified all adults who died either of non-malignant or malignant (primary liver cancer) liver disease in Finland in 2019. We used National Care register to examine use of SPC and contacts to emergency department (ED). Primary outcome was an access to SPC services during the last 6 months of life, and secondary outcome the association of SPC services with the prevalence of ED contacts during the last of month of life.
Results: Overall, 896 (30.9% females, mean age 63.5 years) patients with non-malignant and 572 (32.7%; 75 years) with malignant liver disease died in 2019. Most of the patients died in-hospital (70.2% non-malignant and 82% malignant cases; $p < 0.001$). Non-malignant patients died more often at home (25.3% vs. 11.2%; $p < 0.001$, respectively).
During the last 6 months of life, SPC was provided for 7.5% (n = 67) of the patients with non-malignant, compared to 32.2% (n = 184) of the patients with malignant liver disease ($p < 0.001$). During the last month of life, respectively 5.0% (n = 45) and 27.8% (n = 159) of the patients received SPC ($p < 0.001$). Median time between the first contact with SPC service and death was 26.5 days (IQR 74) in non-malignant and 33 days (IQR 62) in malignant groups, respectively ($p = 0.695$). In the malignant group, the prevalence of ED contacts during the last month of life was lower among those who had received SPC contacts >30 days before death as compared to ≤30 days before death (53.8% vs. 76.6%; $p = 0.008$).
Conclusion: SPC services were utilized at the end of life in less than one in ten patients with non-malignant liver disease although one in four died at home. Initiatives to improve access to SPC in patients with liver disease are urgently needed.

SAT-178

Quantitative measurements of prothrombin in patients with cirrhosis and ascites: a validation study

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Background and aims: Prothrombin (coagulation factor II) is a coagulation cascade protein synthesized exclusively by the liver which results in decreased concentrations in patients with cirrhosis. The international normalized ratio (INR) is normally used to estimate prothrombin but is only an indirect measure, as INR also reflects coagulation factors VII and X, and can furthermore be affected by physiological factors and medications.
We aimed to validate a novel aptamer-based biosensor to quantify prothrombin as a potential point of care biomarker.
Method: We included 23 patients with cirrhosis and ascites together with 5 healthy individuals who served as controls. The endogenous molar concentration of prothrombin (C_{PT}) was quantified directly in EDTA-plasma stored at −80°C until sample analysis for the patients with cirrhosis. EDTA-plasma was taken from controls immediately ahead of analysis. Measurements were performed in a single 5 min reaction step by the aptamer-based electrochemical biosensor. We correlated C_{PT} levels with INR and albumin while assessing if C_{PT} was associated with liver disease severity. We followed patients from time of study inclusion (2014–2018) until November 2024.
Results: Mean age of patients with cirrhosis and ascites was 57 years (±8) while 30% were female. In the patients with cirrhosis and ascites median MELD-Na = 10 (IQR: 8–14) and Child-Pugh class distribution was B: 74% and C: 26%. Prothrombin levels were significantly lower in patients with cirrhosis (C_{PT} = 753 nM IQR: 531–961) compared to healthy controls (C_{PT} = 1654 nM IQR: 1511–1816, $p < 0.001$). In the patients with cirrhosis, prothrombin was negatively associated with INR ($r = -0.6488$, $p < 0.001$) and positively with serum albumin ($r = 0.6495$, $p < 0.001$). Similarly, INR exhibited a negative correlation with albumin ($r = -0.7408$, $p < 0.001$). There were lower prothrombin levels in patients with MELD-Na >10 (C_{PT} = 614 nM IQR: 499–753) compared to MELD-Na ≤10 (C_{PT} = 886 nM IQR: 696–1065, $p = 0.03$). Similarly, we observed a trend towards lower prothrombin levels in Child-Pugh C (C_{PT} = 503 nM IQR: 439–717) compared to Child-Pugh B (C_{PT} = 830 nM IQR: 696–960, $p = 0.0524$).
At end of follow up 8 of 23 patients were alive. 3 of these 8 (38%) scored low MELD-Na (≤10). Replacing INR with C_{PT} in MELD (MELD-Na_{PT}) resulted in 6 of 8 (75%) being classified with a low MELD-Na_{PT} (≤10).
Conclusion: Prothrombin levels measured using an aptamer-based biosensor were significantly reduced in patients with cirrhosis and correlated with established markers of liver function and disease severity. These findings suggest that the biosensor provides a fast and direct method for quantifying prothrombin as point of care diagnostics which in turn opens avenues for expanding home or remote testing of liver function in patients with cirrhosis.

SAT-179

The prognostic role of LiverRisk score in patients with compensated cirrhosis

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Background and aims: The LiverRisk score is a non-invasive test that has been recently proposed for assessing the risk of compensated advanced chronic liver disease and liver-related events in the general population. Recently, its diagnostic and prognostic ability in tertiary settings was questioned. The aim of this study was the evaluation of the ability of LiverRisk score in predicting first decompensating event and mortality in outpatients with compensated cirrhosis.
Method: 271 outpatients with compensated cirrhosis and different etiologies evaluated at a single center from 2004 to 2023 were enrolled in the study. LiverRisk score was calculated for each patient using biochemical parameters at first visit. Patients were followed until death, liver transplantation or the end of follow up (October 2023).
Results: 271 outpatients (64% males, mean age 56.7 ± 13.0 years, mainly HCV cirrhosis [48.7%], median MELD = 8, median CTP = 6) were included in the study. During follow up, 60 patients developed ascites (22.1%), 30 hepatic encephalopathy (11.1%), 17 variceal bleeding (6.3%). Fifty-six patients died (20.7%, 33 for hepatic cause) and 31 were transplanted (11.4%). At multivariable analysis (adjusted for age, MELD, varices at inclusion and effective etiological treatment), LiverRisk score was associated with higher risk of developing decompensation of cirrhosis (HR 1.08, 95% CI 1.02–1.14, $p = 0.015$) and in particular with the risk of developing ascites (HR 1.07, 95% CI 1.02–1.13, $p = 0.012$). LiverRisk score was not indepently associated with the risk of mortality (HR 1.06, 95% CI 0.96–1.18, $p = 0.245$).
Conclusion: In patients with compensated cirrhosis LiverRisk score is associated with a higher risk of decompensation, but its association with mortality risk is weak.

SAT-180

Determinants of muscle mass in patients with liver cirrhosis

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Background and aims: The interaction between liver function and muscle mass has a clinically and prognostically relevant impact on patients with liver cirrhosis (LC). In order to evaluate the effects of medication, diet, lifestyle and possible interventions on muscle mass, it is essential to have a precise understanding of the parameters that determine muscle mass in LC.
Method: We used skeletal muscle mass index (SMMI) determined by bioelectrical impedance analysis to investigate muscle mass in patients with LC. Complete data were available for 80 patients (68% male, median model of end-stage liver disease (MELD) 10, 84% with history of portal decompensation). A linear regression model was used to identify parameters influencing SMMI. The initial model included age, sex, presence of a transjugular intrahepatic portosystemic stent (TIPS), presence of tense ascites, hepatic encephalopathy based on Number Connecting Test (NCT), bilirubin, creatinine, albumin, INR and cystatin C.
Results: After stepwise backward elimination, sex, bilirubin, cystatin C, TIPS, INR, ascites and NCT remained in the final model with in decreasing order of relative importance. A negative correlation with SMMI was found for female sex ($p < 0.01$), cystatin C ($p = 0.01$), INR ($p = 0.03$), ascites ($p = 0.02$) and NCT ($p = 0.054$). TIPS ($p = 0.02$) and bilirubin ($p < 0.01$) had a significant positive correlation. Albumin, age and creatinine had only small effects. Using aggregated scores such as MELD or Child-Pugh instead of the separate parameters contained in each score resulted in a significantly worse model (multiple R-squared 0.44 or 0.42 vs. 0.54).
Conclusion: MELD and Child score have only a weak correlation with SMMI. Due to the involvement of creatinine in both renal and muscle metabolism and the positive correlation of bilirubin with muscle

mass, MELD and Child score should not be used to adjust for liver function in studies of muscle mass in LC. Parameters correlated with SMMI are sex, renal function (cystatin C), portal hypertension (ascites, TIPS), INR and NCT. Multivariate linear regression models based on these parameters will allow for a more accurate assessment of the impact of other factors (e.g. medication, lifestyle, diet) and interventions on muscle mass in patients with LC.

SAT-181

Attitudes towards exercise among patients with advanced chronic liver disease: a survey

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Background and aims: Sarcopenia, the reduction of skeletal muscle mass and strength, is common for patients with advanced chronic liver disease (ACLD). This confers an increased risk of ascites, encephalopathy, hospital admission and mortality compared to patients with ACLD who do not have sarcopenia. A number of interventions have been proposed to reverse sarcopenia including diet and exercise interventions. In addition to its impact upon muscle function, exercise may have positive impact on patients' mood, body image and quality of life.
Method: A 21 point anonymised paper-based survey was distributed to patients attending a liver support clinic for patients with decompensated advanced chronic liver disease between July and November 2024. Questions included aetiology of chronic liver disease, age range, gender, current exercise times and modalities, attitudes towards exercise and limitations from exercise. All items were self-reported.
Results: 54 surveys were completed. 23 (42.6%) patients were aged between 45–60. 20 (37.0%) patients are female. 24 (44.4%) patients had alcohol related liver disease.30 (55.6%) patients reported current exercise. The median number of days exercised per week was 3 (IQR 2–5). The median cumulative weekly duration of exercise was 2 hours (IQR 0.71–5.35) and 22 (40.7%) exercise for 2.5 hours or greater per week in line with EASL guidelines. 30 (55.6%) patients attributed the maximum score (5/5) to the importance of exercise with a further 16 (29.6%) scoring it at 4/5. 39 (72.2%) patients walk for exercise, 11 (20.4%) swim and 5 (9.3%) use weights. 3 (79.6%) patients identified physical benefits from exercise, 40 (74.1%) patients experienced increased energy, 44 (81.5%) experienced improved mood and 41 (75.9%) experienced a reduction in anxiety. 28 (51.9%) patients would welcome advice on appropriate exercise and 31 (57.4%) patients would avail of a structured exercise program. The exercise habits of 23 (42.6%) patients were limited by a lack of energy and 16 (29.6%) patients were limited by pain.
Conclusion: This survey demonstrates that patients with ACLD greatly value exercise. Although the majority of patients with ACLD report exercising multiple times per week a sizeable proportion (44.4%) do not engage with regular exercise. The vast majority of respondents identify physical and mood benefits from exercise. Common symptoms of chronic illnesses limit the ability of patients to take part in exercise as they wish. Structured exercise programs should be made available to patients with liver disease in line with their preferences.

SAT-182-YI

Transjugular intrahepatic portosystemic shunt implantation is associated with resolution of hepatopulmonary syndrome

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Background and aims: Hepatopulmonary syndrome (HPS) is a severe complication of portal hypertension, characterized by intrapulmonary vascular dilatations (IPVD) and elevated alveolar-arterial oxygen gradient (P(A-a)O2) leading to increased mortality. As of now, liver transplantation is the only curative treatment. While transjugular intrahepatic portosystemic shunt (TIPS) placement is an effective therapy for other complications of portal hypertension, its impact on HPS remains unclear. Some case reports suggest potential benefits, but concerns persist about exacerbating the pre-existing hyperdynamic circulation and aggravating HPS. Thus, this study aimed to evaluate the effect of TIPS placement on HPS.
Method: A prospective cohort study was conducted, including patients who underwent covered TIPS placement at MHH between 01/2021 and 01/2024. Patients were eligible for inclusion if they had contrast-enhanced transthoracic echocardiography (cTTE) and blood gas analysis (BGA) performed prior to TIPS placement (baseline; BL) and at least once at 6–18 months post-intervention (follow-up; FU). Patients with intracardiac shunt were excluded. Longitudinal effects of TIPS placement on HPS were assessed using linear mixed models (LMM).
Results: Forty-three patients (72% male, 74% TIPS indication refractory ascites) were included. The leading etiology was alcohol-related liver disease (60%) and the median MELD score was 10. At BL 30 patients (70%) had IPVD and 28 (68%) met HPS criteria. The median $P(A\text{-}a)O_2$ was 30.0 mmHg (interquartile range [IQR]: 23.0–39.9). At FU HPS prevalence significantly decreased to 12 patients ($p < 0.001$) while 27 still showed IPVD ($p = 0.581$). Nineteen patients (46%) reduced their $P(A\text{-}a)O_2$ by ≥10 mmHg. The median $P(A\text{-}a)O_2$ decreased to 23.5 mmHg (IQR: 9.0–35.2) ($p < 0.001$). Nineteen patients (67.9%) resolved their HPS: 11 via improvement in $P(A\text{-}a)O_2$, five by alleviation of IPVD, and three via improvements in both. HPS resolution was not associated with symptom control for TIPS indication (i.e. absence of ascites persistence or recurrence of portal hypertensive bleeding) at FU (74% vs. 77%, $p = 1.00$). Among patients without BL IPVD or HPS ($n = 13$), six (46%) developed IPVD, and five (38%) subsequently met HPS criteria. Notably, FU oxygenation improved even in patients without BL IPVD or HPS, as five (38%) achieved a reduction ≥10 mmHg in $P(A\text{-}a)O_2$. In LMM analysis, HPS prevalence was significantly reduced at 6 months post-TIPS ($p = 0.017$), along with a significant decrease in $P(A\text{-}a)O_2$ ($p = 0.013$). The presence of pathological $P(A\text{-}a)O_2$ was significantly lower at 6 months ($p < 0.001$) and 12 months ($p = 0.017$) compared to BL. Partial pressure of carbon dioxide did not differ significantly across time points.
Conclusion: TIPS implantation is associated with a significant improvement of $P(A\text{-}a)O_2$ and can lead to improvement or even resolution of HPS in a majority of patients.

SAT-183

The association between familial mediterranean fever and incidence liver cirrhosis: a population based matched cohort study

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Background and aims: Familial Mediterranean Fever (FMF) usually does not involve the liver, although some evidence correlates FMF to cryptogenic cirrhosis. A previous work by our group, presented in the EASL congress 2022, showed that FMF was independently associated with incident cirrhosis among a cohort of chronic colchicine uses. The aim of this study is to examine the association between FMF and incident cirrhosis.
Method: Using the Maccabi Healthcare Services (MHS) computerized database, we extracted data of all patients aged ≥18 years, diagnosed with FMF according to ICD-9 code 277.31, between January 1, 2000 to December 31, 2022. A control group of patients was matched in 1:1 ratio by age and gender. Index date for FMF group was the date of diagnosis (or 18 if the diagnosis was made earlier in life) and for control group the date of study enrollment. We excluded patients with cirrhosis prior to index date as well as any chronic liver disease other than metabolic dysfunction-associated steatotic liver disease. Primary outcome was the incident cirrhosis, while event was defined by any of the following: incident cirrhosis, liver transplantation, end of follow-up, leaving MHS or death. We used cox proportional hazards models to assess the risk factors associated with cirrhosis and Kaplan-Meier curves to estimate the time to cirrhosis.
Results: Each group included 5236 patients, well matched in terms of age and gender. FMF group included higher proportion of obese patients (59.05% vs. 50.63%, $p < 0.01$) and higher proportion of diabetes (8.10% vs. 5.83%, $p < 0.01$). During follow-up, patients with FMF had higher incidence of cirrhosis compared to control group (2.10% vs 0.40%, p-value < 0.01). Cox proportional hazards model indicated that FMF was significantly associated with incident cirrhosis (HR = 2.60, 95% CI: 1.54–4.38, $p < 0.01$). Kaplan-Meier analysis demonstrated that cirrhosis free-survival rate in 7 years was significantly lower among FMF patients when compared to control (98.24% vs 99.66%, $p < 0.01$).
Conclusion: FMF patients have higher risk of incident cirrhosis, when compared to age and gender matched controls. The association between FMF and incident cirrhosis was irrespective to other metabolic risk factors for liver cirrhosis.

SAT-184-YI

Impact of diabetes mellitus on clinical outcomes in patients with acutely decompensated cirrhosis

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Background and aims: Diabetes mellitus (DM) is common in patients with chronic liver disease, it is involved in the progression of fibrosis and significantly increases the risk of liver-related complications and mortality. However, its impact on decompensated hospitalized patients remains poorly addressed.
Method: Patients with cirrhosis hospitalized for acute decompensation (AD) between July 2022 and October 2024 were prospectively evaluated and followed-up until liver transplantation (LT) or death.
Results: 304 patients were included. One-third had DM (101/304, 33%). Compared to non-DM patients, DM patients were older (66 *vs* 57 years, $p < 0.001$) and with higher rates of arterial hypertension (45% *vs* 26%, $p = 0.002$); the prevalence of chronic kidney disease was similar (24% *vs* 19%, $p = 0.36$). The predominant etiology was metabolic dysfunction-associated steatotic liver disease (MASLD) in DM patients (30% vs. 8%, $p < 0.001$) and alcohol-related liver disease in non-DM patients (26% *vs* 54%, $p < 0.001$). The most common cause of hospitalization in each group was ascites (63% and 58%, respectively). Both groups had a median MELD-Na score of 20. Acute kidney injury (AKI) occurred in 36% in both groups during index hospitalization ($p = 0.89$). AKI stage ≥2 was more frequent in DM patients, although not significantly (47% *vs* 30%, $p = 0.09$). Among patients discharged from the index hospitalization (278), 33/93 (35%) of DM patients and 71/185 (38%) of non-DM patients experienced further hospitalizations ($p = 0.69$). The 3-month cumulative probability of rehospitalization was similar (25% *vs* 29%, log-rank $p = 0.84$). After a median follow-up of 5.7 (IQR 1.7–13.2) months, a comparable number of patients with- and without DM died (27% *vs* 26%, $p = 0.89$) or underwent LT (27% *vs* 30%, $p = 0.69$). The 6-month LT-free survival was 78.8% and 79.1%, respectively (log-rank $p = 0.99$).
Conclusion: Diabetes mellitus is frequently observed in patients with cirrhosis hospitalized for AD, particularly among older individuals and those with MASLD. In this high MELD cohort, DM did not significantly impact short- or medium-term outcomes, as evidenced by similar AKI rates, rehospitalization risk and 6-month LT-free survival.

SAT-185

Impact of PPIs, PCABs, and Rifaximin on SBP risk in cirrhotic patients with moderate-to-severe ascites

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Background and aims: The role of acid-suppressive therapies, particularly proton pump inhibitors (PPIs) and potassium-competitive acid blockers (PCABs), in the risk of spontaneous bacterial peritonitis (SBP) among cirrhotic patients remains controversial. While rifaximin has been suggested to lower SBP incidence, its protective effect is unclear. This study aimed to evaluate the differential impact of these medications on SBP risk.
Method: This retrospective study analyzed 105 cirrhotic patients with moderate-to-severe ascites undergoing diagnostic paracentesis between April 2018 and March 2024. Patients on steroids or immunosuppressants were excluded. SBP was defined as an ascitic neutrophil count ≥250/mm^3 or positive ascitic fluid culture within 5 days of admission. Clinical factors, including medication use, were compared between SBP and non-SBP groups, and multivariate logistic regression was performed.
Results: The median age was 64 years, with 68 males and 37 females. Child-Pugh grade B and C were observed in 25 (23.8%) and 80 (76.2%) patients, respectively. SBP was diagnosed in 27 patients (22.9%). Significant differences between SBP and non-SBP groups were observed in Child-Pugh score ($p = 0.024$), leukocyte count ($p = 0.017$), prothrombin time ($p = 0.047$), and PCAB use ($p = 0.018$). The 90-day/180-day survival rates (excluding transplant cases) were 69.7%/50.8% for non-SBP and 46.2%/30.8% for SBP patients. Stratified by medication, the SBP incidence was 14.3% in the no-PPI/PCAB

group, 21.8% in the PPI group, and 46.7% in the PCAB group, with a significantly higher rate in the PCAB group. No significant difference was observed in SBP incidence based on rifaximin use (22.2% vs. 26.7%). Multivariate logistic regression identified PCAB use as the sole factor associated with SBP (Odds Ratio: 3.80, p = 0.030).
Conclusion: This study highlights the significant association between PCAB use and increased SBP risk in cirrhotic patients, while PPI and rifaximin use showed no such association. The findings underscore the importance of cautious prescribing of PCABs in this population to mitigate the risk of SBP. Tailored treatment strategies considering the differential effects of acid-suppressive therapies are warranted.

SAT-186-YI
Comparison of the animal naming test 1 minute versus 2 minutes for the screening of covert hepatic encephalopathy in a prospective cohort of outpatients with cirrhosis
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Background and aims: Hepatic encephalopathy (HE) is the most severe complication of cirrhosis. In its lightest form, "covert" HE (CHE) is characterized by isolated neurocognitive disorders (NCDs) that are difficult to diagnose, especially in patients with comorbidities (alcohol sequelae, obesity, diabetes) also affecting cognition. Several tools exist for screening, including cognitive tests like the Animal Naming Test (ANT). Conducted in 1 minute (ANT1), the French recommendation threshold is 20. However in neuropsychology, the test is validated for the general population in its 2-minute version (ANT2), standardized by age, sex, and education. This study aimed to compare ANT1 thresholds with ANT2 standards.
Method: We conducted a retrospective study on a prospective cohort of cirrhotic outpatients (March 2018-April 2024) referred for suspected CHE. NCD assessment included clinical exams (hepatologist, neurologist), neuropsychological tests (ANT1, ANT2, PHES), biomarkers, EEG, and brain MRI with spectroscopy. CHE diagnosis was established during multidisciplinary consultations by an adjudication committee based on examination results. Follow-up focused on clinical HE occurrence. Continuous values are medians, categorical values as numbers (%). Survival analysis used Kaplan-Meier and log-rank tests.
Results: 159 patients were included (71% male) aged 62 (55–67) years. Main causes of cirrhosis were: alcohol/metabolic/virus for 65/51/14%, 29% with ≥2 causes. Child-Pugh scores were: A/B/C for 26/63/11%; MELD score: 12 (9–15). Brain injury occurred in 10%, obesity in 30%, and TIPS in 25%. In total, CHE was diagnosed in 66% by the adjudication committee. Median ANT1, ANT2 and PHES scores in CHE patients were 14 (10–19), 21 (15–31) and −3 (−7; −1) vs. 18 (14–23), 29 (21–35) and −1 (−3; 0) in non-CHE patients (p = 0.002, p = 0.001, p = 0.002). ANT1, ANT2 and PHES were pathological in 69%, 21% and 33% of patients. 70% of patients with a pathological ANT1 had a normal ANT2, and 2% of patients with a normal ANT1 had a pathological ANT2. For CHE patient, ANT1threshold 20 had sensitivity (Se) and specificity (Sp) of 75% and 42%, while ANT2 (personalized thresholds) achieved Se 28% and Sp 92%. PHES (threshold: −4) had Se 39% and Sp 77%. Median follow-up was 60 months: 42% of patients experienced OHE. ANT1, ANT2 were significantly associated with the apparition of OHE (LR = 0.033, LR = 0.008), but not PHES (LR = 0.47).
Conclusion: In this study, only ANT1 and ANT2 are associated with Overt HE occurrence and not PHES. ANT1 and ANT2 seem to be better diagnostic tests for CHE than PHES, because they are correlated with the occurrence of OHE. There is a significant discordance between ANT1, whose threshold does not take into account age and education, which are known to impact verbal fluency, and ANT2, a robust and validated test in neuropsychology, for the screening of CHE. ANT1 is a good screening test because of its high Se, and ANT2 is more specific. A combination of the 2 tests would allow to refine the diagnosis of CHE using a rapid test.

SAT-187
Rehabilitation classes for sarcopenic cirrhotics, a proof of concept
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Background and aims: Patients with liver cirrhosis present an estimated 40% prevalence of sarcopenia and 30% of frailty. Both sarcopenia and frailty are associated with greater risk for hepatic decompensation and mortality. There is a general consensus that patients with cirrhosis should engage rehabilitation programs with physical exercise to prevent and rescue from sarcopenia/frailty. However, it is still to be determined which would be the ideal rehabilitation program for patients with cirrhosis.
Method: Pilot study, with the enrolment of liver cirrhosis outpatients in a muscle rehabilitation program, with classes of 4 to 5 patients with cirrhosis, engaging physical exercise supervised by a physical rehabilitation therapist, with sessions of one hour, twice a week, for 10 weeks. All patients were advised to take a late evening snack with a high protein (20 g of protein) yoghurt. Before and after the intervention, 6-minute walk (6MW), 5-chair stand test (5-CST), handgrip strength, and bioimpedance measurements were done.
Results: 20 patients were enrolled (80% male, age 65 ± 6 years), 15 of whom already finished the program. Aetiology of cirrhosis was: 75% alcohol-associated, 15% MASLD, and 10% viral hepatitis; CPT class: A 50%, B 45% and C 5%, MELD3 was 13.1 ± 5.5 points. Adhesion rate to the program was 93%. At enrolment, the 6MW test was 336 ± 103 m, 5-CST 18 ± 20 s and handgrip strength 27 ± 2 kg. The performance of frailty tests was not associated with the severity of liver disease (assessed by Child-Pugh-Turcotte class, ALBI or MELD3). Evaluating patients that ended the program, we found an increase in muscle mass (48.8 ± 7.9 *vs.* 49.6 ± 7.8 kg, P = 0.038) and 6MW distance post intervention (361 ± 103 *vs.* 395 ± 94 m, P = 0.038), with a trend to lower proportion performing poorly (25% *vs.* 7% < 250 m, 65% *vs.* 64% 250–450 m, and 10% *vs.* 29% >450 m, P = 0.236). There was a trend to a decrease in 5-CST duration post intervention (20 ± 23 *vs.* 11 ± 3 s, P = 0.207), and to lower proportion performing poorly (26% *vs.* 7% >15 s, 42% *vs.* 57% 10–15 s, and 32% *vs.* 36% < 10 s, P = 0.353); no difference in handgrip strength (29.7 ± 8.7 *vs.* 30.8 ± 8.0 kg, P = 0.101), with a trend to lower proportion performing poorly, i.e. < 30 kg in men and < 15 kg in women (53% *vs.* 21%, P = 0.072).
Conclusion: A hospital class-based muscular rehabilitation program in patients with cirrhosis is feasible and associates with a high adhesion rate. The short-term effects of these programs seem promising, associating with improvement in frailty.

SAT-191-YI
Regulation and prognostic value of Fibroblast Growth Factor 23 in advanced chronic liver disease
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Background and aims: Fibroblast growth factor 23 (FGF23) is a key regulator of phosphate homeostasis linked to kidney disease and cardiovascular risk. We assessed FGF23 levels across stages of advanced chronic liver disease (ACLD) and its prognostic value.
Method: FGF23 levels were assessed in consecutive compensated (cACLD) and decompensated (dACLD) patients included in the Vienna Cirrhosis Study (VICIS; NCT03267615) characterized for portal hypertension (HVPG) and hepatic dysfunction (Child-Turcotte-Pugh: CTP-Score). Correlations of FGF23 with Creatinine (sCrea), Phosphate, Calcium, Vitamin D, PTH, and proBNP were tested. Patient characteristics and outcomes (first/further decompensation; overall survival) were compared between ACLD patients with elevated vs. non-elevated FGF23 levels.
Results: In 367 patients median FGF23 was higher in dACLD (n = 229; 51.4 pg/mL) vs. cACLD (n = 138, 46.1 pg/mL; p = 0.002) patients. FGF23 was elevated (>95.4 pg/mL) in n = 47 (12.8%; $FGF23^{high}$). Main characteristics of $FGF23^{high}$ patients were higher CTP-Score (p = 0.014), sCrea (p < 0.001; n = 11 [23.4%] with sCrea >1.5 mg/dL), phosphate (p < 0.001), proBNP (p < 0.001) and lower Vitamin D (p = 0.001), while no differences were found for PTH (p = 0.849). Accordingly, patients with abnormal sCrea (p < 0.001), phosphate (p = 0.004), calcium (p = 0.008), Vitamin D (p < 0.001) and proBNP (p = 0.001) had significantly higher FGF23 levels. Follow-up data (median 21.9 months) was available in 263 patients: $FGF23^{high}$ (n = 28) had no predictive value for decompensation (p = 0.12). While $FGF23^{high}$ patient showed higher mortality (log-rank p < 0.001), on multivariate analysis $FGF23^{high}$ was not independently associated with mortality (adjusted hazard ratio, aHR: 1.002, 95% CI: 0.9990–1.005; p = 0.197), while CTP (aHR: 1.489, 95% CI: 1.301–1.705; p < 0.001) and CRP (aHR: 1.294, 95% CI: 1.153–1.451; p < 0.001) remained independent risk factors for mortality.
Conclusion: FGF23 levels are higher in dACLD vs. cACLD and elevated FGF23 levels were linked to abnormal phosphate, calcium and Vitamin D levels and to renal and cardiac dysfunction. When adjusted for CTP, renal dysfunction and inflammation, elevated FGF23 did not impact on the risk for decompensation and mortality – indicating no independent prognostic value of FGF23 in ACLD.

SAT-192

Identifying potential baseline risk factors for further decompensation in patients with cirrhosis and early decompensation: analysis of data from a phase 2 randomized trial

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Background and aims: In patients with cirrhosis and ascites, additional decompensating events may occur; however, data characterizing further decompensation (DC) and associated risk factors in this population are limited. The aim of this analysis was to characterize a population with early decompensated cirrhosis who subsequently progressed (ie, further DC) vs those who did not, within a controlled trial setting.
Method: A phase 2, dose-ranging, randomized, double-blind trial (Bajaj et al. *Clin Gastroenterol Hepatol.* 2023;21[3]:723–731.e9) enrolled adults with cirrhosis and documented ascites (≥ grade 1; not medically refractory) and Conn score < 2, with no history of esophageal variceal bleeding (EVB), spontaneous bacterial peritonitis (SBP), or renal failure in the presence of comorbid ascites. Patients were randomly assigned to 24 weeks of treatment (6 arms; placebo/investigational rifaximin soluble solid dispersion tablets). A DC event was defined as a hospitalization for EVB, hepatic encephalopathy, hepatorenal syndrome, or SBP, or death due to liver complications during the 24-week period. Data were pooled across all treatment arms and stratified (with vs without DC event[s]); baseline demographic/baseline parameters were evaluated for the 2 subgroups post hoc.
Results: A total of 516 patients were included; 81.4% were aged < 65 y (median, 57.0 y [range, 26–83 y]), 61.0% were male, and 61.4% had a Conn score = 0. The mean (SD) MELD and MELD-Na scores were 11.5 (3.4) and 12.9 (3.9), respectively. Patients with (n = 61) vs without (n = 455) a DC event were more likely to have a higher baseline Child-Pugh (CP) class (A [0% vs 13.4%; p < 0.001], B [78.7% vs 80.9%; p > 0.05] or C [21.3% vs 5.7%; p < 0.001]), MELD score (≤10 [23.0% vs 45.1%; p < 0.001], 11–18 [70.5% vs 52.1%; p < 0.01], or 19–24 [4.9% vs 2.9%; p > 0.05), and MELD-Na score (≤10 [11.5% vs 31.6%; p < 0.001], 11–18 [68.9% vs 62.6%; p > 0.05], or 19–24 [14.8% vs 5.5%; p = 0.01). Significantly more patients with vs without a DC event had both a MELD score >10 and CP class B or C (77.0% vs 49.2%; p < 0.0001). Comorbid diabetes and cirrhosis etiology rates were similar between the 2 groups.
Conclusion: These trial data affirm that cirrhosis-related parameters, monitored to help determine patient prognosis (eg, MELD/MELD-Na score), identified patients with early DC at risk for further DC.

SAT-193-YI

Economic evaluation of LivR Well, a multidisciplinary, multimodal, home-based program for acute hepatic decompensation: interim analysis

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Background and aims: Chronic liver disease is a clinical and economic challenge with rates of mortality and re-admission greater than 30%. We compared LivR Well, a 28-day, home-based, program following acute hepatic decompensation to standard care, and herein report the economic evaluation.
Method: A randomized controlled trial was conducted at an Australian, non-liver transplant health service from February 2022 to May 2024. Patients with acute hepatic decompensation were recruited from inpatient or ambulatory care and randomized 1:1 to LivR Well, or standard care. The LivR Well group received weekly hepatology consultation, and physiotherapy, dietetics, pharmacy, social work, and/or addiction medicine when indicated. The program was delivered through Hospital in the Home (HITH) acute bed substitution model and both groups were coordinated by a liver clinical nurse consultant. We performed both a within-trial and modelled economic evaluation. Quality-adjusted life years (QALY) were calculated using utility weights extracted from EuroQoL-5 dimensions (EQ-5D-5L) at baseline, week 6, and week 12 with missing data imputed using multiple imputation. Costs included were HITH admission, unplanned, liver-related hospitalisation, regular albumin infusions, elective paracentesis and staff costs. The modelled evaluation took a lifetime horizon and used a Markov cohort structure with patients transitioning between 'compensated', 'decompensated', 'acute-on-chronic liver failure', and 'dead'. Transition probabilities were calculated using a historical cohort of patients with chronic liver disease. The primary outcome of both evaluations was incremental cost-effectiveness ratio (ICER).
Results: A total 106 patients were enrolled and randomized (n = 54 intervention, n = 51 control) with costs data available for 94 enrolled

to 7 April 2024. Ten intervention group patients dropped out (including 6 prior to program commencement), and 2 control group patients dropped out following randomization. EQ-5D-5L data were missing in 36%, 45%, and 59% at baseline, week 6, and week 12, respectively. The within-trial economic evaluation demonstrated median costs per patient for LivR Well and control were AU$1,542 (IQR: $381-$2,576) and AU$1,290 (IQR: $856-$2,969) respectively. Median QALYs generated per patient were 0.178 (IQR: 0.170–0.188) and 0.180 (IQR: 0.171–0.186) respectively resulting in a within-trial ICER of AU$356,402/QALY. The modelled evaluation had a deterministic ICER of AU$123,353/QALY. In the probabilistic sensitivity analysis LivR Well met the AU$50,000/QALY threshold in 0% of 2,000 iterations.

Conclusion: Interim results suggest that the existing protocol for LivR Well is unlikely to be cost-effective compared to standard care. Low rate of EQ-5D-5L completion may have contributed to the lack of difference in QALYs. A future adaptation which is simpler and cheaper may result in an ICER closer to the willingness-to-pay threshold.

SAT-194

Transcatheter closure of acquired portosystemic shunts for the management of refractory hepatic encephalopathy. A case-series

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Background and aims: Hepatic encephalopathy (HE) occurs in 30–40% of patients with cirrhosis, and has a significant impact on quality of life, hospitalisation, and mortality. Transcatheter closure of large acquired portosystemic shunts (SPSS) may improve HE grading, overall performance status, and rates of rehospitalisation. We aim to describe characteristics and outcomes of patients with refractory HE following SPSS closure.

Method: We report a case series of 12 patients who underwent attempted angiographic obliteration of SPSS for treatment of refractory HE between January 2019 and November 2024 at a tertiary Australian hospital. Outcomes include radiological success, reduction in Westhaven HE grade at 4 weeks, and time to subsequent HE hospitalisation.

Results: A total of 12 patients were identified for inclusion. The median age was 64 years (Interquartile Range (IQR): 57–69), n = 7 were male, and n = 11 had cirrhosis, with portal hypertension attributed to chronic portal vein thrombosis in one patient (Type B). Baseline median Model for End-stage Liver Disease (MELD) score was 15 (IQR): 13–19) and median Child-Pugh score 9 (IQR: 8–11). One patient had no prior hospitalisation for HE and 2 had previously required intensive care unit support. Baseline Westhaven grades were 1 (n = 1), 2 (n = 8), 3 (n = 1), and 4 (n = 2) with 9 patients requiring assistance with self-care. All patients were prescribed lactulose and 11/12 were prescribed rifaximin at the time of the procedure. The main target shunt locations were splenorenal (n = 4), and left gonadal (n = 2). All SPSS were identified on four-phase computed tomography. Radiological closure of target SPSS was achieved in 10/12. Mean follow up was 450 ± 414 days with two deaths at 8 days and 199 days from SPSS closure. The first patient died during the index hospital admission with persistent grade 4 HE, the cause of the second is unknown, and both patients had successful obliteration of the target SPSS. At 4 weeks, 7 of the 11 surviving patients had documented resolution of overt HE, and the remaining 4 had grade 1 HE. Screening gastroscopy was performed post closure in 9 of which 6 had known varices. There were no procedure-related complications including subsequent variceal haemorrhage. A total 5 patients had subsequent admissions with HE at a mean 307 ± 226 days.

Conclusion: Transcatheter closure of large SPSS for refractory HE appears safe and effective in this small case-series. Whilst clinical success is difficult to establish retrospectively, positive results include readmission for HE in fewer than half and at a mean interval of 10 months. Findings support use of targeted imaging reviewed by an experienced radiologist to identify accessible SPSS in patients with portal hypertension and refractory HE in settings where shunt closure is available.

SAT-195

Daily step count using pedometer for sarcopenia management in patients with cirrhosis: a randomized controlled trial

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Background and aims: Sarcopenia, a condition characterized by reduced muscle mass and strength, affects nearly 40% of cirrhosis patients and is linked to increased mortality and hospitalization. Studies suggest that adequate nutrition and increased physical activity, as measured by daily step counts using pedometers, can improve muscle health in these patients. This study aims to compare the effectiveness of full pedometer recording (FPD) versus partial pedometer recording (PPD) on skeletal muscle index (SMI), sarcopenia resolution and mortality/hospitalization rates in patients with cirrhosis.

Method: In this prospective, open-label, randomized trial, sarcopenic cirrhotic patients were assigned to wear pedometer for 24 weeks (n = 27) or wearing pedometer for 12 weeks (n = 26). Both groups received standard medical care and protein supplements (16 grams) with albumin powder and soy-milk. Patients were encouraged to engage in active physical activity or walking for at least 30 minutes per day (minimum of 3000 steps/day) and all were remined twice per week via line app or by phone call. At baseline, 12 weeks, and 24 weeks complete blood count (CBC), serum creatinine, albumin (Alb), total bilirubin (TB) were collected. Anthropometric assessments and analysis of body fat percentage and measurement of skeletal muscle index (SMI) using bioelectrical impedance analysis (BIA). Standard frailty metrics were assessed, including the liver frailty index (LFI), handgrip strength, chair stand test, balance (3-positions), 6-minute walk test (6MWT), and gait speed test (GST).

Results: Total of 53 patients were enrolled (average age 65.2 years, 49.1% female, 39.6% with hepatitis C virus (HCV), 98% with Child-A cirrhosis. Both groups had similar demographics. At the 24-week follow-up, the change in SMI showed a slight improvement in the PPD group compared to the FPD group (1.45% ± 4.89% vs 1.22% ± 3.95%, p = 0.859). The daily step count was higher in the FPD group than in the PPD group (3992 steps [3042–7847] vs 2410 steps [1476–6466], p = 0.053). Thirteen (48.1%) patients in FPD and 10 (38.5%) patients in PPD group had resolution of sarcopenia (p = 0.47). The change in balance test in FPD group showed significant improvement compare to PPD group (0.00% [0.00–11.11] vs 0.00% [−0.83–0.00], p = 0.032). More than 72% of patients in both groups had stable or improved SMI. Two patients were hospitalized due to upper gastrointestinal bleeding, and no deaths were observed.

Conclusion: In sarcopenic cirrhotic patients who received nutritional supplements and continuous daily step count notifications via pedometer, no significant changes in SMI or resolution of sarcopenia were observed compared to the partial-monitor pedometer group. However, balanced test improvements were observed, reflecting improvements in liver frailty index. These findings suggest a trend toward improvement in sarcopenia in the FPD group.

SAT-196-YI

Prognostic performance of MELD and MELD 3.0 in 777 patients hospitalized with an acute decompensation of cirrhosis

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Background and aims: The Model for End-Stage Liver Disease (MELD) score prioritizes organ allocation for liver transplantation. While multiple prognostic scores exist for acute-on-chronic liver failure, clinicians often use MELD for ward-based management of complications to cirrhosis, despite its design for transplant allocation. We evaluated and compared the ability of MELD and MELD 3.0 to predict 90-day mortality in patients hospitalized with acute decompensation of cirrhosis.
Method: We analyzed data from the ATTIRE trial, which enrolled 777 patients with cirrhosis. Trial included patients admitted with acute decompensation and excluded those receiving palliative care or diagnosed with advanced hepatocellular carcinoma with a life expectancy of less than eight weeks. We calculated MELD and MELD 3.0 scores at randomization and evaluated their performance in predicting 90-day mortality using Akaike's Information Criterion for model fit. For prognostic discrimination, we used C-statistic, which is similar to time-dependent area-under-the-curve, and goodness of fit plots with Hosmer and Lemeshow tests for model calibration.
Results: Mean age was 53.8 years (±10.6) with 29% being female and with alcohol-related cirrhosis as the dominant etiology (90%). Majority of patients (97%) were admitted to the ward and 18 (3%) to the intensive care unit. Most admitted patients were due to new onset or worsening of ascites (67%), while the number of patients with organ dysfunction at admission was around 10%. At randomization, median MELD = 20 (IQR: 15–23) and MELD 3.0 = 23 (IQR: 18–27). The 90-day mortality was 24% and 4 patients (<1%) were transplanted during this period. The 90-day mortality C-statistic for MELD was 0.675 and 0.699 for MELD 3.0, which also had overall improved model fit (P = 0.0003). Model calibration for predicted and actual probability of 90-mortality was adequate for MELD, but poor for MELD 3.0 (p = 0.0295).
Conclusion: Our results highlight the limitations of MELD and MELD 3.0 when predicting mortality in hospitalized patients with predominantly alcohol-related cirrhosis where few were transplant candidates. In a ward-based setting, we recommend caution using these models in discussions with patients and relatives regarding prognosis, treatment escalation or palliation.

SAT-197-YI
Smoking aggravates inflammation, fibrogenesis, angiogenesis and cancer risk in patients with cirrhosis
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Background and aims: Smoking induces a proinflammatory state, yet the role of smoking in advanced chronic liver disease (ACLD) remains understudied. This study evaluated the impact of smoking on disease-driving mechanisms and clinical outcomes in ALCD patients.
Method: ACLD patients undergoing hepatic venous pressure gradient (HVPG) measurements from 2017–2021 were included. The association of smoking with biomarkers of inflammation, fibrogenesis, angiogenesis, and the incidence of hepatocellular carcinoma (HCC), extrahepatic malignancies, and mortality was examined.
Results: Among 339 ACLD patients (66.1% men, median age: 56.8 years, MELD: 11, HVPG: 17 mmHg), 62% (n = 210) were ever-smokers (n = 78 former, n = 132 active). Compared to never/former smokers, active smokers exhibited significantly higher white blood cell counts (5.49 vs. former: 4.74 vs. never: 4.25 G/L; p < 0.001) and C-reactive protein levels (CRP: 0.36 vs. former: 0.29 vs. 0.21 mg/dL; p = 0.035). Active smokers showed upregulated fibrogenesis (TIMP-1: 364 vs. former: 324 vs. never: 278 ng/mL, p < 0.001; P3NP: 20.9 vs. former: 15.6 vs. never: 17.2 µg/L, p = 0.008) and angiogenesis (PLGF: 21.7 vs. former: 18.2 vs. never: 19.0 pg/mL, p = 0.004) markers. Over a median follow-up of 30.4-months, ever-smokers exhibited a higher incidence of extrahepatic malignancies (HR: 11.04; p = 0.020) and numerically higher HCC incidence (HR: 2.28; p = 0.147; mostly evident in Child-Pugh A patients: HR: 7.34, p = 0.056). All-cause or liver-related mortality risk did not differ significantly between ever-smokers and never-smokers.
Conclusion: Smoking is linked to an upregulation of disease-driving mechanisms in ACLD and increases the risk of extrahepatic malignancies and potentially HCC. These findings underscore the importance of strategies supporting smoking cessation in ACLD patients.

SAT-198
Clinical and hemodynamic factors associated with hemoglobin levels in patients with liver cirrhosis
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Background and aims: Liver cirrhosis with portal hypertension leads to hemodynamic alterations including hydrosaline retention, increased plasma volume and cardiac index (CI) and decreased systemic vascular resistance (SVR). The effect of these hemodynamic changes on haemoglobin (Hb) levels has not been specifically assessed. Though cross-sectional studies suggest that anemia may worsen hyperdynamic circulation, it is unclear whether anemia is a cause or consequence of this condition. We aimed was to study the association between Hb levels and hepatic and systemic hemodynamic variables, as well as clinical variables in cirrhotic patients, both at baseline and in relation to temporal changes in these variables.
Method: retrospective cohort study of cirrhotic patients who underwent two serial hemodynamic studies (hepatic and systemic) separated by at least 3 months. Between these two assessments, most patients received treatments known to modulate systemic and hepatic hemodynamics. Baseline clinical and hemodynamic variables associated with Hb levels were studied, as well as the association of temporal changes in these variables with changes Hb levels.
Results: 242 patients were included: 88 with HCV eradication, 71 with TIPS placement, 33 with β-blocker initiation, and 50 with no significant events between assessments. At baseline, several clinical and liver function variables (prothrombin, albumin, Child score, MELD score, sodium, ascites), systemic hemodynamics (CI, SVR, mean arterial pressure-MAP, and hepatic hemodynamics (HVPG, wedge hepatic venous pressure (WHVP) were correlated with Hb levels. At multivariate analysis only albumin (β = 0.41), ascites grade (β = −0.24), and CI or indexed SVR (β = −0.20 and β = 0.23, respectively) were correlated with Hb (adjusted $R^2 = 0.38$). When analyzing temporal changes between hemodynamic studies, changes in Hb correlated with changes in albumin (β = 0.45), CI (β = −0.21), and MAP (β = 0.13) (or indexed SVR, β = 0.24); global adjusted $R^2 = 0.34$. Changes in hepatic hemodynamics did not independently correlate with changes in Hb. Subgroup analysis showed similar results.

Albumin had the strongest correlation with Hb and its changes across all comparisons.
Conclusion: Haemoglobin levels and their temporal changes in cirrhotic patients are largely correlated with albumin levels and variables related to hyperdynamic circulation and hydrosaline retention, suggesting a significant dilutional component in its values.

SAT-199-YI
A systematic review and meta-analysis of the ability of novel biomarkers to differentiate subtype of acute kidney injury and predict response to terlipressin treatment
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Background and aims: Acute kidney injury (AKI) in patients with cirrhosis carries significant morbidity and mortality and accounts for 20% of acute decompensation admissions. Plasma creatinine (pCr) is used to measure severity of kidney dysfunction but is not a sensitive marker for early AKI detection and overestimates glomerular filtration rates in cirrhosis patients. pCr is also unable to differentiate between subtypes of AKI; pre-renal, acute tubular necrosis (ATN) and hepatorenal syndrome (HRS-AKI), which have different treatment options and prognoses. Current guidelines advise assessing response treatment over an initial 24–48 hours of AKI diagnosis to differentiate between subtypes. However, response to terlipressin in patients with HRS-AKI is reported as low as 35–50% with contributing factors being incorrect diagnosis and delayed treatment. We performed a literature search and metanalysis to assess the ability of novel biomarkers to diagnose subtype of AKI and predict response to terlipressin in HRS-AKI.
Method: Searches of OVID EMBASE and MEDLINE databases from inception to 6th June 2024. The search strategies included terms for cirrhosis, biomarkers and outcomes of interest. We included prospective and retrospective studies including cohort studies and randomised control studies and excluded conference abstracts, letters, reviews, experimental studies and case studies. Our primary outcome was the ability of a novel biomarker to predict the subtype of AKI in patients with cirrhosis. The secondary outcome was the ability of a novel biomarker to predict patients' response to terlipressin in HRS-AKI. 657 records were identified with 506 abstracts screened and 109 papers assessed for eligibility. 25 papers were found which fulfilled this study's objectives.
Results: 25 studies assessed the ability for biomarkers to diagnose subtype of AKI. 46 plasma and urinary biomarkers were assessed in 17493 patients. Urinary neutrophil gelatinase-associated lipocalin (NGAL) was the most investigated biomarker in 19 papers. A metanalysis was performed on the ability of 4 urinary biomarkers to predict ATN using the Area Under the Receiver Operating Characteristic curve (AUROC) with 95% CI values; NGAL 0.88 (0.85–0.91), interleukin 18 (IL-18) 0.92 (0.88–0.95), kidney injury molecule 1 0.66 (0.57–0.76), and B2-microglobulin 0.71 (0.63–0.91). 15 plasma and urinary biomarkers were assessed in 1717 patients in 8 studies to predict a response to terlipressin. The studies were unable to show a statistically significant correlation for any biomarker studied.
Conclusion: Urinary NGAL and urinary IL-18 demonstrate a strong ability to differentiate AKI subtypes which provides an opportunity for directing therapy earlier. However current biomarkers lack predictive utility for response to terlipressin. A limited number of studies with low patient numbers likely contribute to a lack of positive findings. Better diagnostic tools are required to improve early diagnosis and treatment of AKI in cirrhosis.

SAT-200
Effect of human albumin solution on coagulation parameters in decompensated cirrhosis (CoPA-D): an open-label randomized control trial
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Background and aims: Albumin is commonly used in cirrhosis for multiple indications and is a disease modifying agent. Due to rapid transformation of exogenous albumin into nitroso-albumin and its effects on platelets, albumin infusion may alter the coagulation system. Since cirrhosis is a state of dysregulated clotting and bleeding, we evaluated the effect of serial human albumin solution (HAS) infusion on coagulation parameters in decompensated cirrhosis.
Method: Decompensated cirrhosis patients (18–70 years) with serum albumin ≤2.5 g/dl were randomised to standard-of-care (SOC) arm or SOC + HAS (Albumin) arm. Patients in albumin arm received standard medical treatment (SMT) with 20% HAS daily to raise and maintain serum albumin levels ≥3 g/dl. Those in SOC arm received SMT without HAS. Derangement of coagulation was assessed by battery of coagulation tests and serial rotational thromboelastometry (ROTEM) at day 0, 1 and 3. Data analysed using independent t-test, repeated measures and paired t-test.
Results: 90 patients completed the study, 50 in albumin and 40 in SOC arm. Baseline parameters including MELD [17.18 ± 4.94 in albumin and 17.15 ± 4.74 in SOC group (p = 0.980)] were comparable. 9 patients achieved target serum albumin ≥3 g/dl on day 1 and 38 by day 3. In the albumin arm, within the first 24 hours, an increase was seen in activated partial thromboplastin time test (apTT) (seconds) from 39.4 ± 9.6 to 43.4 ± 10.2 (p < 0.001), international normalized ratio (INR) from 1.77 ± 0.4 to 1.88 ± 0.44 (p = 0.001), clotting time (CT) of extrinsically activated thromboelastometric test (EXTEM) (seconds) from 82.64 ± 27 to 98.18 ± 33 (p < 0.001), clot formation time (CFT) EXTEM (seconds) from 210.9 ± 117.17 to 263.34 ± 130.67 (p < 0.001). Significant reduction seen in fibrinogen (mg/dl) from 165.1 ± 101.2 to 140.96 ± 86.56 (p < 0.001), maximum clot firmness (MCF) EXTEM (mm) from 45.14 ± 12.10 to 42.58 ± 11.70 (p < 0.001), A10 fibrinogen-based thromboelastometry (FIBTEM) (mm) from 10.6 ± 6.14 to 8.54 ± 5.69 (p < 0.001), A20 FIBTEM (mm) from 11.18 ± 6.31 to 9.02 ± 5.63 (p < 0.001) and MCF FIBTEM (mm) from 11.32 ± 6.97 to 9 ± 6.06 (p < 0.001). Subsequent albumin transfusions on day 2 and 3 showed further worsening of coagulation parameters. Human von-Willebrand factor (ng/ml) was unchanged on day 1 [43.19 ± 19.27 and 43.80 ± 21.21 (p = 1)] but subsequently reduced to 31.60 ± 14.70 at 72 hours (p < 0.001). ADAMTS levels remained unchanged at 24 and 72 hours. No similar significant changes seen in coagulation parameters in SOC arm. Total of 9 (10%) patients required coagulation correction for therapeutic interventions, 6 (12%) in SOC and 3 (7.3%) in albumin arm (p = ns), but none had clinically significant bleeding.
Conclusion: Human albumin solution in standard doses causes significant derangement in ROTEM-based coagulation parameters within 24 hours. Monitoring of coagulation parameters is advisable for decompensated cirrhosis patients receiving HAS.
[Trial registration - NCT05937048].

SAT-205
Dynopenia predicts mortality in patients with liver cirrhosis and hepatocellular carcinoma
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Background and aims: Sarcopenia is a common complication in patients with liver cirrhosis and hepatocellular carcinoma (HCC). Recent advances in geriatric research have led to a paradigm shift, identifying low muscle strength as the primary determinant of negative outcomes in sarcopenia. However, few studies have thoroughly investigated the clinical impact of muscle strength in liver disease. The aim of this study was to evaluate the role of dynopenia (reduced muscle strength) in predicting mortality among patients with liver cirrhosis and HCC.
Method: The study included consecutive adult outpatients attending the Hepatology Unit of the Fondazione Policlinico Campus Bio-Medico of Rome. Muscle strength was assessed using handgrip dynamometry, following the recommendations of the EWGSOP 2019 (<27 kg for men and < 16 kg for women). Diaphragmatic excursion was assessed with ultrasound and considered a proxy of low muscle strength. In a subgroup of population, we assessed muscle mass by bioimpedance analysis (appendicular skeletal muscle mass calculated according to the Sergi equation - EWGSOP 2019). The associations between sarcopenia proxies and 24-month all-cause mortality were evaluated using both crude and adjusted Cox regression models. Survival was estimated through Kaplan–Meier estimates, and survival curves were compared using the log-rank test.
Results: A total of 158 patients were included in the analysis [mean age 73.1 years (SD 7.4), 77% male, median BMI 27.3 kg/m^2 (IQR 24.6–29.8)]. Viral cirrhosis was the most common etiology (37%), with 77% of patients classified as Child-Pugh class A. Active HCC was observed in 61% of patients, most of whom were classified as BCLC stage A or B (74%). Low muscle strength and diaphragmatic excursion were independently associated with 24-month mortality [aHR 1.66 (1.22–2.27), p = 0.001, and aHR 0.64 (0.42–0.98), p = 0.042, respectively] after adjustment for age, gender, and MELD. Kaplan–Meier analysis showed significantly reduced survival in patients with dynopenia compared to those without (60% vs 78%; log-rank test, p = 0.0047). In the subgroup analysis of 65 patients, low muscle strength was the only factor independently associated with 24-month mortality [aHR 1.96 (1.15–3.35), p = 0.014], while diaphragmatic excursion showed a trend toward significance [HR 0.48 (0.22–1.04), p = 0.06]. Conversely, muscle mass indices were not associated with all-cause mortality. Finally, Kaplan–Meier analysis confirmed a significantly reduced survival in patients with dynopenia compared to those without in this subgroup (log-rank test, p = 0.0068).
Conclusion: Dynopenia has emerged as a key prognostic determinant in cirrhotic patients with HCC, particularly in the earlier stages of the disease. In our small cohort, it was identified as the only muscle-related parameter significantly associated with mortality. If validated in larger, independent cohorts, dynopenia could serve as a robust early marker to identify patients at higher risk of poor outcomes.

SAT-206

Hepatic perfusion measured with 15Oxygen-water-Positron emission tomography/computed tomography correlates with severity of cirrhosis

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Background and aims: There is a need for accurate non-invasive diagnostic tools for evaluation of liver function and prognosis in liver cirrhosis. As intravenously administered water follows blood flow, radioactive ^{15}O-water serves as a reliable tracer for perfusion studies. In this study we investigated liver perfusion in patients with cirrhosis using ^{15}O-water-PET/CT aiming to correlate the resulting quantitative hemodynamic parameters with clinical parameters relating to the severity of cirrhosis.
Method: Twenty-three patients with varying degrees of liver cirrhosis and three controls without cirrhosis were examined using dynamic ^{15}O-water-PET/CT. The quantitative perfusion measurements calculated included total hepatic perfusion, portal hepatic perfusion, arterial hepatic perfusion, portal hepatic flow, and arterial hepatic flow. The severity of cirrhosis was assessed by Child-Pugh score and model of end-stage liver disease (MELD) score, liver stiffness measurement (LSM) by transient elastography, and the presence or absence of esophageal varices on gastroscopy. Spearman's correlation coefficient was used to calculate the correlation of the perfusion measurements with clinical factors.
Results: Total hepatic perfusion negatively correlated with Child-Pugh score (r = –0.609, p = 0.002), MELD-score (r = –0.449, p = 0.032) and LSM (r = –0.483, p = 0.019). Portal hepatic perfusion negatively correlated with Child-Pugh score (r = –0.614, p = 0.002) and MELD-score (r = –0.548, p = 0.007) and LSM (r = -0.422, p = 0.045). Portal hepatic flow also negatively correlated with Child-Pugh score (r = –0.681, p = <0.001) and MELD-score (r = –0.584, p = 0.003), but not with LSM. No correlation was found between clinical parameters and arterial hepatic perfusion or arterial hepatic flow. Total hepatic perfusion (r = –0.597, p = 0.004), portal hepatic perfusion (r = –0.604, p = 0.004) and portal hepatic flow (r = –0.540, p = 0.011) negatively correlated to presence of esophageal varices on gastroscopy.
Conclusion: Hepatic hemodynamic parameters in liver cirrhosis measured with ^{15}O-water-PET/CT correlated with Child-Pugh score, MELD-score, LSM, and the presence of esophageal varices. PET measurements of total hepatic perfusion, portal hepatic perfusion, and portal hepatic flow decreased with increasing severity of cirrhosis and with presence of esophageal varices. Future studies will further develop this technique and explore its clinical potential.

SAT-207

High mortality of further decompensation of liver cirrhosis: validation study

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Background and aims: To validate the concept of further decompensation (FD) as a more severe stage in the progression of cirrhosis and its association with outcomes in a cohort of hospitalized patients experiencing their first decompensation of liver cirrhosis.
Method: A retrospective analysis of patients hospitalized with their first episode of decompensation at a tertiary center over a 5-year period. Diagnosis of liver cirrhosis relied upon histology or a combination of clinical criteria in patients with a history of chronic liver disease. We analyzed clinical, laboratory, imaging features and mortality of the first decompensation and outcomes of patients who survived the first decompensation, based on the development of FD. Patients were followed until death or liver transplantation, which were considered composite adverse outcome, or until the censored date.
Results: The analysis included 247 patients hospitalized for their first decompensation of cirrhosis (average age 60 years, 74.1% male, 77.7% alcohol-associated liver disease, 10.1% metabolic dysfunction-associated steatotic liver disease, MELD-Na 19, Child-Pugh score (CPS) 10), without concomitant chronic heart disease, respiratory or renal failure, or malignancy, who were followed for an average (median) 28 months. Of them, 58 (23.8%) presented with non-acute (NAD), and 186 (76.2%) with acute decompensation (AD). During the first

hospitalization, 44 (17.8%) patients died. Out of 203 surviving patients, 102 (50.2%) developed FD. During the follow-up adverse outcome occurred in 59/102 (57.8%) patients who experienced subsequent decompensation, compared to 28/101 (27.7%) patients who did not have additional decompensation ($p < 0.001$). The risk of 3-year mortality was significantly higher for patients who developed FD (HR = 1,712, 95% CI 1,012–2,97, p = 0,04), whereas the type of initial decompensation (AD vs. NAD) did not influence survival. In univariate logistic regression none of the tested clinical, laboratory, or imaging features from the first decompensation were associated with the risk of developing FD. Higher initial CPS, MELD-Na scores, and occurrence of FD, were associated with the increased 3-year risk of dying. In multivariate analysis only CPS (HR 1.420, CI 1.093–1.844, p = 0.008) remained independently associated with the 3-year mortality. Patients with CPS>8 at initial decompensation who subsequently developed FD experienced adverse outcome more frequently compared to patients who did not develop FD (64.3% vs 29.6%, $p < 0.001$).

Conclusion: Further decompensation represents an advanced stage of cirrhosis with high mortality. It is essential to define risk factors for the development of this disease stage and further investigate its relationship with conventional indicators of liver function, such as CPS and MELD score.

SAT-208

Elevated serum ammonia is a poor prognostic marker for 1 year liver related outcomes and external validation of AMMON-OHE prediction model in stable outpatient cirrhosis

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Background and aims: Prediction of the liver related outcomes in stable cirrhosis patient poses a challenge. Traditional scores like MELD and Child-Pugh (CTP) score perform poorly. Ammonia is central to the pathogenesis of hepatic encephalopathy (HE). Although CTP score includes HE, it is limited by interobserver variability. Recently serum ammonia has been reported to predict the long-term outcomes in stable cirrhosis patients and a new "AMMON-OHE" score has been proposed to predict the liver related outcomes (LRE) of these patients. The aim of this study is to test the hypothesis whether serum ammonia can predict the liver related outcomes and to externally validate AMMON-OHE score.

Method: In this ongoing multi-centre study to predict the decompensation, acute on chronic liver failure and mortality in cirrhosis (SoLiDaRity), 206 stable out-patient cirrhotic were recruited since January 2023. Patients were censured at liver related clinical outcomes (LRE), liver transplant or death. The primary endpoint was all non-elective admissions for LRE defined as worsening ascites requiring admission, HE, variceal bleeding or infection at 1 year. The 1-year clinical outcomes were reviewed from 1st ammonia measurement. Standard statistical tests were applied.

Results: The median follow up duration of the cohort was 373 (IQR: 193–467) days. Majority of the patients were male (59.2%) with mean age of 66 ± 10.3 years. MASLD was the most common aetiology (47.6%) followed by HBV (23.8%). A total of 37.4% patients had decompensated cirrhosis, rest were in compensated stage. Patients with CTP classes A/B/C were 75%, 21% and 4% respectively. The median MELD of the cohort was 8 (IQR: 6–11). A total of 31 (15%) patients developed LRE within 1 year of ammonia measurements. The median ammonia in patients who achieved LRE and those who did not was 53 (IQR:38–63) and 25 (IQR:18–39) respectively. Similarly, the median AMMON-OHE scores were 0.17 (0.08–0.20) and 0.02 (IQR: 0.01–0.10) ($p < 0.001$ for both). The MELD and CTP score as well CRP and white cell count were higher in patients developing LRE ($p < 0.05$ for all). The univariate cox regression showed MELD, CTP, CRP, WCC, ammonia and AMMO-OHE score as predictors of LRE. Ammonia and OHE scores remained an independent predictor or 1-year LRE in multivariable analysis. Performance of MELD, AMMON-OHE score and ammonia in predicting 1-year LRE was then assessed based on area under receptor operator curve (AUROC). CTP score had the best AUROC of 0.837 followed by AMMON-OHE score of 0.818 followed. Ammonia and MELD had AUROC of 0.799 and 0.734 respectively. The best cut off to predict LRE at 1 year for ammonia was 33 umol/L with 84% sensitivity and 71% specificity.

Conclusion: Measurement of ammonia for outpatient stable cirrhosis patients may aid in the prediction of LRE within 1 year. AMMON-OHE score fairs well in predicting 1-year LRE in this external cohort and can be used as a tool for patient monitoring.

SAT-209

Randomized, open-label, phase 2a comparator study to assess the pharmacodynamics, safety and pharmacokinetics of oral administration of mnk6106 (l-ornithine phenylacetate) vs. rifaximin in subjects with hepatic cirrhosis and a previous history of hepatic encephalopathy

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Background and aims: Ammonia plays a central role in the pathogenesis of hepatic encephalopathy (HE). There are no approved treatments targeting ammonia. L-Ornithine Phenylacetate (L-OPA) has a unique mechanism of action involving its permanent excretion as phenylacetylglutamine (PAGN). It lowers ammonia rapidly when administered by iv. The aims of this dose response study were to evaluate the efficacy of oral L-OPA on reducing plasma ammonia (AMM). Safety, tolerability, pharmacokinetics and exposure response relationships were also evaluated.

Method: 48-decompensated cirrhosis patients with previous history of overt HE (28 male, mean 57.2 years; mean MELD (range): 8.8–12.1; Pugh (range): 7–8) were randomized 1:1:1:1 to receive 1 of the 3 dosing regimens of L-OPA [Group A, 2 g TID; Group B, 4 g BID, Group C, 4 g TID], or rifaximin (Group D, 550 mg bd), for 5-days. Subjects were assessed for clinical functional scoring and liver scores. All biochemical variables were measured in a central laboratory. Adverse events (AEs) were recorded.

Results: AMM levels decreased significantly more in Groups B and C compared with the rifaximin, Group D. The levels between baseline and Day 5 [umol/L; mean (SD)] were; Group A: 68.1 (26.8) to 75.2 (27.3); Group B: 88.9 (34.4) to 59.3 (13.6); Group C: 87.5 (33.8) to 74.1 (11.6); Group D: 81.5 (23.8) to 75.4 (29.7). Percentage change from baseline to Day 5 were +2.04 (35.6); −26.3 (27.0); −11.9 (30.6); and −4.20 (26.8) in Groups A, B, C and D respectively. In general, in the L-OPA groups, mean increases in plasma L-ornithine, phenylacetate and PAGN concentrations were observed with increase in dose and dosing regimen. Cumulative amount of urinary excretion of PAGN in general was similar on all days for each group. Overall, 20 (55.6%) patients who received L-OPA and 5 (41.7%) subjects who received rifaximin had at least 1 treatment-emergent adverse event. No significant differences in adverse events (AEs) were observed between groups. No significant trends were seen in laboratory results, neuropsychiatric tests, vital signs or ECGs (no subject had a QT or QTcF interval >500 ms or increased by >60 ms) between groups. Overall, the

subjects reported improvement in clinical function during treatments.
Conclusion: Group B (L-OPA 4 g BID) showed the highest decrease in plasma AMM concentrations which was about 6 times greater than Rifaximin and this dose may be selected for future trials. All doses of L-OPA were safe and well tolerated.

SAT-210
Development and validation of the modified hepatic encephalopathy staging tool (mHEST) for grading of hepatic encephalopathy for accurate assessment and regulated clinical trials
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Background and aims: Hepatic encephalopathy (HE) is one of the most common complications of liver cirrhosis for which treatment options are limited. Although the West Haven (WH) scale is recommended by guidelines for defining severity, it is considered inadequate by regulatory bodies such as the FDA due to significant intra- and inter-rater variability between observers. Therefore, the Hepatic Encephalopathy Staging Tool (HEST) test was developed but considered inadequate due to inclusion of asterixis as a variable. Therefore, the modified HEST (mHEST) was developed, which excludes asterixis and includes variables that are unlikely to be influenced through interpretation. The aims of this study were to determine the inter-rater and intra-rater agreement of the mHEST test.
Method: 49-healthcare workers including doctors, nurses and physician assistants from 6 countries participated in the study. 6-brief video vignettes of actors in various stages of HE were created. Two rounds of evaluations were conducted. In the first round, a mHEST introductory video was shown, and then participants were asked to assess the video vignettes and stage them according to mHEST. Second round was 5 to 10 days later, whereby participants reassessed the same videos and staged them again.
Results: For the inter-rater reliability results in Round 1, 44 participants (89.8%) correctly rated Vignette A as Stage 0/1 and Vignette C as Stage 3; 45 participants (91.8%) correctly rated Vignette B as Stage 2; 49 participants (100%) correctly rated Vignette D as Stage 4; and 46 (93.9%) correctly rated Vignettes E and F as Stage 2 and Stage 3, respectively. For intra-rater (test-retest) reliability, concordance between participants' Round 1 responses and their Round 2 responses was as follows: 88.1% (Vignette A, Stage 0/1); 81.0% (Vignette B, Stage 2); 88.1% (Vignette C, Stage 3); 100% (Vignette D, Stage 4); 90.5% (Vignette E, Stage 2); and 92.9% (Vignette F, Stage 3).
Conclusion: mHEST demonstrated excellent inter-rater and intra-rater reliability. Specifically, results from the current study suggests that clinical support staff, irrespective of experience, can accurately and consistently identify the HE severity of cirrhosis patients using the mHEST grading system. This HE staging system has been approved by the regulators such as the FDA, EMA and PMDA for use as an end point for Phase-3 trial of ornithine phenylacetate in cirrhotic patients with overt HE.

SAT-211
Risk of hepatocellular carcinoma and cirrhosis decompensation in a large retrospective cohort of cirrhotic patients with autoimmune hepatitis
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Background and aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that can lead to cirrhosis in up to 30% of patients. Cirrhotic patients are at risk of high morbidity and mortality due to cirrhosis decompensation and hepatocellular carcinoma (HCC). This retrospective study aimed to assess the rates of decompensated cirrhosis and HCC in patients with AIH- related cirrhosis.
Method: This retrospective population-based study included adult patients diagnosed with AIH between the years 2000 and 2020 in a cohort of approximately 2.7 million adults. We investigated the rates of cirrhosis development, cirrhosis decompensation, and HCC among 774 AIH patients. The primary outcomes were rates of decompensated cirrhosis and HCC in patients who developed cirrhosis.
Results: Among the 774 AIH patients, 40% developed cirrhosis. During a median follow-up of 8.2 years (IQR 2.9–12.3), the annual incidence of decompensated cirrhosis was 4.25%, with a mean time of 8.2 years from cirrhosis diagnosis to decompensation. Nineteen cirrhotic patients (6.2%) developed HCC, with a yearly incidence rate of 0.63%. Most HCC cases occurred within the first years of cirrhosis diagnosis.
Conclusion: The rate of decompensated cirrhosis in AIH patients was lower than in other cirrhotic liver diseases, suggesting AIH may follow a different clinical course. The annual incidence of HCC was also significantly lower than the threshold for HCC surveillance, indicating the need to reassess current surveillance guidelines, particularly in the late years following cirrhosis diagnosis.

SAT-212-YI
Lipopolysaccharide-binding protein indicates risk for infections and liver-related death in patients with compensated and decompensated liver cirrhosis
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Background and aims: Translocation of bacteria or endotoxins represent an important mechanism contributing to hepatic decompensation in cirrhosis. Lipopolysaccharides (LPS) are components of the cell envelope of gram-negative bacteria, and LPS-binding protein (LBP) is a stable marker of bacterial translocation (BT) that may hold prognostic value in patients with cirrhosis. BT and infections indicate immune dysfunction in cirrhosis, which hold a high risk for mortality, underlining the unmet clinical need for an accurate and early risk prediction for infections in this population. Thus, the aim of our study was to investigate the association of LBP with development of infections or death in patients with liver cirrhosis.

Method: Patients with cirrhosis w/o infections or malignancies undergoing hepatic venous pressure gradient (HVPG) measurement at the Medical University of Vienna between 2017–2023 and with available LBP results were prospectively enrolled (VICIS; NCT03267615). Infections, liver-related deaths and transplant-free survival were recorded. Spearman correlation analysis and Kaplan-Meier estimation were performed.
Results: A total of 413 patient (median age of 57 years; 138 [33%] women) with a median MELD of 11 (IQR 9–15) and median LBP of 6.75 (IQR 5.16–8.77) µg/mL were included. The 216 (52.3%) compensated cirrhosis (CC) patients showed no difference in median LBP levels compared to the 197 (47.7%) decompensated cirrhosis (DC) patients (6.99 vs 6.66 µg/mL; p = n.s.). LBP levels showed direct correlations of weak (Spearman $\rho = 0.32$; $p < 0.001$) and moderate ($\rho = 0.504$; $p < 0.001$) strength with IL-6 and CRP, respectively, while there was no correlation between LBP and HVPG ($\rho = -0.083$, $p = 0.096$). Based on LBP tertiles, patients were categorized into groups with different risks for BT: low-LBP (n = 139; 45.3% CC), median LBP 4.67 [range, 1.57–5.61] µg/mL; mid-LBP (n = 137, 61.3% CC), median LBP 6.76 [range, 5.63–7.93] µg/mL; high-LBP (n = 137; 50.4% CC) median LBP 10.2 [range, 7.94–32] µg/mL. Patients with low and mid-LBP levels had longer median OS of 25 [95CI 45.07–54.8] months and 28 [95% CI 47.9–56.6] months, as compared to those with high-LBP levels with a median liver-related transplant-free survival of 19 [95% CI 46.8–52.7] months (log-rank p = 0.004). Patients with high-LBP showed a significantly shorter time to develop an infection or to liver-related death (median 15 [95% CI 33.5–45.2] months) than patients with low-LBP (21 [95% CI 39.6–49.9] months) or mid-LBP (26 [95% CI 40.8–49.79] months; log-rank p = 0.014).
Conclusion: LBP levels were linked to severity of systemic inflammation but not to PH severity nor to decompensated state (DC), suggesting that LBP may reflect BT as a pathomechanism rather than disease severity. Importantly, ACLD patients with high-LBP (also including 50% CC patients) had an increased risk for infections and liver-related mortality.

SAT-213-YI
Muscle mass assessed by rectus femoris ultrasound predicts clinical outcomes in cirrhosis: a step beyond the "black-and-white" classification of sarcopenia

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Background and aims: Sarcopenia is common in patients with cirrhosis and is strongly linked to adverse clinical outcomes. Traditionally, sarcopenia is viewed as a binary condition - either present or absent. However, the degree of muscle loss may significantly influence clinical outcomes, highlighting the need to consider muscle mass as a continuous variable rather than a dichotomous one. Despite this, few studies have yet evaluated muscle loss in a linear context. The ultrasound measurement of rectus femoris cross-sectional area (RF-CSA) has demonstrated excellent accuracy in assessing sarcopenia in patients with cirrhosis. This study aimed to evaluate: (a) the prognostic significance of the RF-CSA in patients with cirrhosis hospitalized for an acute decompensation (AD) of the disease.
Method: Thigh ultrasound was performed at bedside in 203 consecutive patients hospitalized for an AD of cirrhosis. RF-CSA was measured at two-thirds of the distance from the anterior superior iliac spine to the superior patellar border; three measurements were collected, and the mean value was calculated. RF-CSA was considered as a continuous variable. Patients were followed up until death, liver transplant or 90 days and data about complications during hospitalization and mortality were recorded.
Results: Among hospitalized patients (mean age: 64 ± 10 years, median MELD 17), median RF-CSA was 3.09 cm^2. During hospitalization, 32 patients (16%) died. RF-CSA was significantly lower in patients who died compared to survivors (2.64 cm^2 vs 3.20 cm^2; p = 0.005). In multivariable analysis (adjusted for age, gender, MELD and infections) RF-CSA was an independent predictor of 90-day mortality (sHR = 0.57; p = 0.006), along with MELD (sHR = 1.11; p < 0.001). Stratification of RF-CSA in tertiles demonstrated that greater severity of muscle loss was associated with a higher cumulative incidence of 90-day mortality (first tertile 39% vs second 26% vs third 12%; p = 0.001). Additionally, RF-CSA was an independent predictor of in-hospital complications, including sepsis (OR = 0.59; p = 0.001), shock (OR = 0.60; p = 0.005), AKI (OR = 0.75; p = 0.019) and hepatic encephalopathy (OR = 0.78; p = 0.023).
Conclusion: Sarcopenia represents a spectrum, with greater muscle loss leading to worse outcomes and higher in-hospital and 90-day mortality. Ultrasound assessment can aid in risk stratification, enabling targeted interventions to slow or prevent muscle loss and potentially improve clinical outcomes.

SAT-214
Micronutrients supplementation in patients with liver cirrhosis: a single-arm prospective cohort study

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Background and aims: Patients with cirrhosis have an increased risk of malnutrition and sarcopenia, which is associated with worse prognosis. Deficiencies of micronutrients specifically have been well described and are associated with complications such as decompensation and death. However, the clinical implications of micronutrient deficiencies in cirrhosis as well as the benefits of supplementation remain incompletely understood. The aim of this study was to investigate the prevalence of micronutrient deficiencies as well as the effects of supplementation on cirrhosis severity, nutritional status, symptoms, function and quality of life (QoL) in a cohort of Australian patients with cirrhosis.
Method: Patients with cirrhosis were recruited between January 2022 to June 2024 from the outpatient liver clinics of 3 tertiary hospitals. Baseline assessments incorporating clinical, nutritional and functional measures included routine blood tests and micronutrient levels, the 36-item short form survey (SF-36), Royal Free Hospital Nutritional Prioritising Tool (RFH-NPT) to stratify nutritional risk, Subjective Global Assessment (SGA) for QoL and handgrip strength (HGS). Patients with any specific deficiencies on blood tests were given supplementation according to a pre-defined protocol for six months, before returning for a final follow-up to repeat all assessments. Statistical analysis was conducted using multilevel linear mixed models, adjusting for age, sex, body-mass-index and other supplements taken concurrently, to determine the impact of supplementation on outcomes variables.
Results: A total of 152 cirrhotic patients were recruited. The median age was 63 (55–69.5) years, and 36% were female. The cohort primarily consisted of Child-Pugh (CP) class A patients (68%) with some B (27%) and C (5%) patients. Micronutrient deficiencies were very common with 87% having at least 1 and 41% >2 deficiencies. The most common deficiencies overall were zinc (70%), vitamins A (43%), C (35%) and D (30%). Supplementation with vitamins A and D correlated with a decrease in CP score of 1.2 (p = 0.005) and 0.53 (p = 0.044), respectively. Vitamin D, magnesium, and iron supplementation were associated with an increase in HGS by 2.09 kg (p = 0.019), 3.7 kg (p = 0.029), and 4.35 kg (p = 0.041), respectively. Magnesium

supplementation was related to improved emotional well-being (p = 0.004), but other supplements, such as B-group vitamins, vitamin C, vitamin D, and iron, were associated with decreased QoL metrics in the SF-36.
Conclusion: This study confirms the prevalence of micronutrient deficiencies in cirrhosis and further evaluated the benefits of relevant supplementation. Vitamins A, D, magnesium and iron supplements were generally associated with improvements in cirrhosis severity, nutritional and functional status. Further study is needed to confirm these findings and determine the role of micronutrient supplementation on clinical outcomes.

SAT-215
A retrospective review of reduced dose argatroban in liver impairment
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Background and aims: Heparin induced thrombocytopenia (HIT) is a rare serious, potentially life-threatening adverse reaction to heparin. Argatroban is an alternative anticoagulant for patients with suspected or confirmed HIT. Guidance suggests reduced dosing of argatroban for patients with liver impairment as there may be increased risk of bleeding. We retrospectively investigated the efficacy and safety of reduced dose argatroban in critically ill patients with suspected or confirmed HIT and varying degrees of liver impairment.
Method: Patients treated with intravenous argatroban were identified using dispensing system records between 2017 and 2023. Patients in critical care with a suspected or confirmed HIT, aged ≥18 years were included. Doses were defined as the critical care standard of 0.5 µg/kg/min or reduced dose of 0.2 µg/kg/min. Efficacy was defined as achieving steady-state concentration within 4 dose changes and absence of thrombotic complications during critical care. Safety was assessed by the absence of haemorrhage as defined by International Society of Thrombosis and Haemostasis.
Results: 139 patients received argatroban of whom 52 met eligibility criteria. Nineteen had liver impairment and 33 did not. In the liver group, 11 were post-liver transplant, 3 had decompensated chronic liver disease, 1 had Budd-Chiari Syndrome, 3 had acute liver failure, and 1 had a liver abscess. The non-liver group included 6 with COVID-19 pneumonitis, 6 with sepsis, 7 with cardiovascular disease, and 14 with other critical care indications. There was no significant difference in the SOFA scores between the liver group (median 10, IQR 4) and the control group (9, IQR 4) (p = 0.83)). Median MELD score for liver patients was 30 (11.5). Groups did not differ in sex, type of heparin, platelet count or baseline APTT but Liver patients were younger (43 (21) vs 63 (26) years, p < 0.001), had higher bilirubin (40 (47) vs 11 (8) mmol/L p < 0.0015) and INR (1.58 (1.685) vs 1.23 (0.34) p = <0.003. In the liver group, 2 (11%) patients did not reach steady state within 4 dose changes, compared to 5 (15%) patients in the non-liver group (p = 1). Two (11%) liver group patients developed thrombosis after starting argatroban, compared to 3 (9%) patients in the non-liver group (p = 1). Three (16%) liver group patients and 1 (3%) non-liver group patient had bleeding events after starting argatroban, but this difference was not statistically significant (p = 0.132).
Conclusion: In this retrospective study of critically ill patients with liver impairment, a reduced dose of argatroban starting at 0.2mcg/kg/min was effective as an anticoagulant in HIT without significant increase in bleeding events.

SAT-216
The most common bacterial isolates in spontaneous bacterial peritonitis in a tertiary hospital center in Croatia and their antibiotic resistance
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Background and aims: Spontaneous bacterial peritonitis (SBP) is a common infection in patients with decompensated liver cirrhosis. The choice of empirical antibiotic treatment is based on the severity and the environment of the infection as well as on local resistance profiles. The aim of this study was to investigate the most common bacteria isolated in ascites of patients with SBP at our institution and their antibiotic resistance profile.
Method: In this retrospective study, we analyzed electronic medical records of patients with SBP and positive ascitic fluid culture hospitalized in a tertiary hospital center in the period between September 1, 2020 and October 1, 2024. There were 20 positive ascitic fluid cultures in patients diagnosed with SBP, with 22 organisms isolated in 17 patients. In the majority of cases (18/20) a single organism was isolated, and 2 organisms were isolated in 2 cases. Two patients had the same organism isolated in 2 or 3 ascites cultures during the same episode of SBP, and these isolates were excluded from antimicrobial resistance analysis.
Results: The most common organisms isolated were Escherichia coli (n = 6), Escherichia coli ESBL (n = 3), Streptococcus viridans (n = 5) and Enterococcus faecalis (n = 2). Other organisms were occasionally isolated: Acinetobacter species, Pseudomonas species, Staphylococcocus aureus, methicillin-resistant Staphylococcus aureus, beta-hemolytic Streptococcus and Bacteroides species. Five patients (29.4%) were considered to have nosocomial or health care-associated infections, while 12 patients (70.1%) had community-acquired SBP. Twelve of 19 isolated organisms (63.2%) were sensitive to a third-generation cephalosporin, ceftriaxone, which represents the standard empirical antibiotic treatment for SBP at our institution. Among these, 15.7% had nosocomial or health care-associated SBP. Sixteen organisms (84.2%) was sensitive to piperacillin/tazobactam, 15.7% of which were nosocomial or health care-acquired infections. Thirteen organisms (68.4%) were sensitive to meropenem; 10.5% of these were not community acquired. Resistance to ceftriaxone was found in 7 (36.8%) organisms, 5 of which were community acquired and 2 were considered nosocomial or health care-associated SBP.
Conclusion: Clinical Practice Guidelines issued by the European Association for the Study of the Liver recommend a third-generation cephalosporin as an empirical antibiotic treatment of community-acquired SBP, assuming a low risk of antimicrobial resistance. In our cohort of patients with SBP, 63.2% of isolated organisms were sensitive to ceftriaxone, while sensitivity to carbapenems and piperacillin/tazobactam was higher (68.4% and 84.2%, respectively).

SAT-221
High incidence of diuretic derived complications among patients with refractory ascites undergoing either TIPS implantation or insertion of tunneled peritoneal catheter
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Background and aims: Onset of refractory ascites (RA) is a severe complication of chronic liver disease. According to the International Ascites Club guidelines, two categories are defined. The first is diuretic-resistant (DR) RA, marked by a lack of response to diuretic therapy. The second is diuretic-intractable (DI) RA, where complications, such as renal impairment, emerge from diuretic treatment. Placement of a transjugular intrahepatic portosystemic shunt (TIPS) or, if contraindications against TIPS arise, tunneled peritoneal catheters (PeCa) offer an additional therapeutic approach to diuretic therapy. As of now, the exact prevalence and the potential relevance of classifying the ascites as either DR or DI remains unclear. Hence, this study aims to assess the clinical outcomes of patients with DR and DI ascites undergoing either TIPS or PeCa implantation.
Method: We evaluated all patients with RA and cirrhosis undergoing TIPS or PeCa insertion from 2009 to 2023. Exclusion criteria were malignancies or missing informed consent. Study endpoints were mortality, acute kidney injury (AKI) and hyponatremia < 130 mmol/l within 365 days after implantation. Analysis was conducted utilizing univariable and multivariable competing risk analysis, treating death and liver transplantation as competing events. All parameters demonstrating a significant association with the outcome of interest in a univariable analysis were included into the multivariable model.
Results: Two separate analyses were conducted. First, 256 patients undergoing TIPS insertion were analyzed. Only 20% (n = 51) patients displayed DR ascites, while 205 (80%) had DI ascites. No significant differences were observed between DR and DI groups in terms of mortality (HR 0.87, p = 0.73), AKI (HR 1.18, p = 0.61), or hyponatremia (HR 1.18, p = 0.66). Mortality was independently associated with age (HR 1.06, p < 0.001) and MELD score (HR 1.10, p = 0.006), while cholinesterase (HR 0.71, p = 0.04) and potassium (HR 0.60, p = 0.02) were protective factors. The second analysis included 177 PeCa patients with PeCa. Again, only 18% (n = 31) classified as DR and 72% (n = 146) as DI. Here, classification as DR or DI was also not associated with mortality (HR 0.97, p = 0.95) or AKI (HR 0.98, p = 0.93), but was independently linked to the risk of hyponatremia (HR 0.51, p = 0.04). Mortality was predicted solely by MELD score (HR 1.07, p = 0.03). Besides the classification into DR or DI, hyponatremia in PeCa patients was linked to cholinesterase (HR 0.65, p = 0.02) and sodium levels (HR 0.94, p = 0.003). Interestingly, presence of diuretics post PeCa implantation was linked to a lower AKI risk (HR 0.63, p = 0.04).
Conclusion: Only few patients with refractory ascites achieve maximum doses of diuretic treatment without complications and can be classified as DR. However, prognosis seems to be overall comparable between those with DR and DI.

SAT-222

Liver cirrhosis detection by canine olfaction using randomized controlled blinded testing: a proof-of-concept study

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Background and aims: Cirrhosis is often diagnosed late as it is initially asymptomatic. Early diagnosis is essential for preventing disease progression and subsequent complications. This study explores whether dogs can detect cirrhosis through scent detection of volatile organic compounds from the breath and urine of patients.
Method: The study, conducted from February 2023 to January 2024, collected breath and urine specimens from cirrhotic patients and non-cirrhotic controls from Ramathibodi Hospital's and Siriraj Hospital's outpatient clinics in Thailand. These specimens were sent to train two scent-detection dogs until the trainer was confident of scent imprinting. One was an experienced scent-detection dog (Dog 1), while the other was newly trained (Dog 2). New specimens were used to test the dogs in a randomized controlled blinded fashion with non-cirrhotic controls (cirrhosis: control ratio of 1:3 per test). The dogs were trained to signal the specimen they thought were from cirrhotic patients.
Results: The study tested 26 sets (cirrhosis n = 26, control n = 78). Dog 1 consistently showed higher accuracy than Dog 2, with diagnostic accuracy of 94.23% (95% CI: 87.86–98.93) for mask samples and 98.08% (95% CI: 93.23–99.77) for urine samples, with an area under the curve (AUC) of 0.92 and 0.97, respectively. In contrast, Dog 2 had a diagnostic accuracy of 73.08% (95% CI: 63.49–81.31) for mask samples and 75% (95% CI: 65.55–82.97) for urine samples, with an AUC of 0.64 for masks and 0.67 for urine samples. The higher accuracy for urine samples compared to masks was not statistically significant (p = 0.2782).
Conclusion: The experienced scent-detection dog demonstrated high diagnostic accuracy of 94.23% for masks and 98.08% for urine samples with AUC of 0.92 and 0.97, respectively. This suggests it is possible to distinguish between cirrhotic and non-cirrhotic patients using scent-detection.

SAT-223

Novel sex-specific cut-offs for subcutaneous adipose tissue radiointensity in patients with cirrhosis: a post-hoc analysis

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Background and aims: While several recent studies have addressed the prognostic impact of sarcopenia and myosteatosis in cirrhosis, less is known about the role of subcutaneous adipose tissue radiointensity (SAT-r). From a retrospective study Ebadi suggested that higher SAT-r (>-83 Hounfield Unit - HU - for men and ≥74 HU for women) may be associated with higher mortality in liver transplant wait-listed patients with cirrhosis. The aim of this study is to prospectively assess the prognostic value of high SAT-r in a heterogeneous cohort of patients with cirrhosis.
Method: This is a post-hoc analysis of the prospective multicentre *EpatoSarco* study, in which 433 patients with cirrhosis were enrolled after CT scan for clinical indication. SAT-r was evaluated using SliceOmatic software at the L3-L4 level and its prognostic impact was assessed by the Fine and Gray model for competing risks.
Results: The median SAT-r was 95 HU (IQR −115 to −83 HU), significantly lower in patients with no muscle changes than in those with other muscle changes (−96 ± 13 vs −90 ± 15, p = 0.0015). Fifty-one patients died during the 1-year follow-up: mean SAT-r was significantly lower in alive than in deceased patients (−92 ± 15 vs −87.1 ± 15, p 0.025). We failed to validate the Ebadi's cutoffs and found that in our population the best discriminant cutoff for death-risk was −89.5 HU for men and −98.4 HU for women. With these cut-offs, 188 patients had high-risk RSAT-r, with a significantly higher cumulative incidence of death (p = 0.006; death and OLT competing. The SHR for mortality of high-risk SAT-r, adjusted for the MELD score was 1.9 (CI 1.006 to 3.6). When type of muscle damage and its interaction term with high-risk SAT-r was added to the model, the interaction was almost significant (p. 0.06) and allowed to identify 4 different risk groups.
Conclusion: New sex-specific cut-offs for high SAT-r may identify patients at high risk of death, especially when combined with other muscle changes.

SAT-224

Management of ascites in elderly patients with cirrhosis: results of an italian survey

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Background and aims: The management of ascites in elderly cirrhotic patients is challenging, given comorbidities and frailty that limit therapies, interventions, and transplantation. We assessed how physicians in Italy manage ascites decompensation in elderly patients (>70 years) with cirrhosis.
Method: AISF members received a 49-question survey addressing care settings, centre expertise, radiology and transplant services, patient comorbidities, ascites therapies, and management challenges. Respondents also identified the main problem in managing these patients.
Results: Twenty-two centres (54.5% from university hospitals) responded. Half of the respondents were gastroenterologists. Day hospital services were available in 90.9% of centres, but only 45.5% performed TIPS directly. A total of 1,064 elderly patients with ascites were included. Alcohol was the main etiology. Two hundred and forty-two (22.7%) patients had refractory or intractable ascites, with kidney injury being the leading cause, followed by hepatic encephalopathy and electrolyte imbalance. Diuretics were the main therapy (63.2%), while 21.7% required periodic paracentesis; procedural complications occurred in 17% of patients. Spontaneous bacterial peritonitis (61 cases) and hepatorenal syndrome (42 cases) were common complications, but the majority of physicians (81%) avoided vasopressor therapy due to age and comorbidities. TIPS was evaluated in 50 patients, but were denied in 26 cases; nine patients underwent transplantation despite their age. Forty-six patients required long-term care, and 209 (19.6%) died, with infections and ACLF as leading causes. Over half were dependent on caregivers, and 566 (53.2%) were malnourished, though only 259 received nutritional support. Respondents highlighted insufficient community medical support and undervalued caregiver roles as key issues.
Conclusion: Elderly patients with ascites face limited therapeutic options. Comprehensive care strategies, enhanced community support, caregiver integration, and targeted nutritional programmes are crucial to improving outcomes in this vulnerable population.

SAT-225

Current incidence of decompensating events, HCC and their prognostic impact on patients with compensated advanced chronic liver disease

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Background and aims: The development of first decompensation is a landmark in the natural history of compensated advanced chronic liver disease (cACLD) with a worsening of prognosis, but most data was obtained for over 30 years. This study examines in a contemporary population of cACLD: (i) the incidence of decompensation, (ii) the most prognostically relevant combination of events defining decompensation, and (iii) the effects of aetiological therapy and hepatocellular carcinoma (HCC) development on decompensation.
Method: Individual patient data meta-analysis of prospective observational studies or RCTs in cACLD with patients included after 2006. To account for heterogeneity, an "individual study term" was added to the multivariate analysis. Aetiological therapy was defined as: viral hepatitis treatment, alcohol abstinence or >10% weight loss. The cumulative incidence function (CIF) of ascites, variceal bleeding, hepatic encephalopathy (HE) and jaundice, and hepatocellular carcinoma (HCC) were assessed with death and liver transplantation as competing events. The specific impact of ascites, bleeding, HE, jaundice and HCC (as time varying covariates) on survival was assessed by Cox proportional hazards model, including Child-Pugh score, oesophagogastric varices, non-selective beta-blocker exposure, cirrhosis aetiology, aetiological treatment and obesity.
Results: A total of 9 studies including 1308 cACLD patients were selected (main etiologies: 26% metabolic dysfunction-associated

steatotic liver disease (MASLD), 51% viral hepatitis, 15% alcohol-related liver disease (ALD), mean age 54 (12), sex female 37%, with a median follow-up of 3.2 (IQR 0.5–5.0) years. Overall, 240 patients (18.3%) developed decompensation and 117 HCC, in 80% HCC developed prior to decompensation. The first decompensating events were: ascites (130, 54%, CIF 0.133), variceal bleeding (48, 20%, CIF 0.048), HE (25, 10.4%, CIF 0.021), jaundice (15, 6.2%, CIF 0.016), and combined events (22, 9%, CIF 0.021). The adjusted hazards ratio (aHR) of decompensation for mortality was 11.6 (95% CI 7.9 to 16.9); specifically for: ascites 5.7 (95% CI 3.6–9.1), bleeding 3.0 (95% CI 1.5–6.1), HE 4.7 (95% CI 1.5–15.3), jaundice 3.7 (95% CI 0.9–15.3), and any combination 30.5 (95% CI 16.5–53.5). HCC increased the risk of decompensation (aHR 2.3, 95% CI 1.8–4.4) and death (aHR 6.6, CI 4.1–10.4). Aetiological treatment significantly reduced the risk of decompensation (aHR 0.68, CI 0.54–0.87).

Conclusion: Ascites and bleeding remain the most common first decompensating events in cACLD and both significantly increase mortality. HE and jaundice are infrequent as sole first decompensating events. Aetiological therapy significantly reduces decompensation risk, whereas HCC development significantly elevated the risk for both decompensation and death.

SAT-226

Impact of infections on the natural history of compensated advanced chronic liver disease: data from an individual patient data meta-analysis

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Background and aims: The impact of bacterial infections (BIs) in compensated cirrhosis remains poorly understood. This study aimed to assess the incidence of infections in compensated advanced chronic liver disease (cACLD) and their influence on the risk of decompensation (ascites, variceal bleeding, overt encephalopathy, and jaundice) and mortality.

Method: An individual patient data meta-analysis was conducted using prospective observational or interventional trials from 2006 onward, involving patients with cACLD. Clinically relevant BIs were defined as those treated with antibiotics. The cumulative incidence of BIs and their adjusted impact on decompensation and mortality were evaluated using competing-risk, time-dependent regression analysis.

Results: Data from 1,308 patients with cACLD extracted from nine studies (51% viral hepatitis, 26% metabolic dysfunction-associated steatotic liver disease (MASLD), 15% alcohol-related liver disease (ALD); mean age 54 ± 12 years; 37% female) followed for a median of 3.2 (IQR 0.5–5.0) years were analysed. Of these, 126 patients (10%) developed BIs before/at time of decompensation, 50 (4%) after decompensation, while 543 (42%) remained infection-free, and 589 had missing infection data, but displayed similar outcomes to the non-infected group. Patients who developed infections were more likely to have ALD (46% vs. 9%, $p < 0.001$) and Child B cirrhosis (39% vs. 25%, $p = 0.003$). In BI-associated decompensation, more patients had ALD aetiology (64% vs. 36%, $p = 0.016$) and a higher prevalence of varices ($p = 0.003$) was observed. Infection site was associated with risk for decompensation ($p = 0.002$). Respiratory infections were more common in patients that developed decompensation (37% vs. 23%). Decompensation occurred in 37% of patients with BIs compared to 15% of those without BIs ($p < 0.0001$), primarily as ascites (21% vs. 9%) and hepatic encephalopathy (13% vs. 3%). BIs significantly increased the risk of decompensation (subdistribution hazard ratio [sHR] 3.5, 95% CI: 2.4–5.1, $p < 0.001$) and mortality (sHR 2.6, 95% CI: 1.7–3.8, $p < 0.001$).

Conclusion: Decompensation following BIs occurs frequently, particularly in patients with more advanced stages of cACLD and markedly increases the risk of decompensation and mortality. Future studies should explore preventative strategies for infections to improve outcomes in this population.

SAT-227

Cirrhotic cardiomyopathy: Prevalence and clinical impact on liver cirrhosis outcomes

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Background and aims: Cirrhotic cardiomyopathy (CCM) is a significant complication of liver cirrhosis, but its prevalence and impact remain unclear. This study aimed to assess the prevalence of CCM in patients with liver cirrhosis and evaluate its impact on clinical outcomes.
Method: This retrospective study included 80 patients with liver cirrhosis confirmed by transient elastography (liver stiffness ≥12.5 kPa) at Hokkaido University Hospital between January 2014 and April 2024. CCM was diagnosed using the 2019 Cirrhotic Cardiomyopathy Consortium criteria. Patient characteristics, survival, and incidence of decompensation and cardiovascular events were analyzed. Propensity score matching was performed to adjust for potential confounding factors between groups with and without CCM.
Results: The prevalence of CCM was 46.3% (37/80), with 78.4% of CCM patients showing isolated systolic dysfunction based on global longitudinal strain. Patients with CCM were significantly older and had lower serum ammonia and bilirubin levels, as well as higher platelet counts. CCM was associated with a significantly higher incidence of decompensation events (HR 3.97, 95% CI 1.64–9.61, p = 0.003) and was an independent risk factor for decompensation in multivariate analysis (HR 3.24, 95% CI 1.29–8.11, p = 0.012). No significant differences were observed in overall survival or cardiovascular events between patients with and without CCM. The analysis of CCM subgroups revealed a statistically significant difference in the cumulative incidence of decompensation events between patients with isolated systolic dysfunction and those without CCM (p < 0.003).
Conclusion: CCM is prevalent among patients with liver cirrhosis and is associated with an increased risk of hepatic decompensation. These findings highlight the importance of cardiac evaluation in cirrhotic patients and suggest that CCM should be considered in the management of liver cirrhosis to potentially improve patient outcomes. The high prevalence of isolated systolic dysfunction based on global longitudinal strain measurements emphasizes the importance of incorporating this parameter into the diagnostic criteria for CCM.

SAT-228

L-ornithine-L-aspertate improves quality of life and ammonia levels but not microbiome dysbiosis in cirrhosis: results of a phase 4 study

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Background and aims: Liver cirrhosis is associated with gut microbiome dysbiosis, intestinal inflammation and gut barrier dysfunction, contributing to reduced quality of life and the development of complications. In a recent retrospective study, we showed that L-ornithine-L-aspartate (LOLA) was associated with less dysbiosis. We aimed to study whether LOLA can improve gut microbiome dysbiosis, sarcopenia, frailty, ammonia levels and quality of life.
Method: In a monocentric, open-label, phase 4 study, patients with liver cirrhosis and hepatic encephalopathy grade 0–2 (assessed by either number connection test or critical flicker frequency or Westhaven criteria) received LOLA 18 g/day orally for 3 months. Endpoints were gut microbiome composition (16 s rRNA sequencing, analysis of alpha and beta diversity, taxonomic differences assessed by ANCOM and LEfSe, Tax4fun to predict function), quality of life (short form 36 questionnaire, SF36), serum ammonia, measurements of sarcopenia and frailty (appendicular lean muscle mass, anthropometric measures, liver frailty index, SARC-F) and biomarkers of sarcopenia (myostatin, irisin, fibroblast growth factor (FGF)-21, insulin like growth factor (IGF-1)).
Results: 193 patients were screened, 65 included and 52 patients (40.4% female, age 62 (58; 65)) completed the study. LOLA did not alter microbiome diversity, taxonomic composition nor predicted function. LOLA significantly improved the SF36 dimension vitality (from 45 (35; 60 to 50 (45; 60), p = 0.019). LOLA also decreased serum ammonia in patients with elevated baseline values (n = 10; from 69.5 (54; 225) µmol/L to 46.0 (22; 66) µmol/L, p = 0.004). Muscle mass declined over the study period, but not in the subgroup of patients with elevated and subsequently improved ammonia levels. Sarcopenia, frailty scores and muscle biomarkers did not improve either.
Conclusion: LOLA improved vitality in patients with cirrhosis, a clinically relevant patient reported outcome parameter but did not alter gut microbiome composition and function and could not prevent cirrhosis associated muscle loss in the majority of the patients. LOLA may be a useful adjunct treatment to improve quality of life in cirrhosis and may prevent muscle loss in patients with elevated ammonia levels.

SAT-229

Urinary microbiome alterations in patients with cirrhosis: a link to an increased urinary tract infection risk

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Background and aims: The pathophysiology of cirrhosis is closely linked to changes in microbiome composition. Cirrhosis-related dysbiosis is not confined to the gut but is also evident on the skin, in saliva, and in serum. This study aimed to characterize the urinary microbiome (UMB) of patients with cirrhosis to explore its connection to an increased susceptibility to urinary tract infections (UTIs).
Method: Midstream urine samples from 137 patients were analyzed via 16S rRNA gene sequencing. After excluding 29 patients who did not meet the inclusion or quality criteria, the UMB of 76 patients with cirrhosis (age 64.0 ± 13.5, 25% female) and 32 non-cirrhotic controls (58.5 ± 16.5, 47% female) was compared in terms of alpha and beta diversity, linear discriminant analysis effect size, and analysis of composition of microbiomes. Further analysis distinguished differences in UMB composition between patients with cirrhosis who developed a UTI within three years of sampling (dUTI group; n = 21) and those who remained free of UTI (no_UTI group; n = 24).
Results: Microbiome profiles of patients with cirrhosis differed significantly from those of non-cirrhotic controls: Alpha diversity was markedly reduced in the urine of patients with cirrhosis. The UMB of controls was predominantly associated with *Streptococcus*. Analysis of differences in UMB composition between dUTI and no_UTI groups demonstrated that the UMB of dUTI patients was strongly associated with Firmicutes and *Enterococcus*, while no_UTI patients displayed higher abundances of Bacteroidetes, *Prevotella* and *Corynebacterium 1*. Analysis of pathogens identified in microbiological examinations in the context of UTI in patients with cirrhosis revealed *Enterococcus* as highly common causative agent (23.3%).
Conclusion: The UMB of patients with cirrhosis shows a significantly altered composition compared to non-cirrhotic controls. Decreases in alpha diversity and *Streptococcus* abundance in the UMB of patients with cirrhosis might support understanding of the increased susceptibility to UTIs in this population. Patients of the no_UTI group exhibited higher abundances of bacteria typically found in a healthy UMB, such as *Prevotella* and *Corynebacterium 1*, whereas patients in the dUTI group exhibited significantly increased counts of *Enterococcus*, a genus containing species which commonly cause UTIs in patients with cirrhosis.

SAT-230

Biomarker-based profiling of pathomechanisms across distinct clinical stages of cirrhosis

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Background and aims: Disease-driving pathomechanisms in cirrhosis involve bacterial translocation (BT), macrophage activation, inflammation, endothelial dysfunction and fibrogenesis but their relative contribution may vary by disease stage and etiology.
Method: This study analyzed biomarkers of well-characterized cirrhosis patients of alcohol-related (ALD), metabolic liver disease (MASLD) and chronic viral hepatitis (VIRAL) recruited in the prospective Vienna Cirrhosis Study (VICIS) with data on hepatic venous pressure gradient (HVPG). Blood levels of 10 biomarkers were compared between compensated (CC) and decompensated (DC) patients and across etiologies. Multivariable linear regression models were used to evaluate the independent association between biomarkers, adjusting for liver disease severity.
Results: A total of n = 120 cirrhosis patients (ALD: 60; MASLD:30; VIRAL:30) with CC (n = 60; MELD: 10 (5); HVPG: 14 (8)) and DC (n = 60, MELD: 12 (6); HVPG: 19 (6)) were included. The soluble CD14 (sCD14), responsible for sensing circulating lipopolysaccharide (LPS) and activating toll-like receptor 4 (TLR4), was increased in DC vs. CC (sCD14: 1.95 (0.83) vs. 1.56 (0.51) µg/mL, $p < 0.001$) and correlated with the LPS-binding protein (LBP) levels in DC (rho = 0.52, $p < 0.001$) and in all etiologies, indicating a key role of BT-mediated TLR4 activation in DC. Macrophage activation was pronounced in DC compared to CC (CXCL9: 0.14 (0.10) vs. 0.22 (0.11) $p = 0.008$) and correlated with sCD14 (CXCL9: rho = 0.37, $p < 0.001$). Systemic inflammation (IL-6, TNF-α) was more pronounced in DC compared to CC and strongly correlated with sCD14 (IL-6, rho = 0.47; TNF-α, rho = 0.42; both $p < 0.001$). Importantly, sCD14 independently associated with biomarkers of endothelial dysfunction (von Willebrand factor antigen: VWF-Ag) and liver fibrogenesis (tissue inhibitor of metalloproteinases 1: TIMP1; Enhanced Liver Fibrosis (ELF) score) on multivariable linear regression analysis adjusted for HVPG and MELD (VWF: $\beta = 0.41$, $p = 0.007$; TIMP1: $\beta = 238.6$, $p < 0.001$; ELF: $\beta = 34.6$, $p = 0.045$).
Conclusion: Biomarkers reflecting specific disease-driving pathomechanisms in cirrhosis such as bacterial translocation and macrophage activation increase in patients with decompensated cirrhosis across common etiologies. Elevated sCD14 was independently linked to endothelial dysfunction and liver fibrogenesis and emphasizes the important role of innate immune system activation related to BT.

SAT-231

Improved glycaemic control over time in patients with type 2 diabetes mellitus (T2DM), with and without cirrhosis: a territory-wide cohort study of 1.2 million patients in Hong Kong

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Background and aims: Patients with cirrhosis are at increased risk of both hyperglycaemia and hypoglycaemia. Meanwhile, there have been major developments in anti-diabetic treatments in the past two decades. This study aimed to examine secular trends of glycaemic control in T2DM patients without cirrhosis and those with compensated and decompensated cirrhosis.
Method: This retrospective study included patients with T2DM aged ≥18 years at the time of T2DM diagnosis in Hong Kong from 2000–2023. Cirrhosis was defined by diagnosis or procedure codes, Fibrosis-4 index >3.25, or aspartate aminotransferase-to-platelet ratio index >2. Decompensated cirrhosis was defined by the presence of hepatic decompensating events. Serial laboratory measurements in each of the five consecutive periods (2000–2004, 2005–2009, 2010–2014, 2015–2019, and 2020–2023) were summarised by time-weighted average. The percentage of patients who achieved time-weighted average haemoglobin A1c (HbA1c) < 7% was compared in the five periods. Mixed effects logistic regression was employed to examine the impact of the period on the achievement of HbA1c < 7%.
Results: Of 1,206,233 patients with T2DM identified (mean age 63.1 years, 52.0% males), 63,200 (5.2%) had cirrhosis, among whom 17,992 (28.5%) had decompensated cirrhosis. The proportion of patients achieving HbA1c < 7% increased over time regardless of cirrhosis status. A higher percentage of patients with compensated cirrhosis achieved HbA1c < 7% (from 2000–2004 to 2020–2023, 49.3% to 75.8% in compensated cirrhotic group vs 47.6% to 64.6% in decompensated cirrhotic group vs 39.2% to 65.9% in non-cirrhotic group, $p < 0.001$). After adjusting for age, sex, body mass index, T2DM duration, aetiologies of liver disease, and important comorbidities, laboratory results and medication use, the compensated cirrhosis group had the biggest increase in the proportion of patients achieving HbA1c < 7% (2020–2023 vs 2000–2004, compensated cirrhotic group: OR 3.95, 95% CI 3.57–4.39; decompensated cirrhotic group: OR 3.71, 95% CI 3.11–4.42; non-cirrhotic group: OR 3.14, 95% CI 3.09–3.20).
Conclusion: After adjusting for confounding factors, patients with compensated cirrhosis had the largest improvement in glycaemic control. From 2000 to 2023, patients with T2DM had improved glycaemic control irrespective of their cirrhosis status, suggesting a universal improvement in diabetes care. Future analysis is needed to clarify the importance of glycaemic control in improving hepatic and extrahepatic outcomes and to establish the optimal glycaemic target for patients with T2DM and cirrhosis.

SAT-232

Direct oral anticoagulants for Budd-Chiari syndrome following percutaneous angioplasty in a chinese cohort

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Background and aims: Direct oral anticoagulants (DOACs) have been widely used to treat various thrombotic disorders. However, data regarding their use in patients with Budd-Chiari syndrome (BCS) are

limited. The present study was designed to assess the efficacy and safety of DOACs in a Chinese population with BCS.
Method: Between August 2020 and August 2024, patients with BCS who received DOACs following percutaneous transluminal angioplasty (PTA) were retrospectively evaluated. The primary outcome was the proportion of patients free from restenosis; secondary outcomes included bleeding and death.
Results: A total of 88 patients who received DOACs following PTA were included in the analysis, with a mean age of 46.4 ± 13.1 years. 44 patients received rivaroxaban, and the other 44 patients received dabigatran. 67 patients (76%) had cirrhosis, and 11 patients (13%) had a history of variceal bleeding. The median duration of DOAC therapy was 20.3 (interquartile range, 8.6 to 28.6) months. The median follow-up time was 22.6 (interquartile range, 14.4 to 31.6) months. The 1- and 3-year accumulative patency rates were 77.8% and 68.7%, respectively. 5 major bleedings (5.7%; incidence rate 3.4 per 100 patient-years; n = 4 upper gastrointestinal bleeding, n = 1 severe epistaxis with a decrease in hemoglobin by more than 2.0 g/L), 9 minor bleedings (10.2%; incidence rate 6.0 per 100 patient-years; n = 5 gingival bleeding, n = 2 epistaxis, n = 2 menorrhagia) occurred during DOAC therapy. Two patients died during follow-up (one from hepatocellular carcinoma and another from hepatorenal syndrome).
Conclusion: DOACs are safe and effective in patients with BCS following PTA. Further study is required to compare them with traditional anticoagulants.

SAT-237

A study of clinical characteristics in 43 patients with porto-sinusoidal vascular disease

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Background and aims: Since the introduction of the term 'Porto-sinusoidal vascular disease' (PSVD) in 2019, understanding of this disease has been limited. It has been reported that PSVD patients have a higher risk of developing portal vein thrombosis (PVT), but it is unclear whether PVT affects the progression of PSVD.
Method: This study retrospectively included patients diagnosed with PSVD at West China Hospital, Sichuan University, from 2019 to 2024. All patients were confirmed not to have liver cirrhosis through liver biopsy. Patient medical records were obtained through the electronic medical record system, collecting basic information, laboratory tests, imaging examinations, gastroenterological endoscopy, and pathological examination data, as well as treatment and prognosis information. Patients were divided into two groups based on the presence or absence of PVT: (1) PVT group, (2) non-PVT group, and then the clinical characteristics of the two groups were compared.
Results: A total of 43 PSVD patients were included in this study, with 26 males (60.5%) and 17 females (39.5%), and the average age was 46 ± 17 years. Among them, 11 (25.6%) patients had PVT. Comparing the two groups of patients with and without PVT, we found no statistically significant differences in age, total bilirubin, transaminase, alkaline phosphatase, and γ-glutamyl transpeptidase levels. Additionally, there were no significant differences in the manifestations of portal hypertension or pathological manifestations between the two groups. Patients with PVT tended to have longer spleen lengths (16.08 ± 3.97 cm, 14.16 ± 2.63 cm, P = 0.097), and pathological examinations found a higher proportion of non-regional sinusoidal dilation (72.7%, 40.6%, P = 0.088). Interestingly, we found that the proportion of males in the PVT group was significantly higher (90.9%, 50%, P = 0.029), and the albumin levels in this group of patients were lower than those without PVT (32.3 ± 12.2 g/L, 40.4 ± 6.9 g/L, P = 0.011), while the INR levels were higher (1.30 ± 0.16, 1.16 ± 0.15, P = 0.020). A total of 13 patients underwent transjugular intrahepatic portosystemic shunt surgery, but there was no difference in the proportion of patients between the two groups, with 5 (45.5%) in the PVT group and 8 (25%) in the non-PVT group, P = 0.262. There have been no deaths in either group to date.
Conclusion: We found that PSVD patients with PVT are predominantly male, and these patients have lower serum albumin levels and higher INR levels, suggesting a potentially more severe condition.

SAT-238

To construct a prediction model of recompensation in HBV-related decompensated cirrhosis patients combined with the inflammation index MLR

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Background and aims: Systemic inflammation plays an important role in the progression of end-stage liver disease. On the basis of effective antiviral therapy, some patients with decompensated hepatitis B cirrhosis can have a certain reversal of liver function, that is, recompensation, but the relationship between systemic inflammation and recompensation in patients with decompensated cirrhosis is still unclear. Therefore, this study aims to further explore the effect of inflammatory factors on liver recompensation in patients with hepatitis B virus-related decompensated cirrhosis.
Method: This is a single-center retrospective observational study. Patients with decompensated hepatitis B cirrhosis were divided into the non-recompensation group and the recompensation group according to the occurrence of recompensation. The differences between the groups were compared, and logistic regression analysis was used to screen the influencing factors. Based on the results of the influencing factors, we constructed a nomogram model and verified the value of the model.
Results: A total of 707 patients were enrolled in this study, 270 patients were excluded according to the exclusion criteria. According to whether recompensation occurred within 2 years, patients were divided into recompensation group (n = 180) and non-recompensation group (n = 257), and the incidence of recompensation was 41.19% (180/437). By comparing the baseline characteristics between the two groups, it was found that there were significant statistical differences in inflammation-related indicators between the two groups. Logistic regression multivariate analysis showed that the occurrence of liver failure, MLR and Child-Pugh score were independent influencing factors for the occurrence of recompensation in the training set. The nomogram model was constructed by combining the multivariate results. The model calibration curve of the training set and the validation set had a good consistency with the clinical decision curve. The area under the ROC curve of the training set and validation set was 0.815 (95% CI: 0.767–0.863) and 0.823 (95% CI: 0.767–0.863), respectively, which was better than MLR, Child-Pugh score, MELD, MELD-Na, iMELD, and ALBI score (P < 0.05).
Conclusion: High inflammation level is a risk factor for recompensation in patients with decompensated hepatitis B cirrhosis. Among the common inflammatory indicators, MLR is an independent influencing factor for patients' recompensation, and the Nomogram model combined with MLR can better predict patients' recompensation.

SAT-239

Comparative study on the efficacy of TIPS versus Non-TIPS treatments for hepatic portal vein thrombosis complicated by upper gastrointestinal hemorrhage

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Background and aims: Portal vein thrombosis (PVT) and upper gastrointestinal bleeding are prevalent complications in patients with liver cirrhosis. PVT can elevate the risk of upper gastrointestinal

bleeding. The objective of this study is to further validate the efficacy of transjugular intrahepatic portosystemic shunt (TIPS) treatment in this patient population.
Method: The clinical data of 72 patients with liver cirrhosis complicated by portal vein thrombosis (PVT) and upper gastrointestinal bleeding were analyzed retrospectively. Twenty-two patients in the transjugular intrahepatic portosystemic shunt (TIPS) group received TIPS treatment along with postoperative anticoagulant therapy, while the non-TIPS group received symptomatic hemostatic therapy and anticoagulant therapy. There were no significant differences in age, gender, or baseline characteristics between the two groups, and the procedures were technically successful for all patients in the TIPS group. The patients were followed up for a median of 13 months, during which the prognosis was assessed based on recanalization rate, rebleeding rate, and survival rate.
Results: The median age of the 72 patients included in the study was 54.5 years (range: 23 to 85 years), with a male-to-female ratio of 1.4:1. In the TIPS group, complete recanalization of portal vein thrombosis (PVT) occurred in 72.3% (16/22) of patients, while rebleeding was observed in 15.8% (3/22) of patients, and no patients died. In the non-TIPS group, complete recanalization of PVT occurred in 28% (14/50) of patients, partial recanalization was noted in 12% (6/50) of patients, and stable PVT was present in 58% of patients. Additionally, one patient died, and rebleeding occurred in 38% (19/50) of patients. The rate of PVT recanalization in the TIPS group was significantly higher than that in the non-TIPS group (72.3% vs. 28%, $P < 0.01$), and the rate of upper gastrointestinal rebleeding in the TIPS group was significantly lower than that in the non-TIPS group (15.8% vs. 38%, $P < 0.05$). In the TIPS group, the bilirubin level was (27.31 ± 10.98) before treatment and (30.62 ± 10.90) after treatment, and there was no statistically significant difference observed between the two groups ($t = -1.11$, $P = 0.28$). INR was (1.47 ± 0.22) before treatment and (1.55 ± 0.18) after treatment, also showing no significant difference between the two groups ($t = -1.36$, $P = 0.19$).
Conclusion: TIPS (Transjugular Intrahepatic Portosystemic Shunt) treatment for patients with liver cirrhosis and portal vein thrombosis, complicated by upper gastrointestinal bleeding, demonstrates a high rate of thrombosis recanalization, a low incidence of rebleeding, and does not exacerbate liver function impairment.

SAT-240-YI
Evaluation of the clinical utility of wearable fitness tracking devices to diagnose frailty in patients with liver cirrhosis – A proof-of-concept study

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Background and aims: Frailty is prevalent among patients with liver cirrhosis and clinically relevant as it negatively impacts quality of live and long-term clinical outcome. Diagnosis of frailty based on the Liver Frailty Index (LFI) is limited in the clinical routine due to the personnel- and time-consuming assessment. Wearable fitness tracking devices (WFTD) have the potential to serve as a resource-efficient alternative to diagnose frailty. This proof-of-concept study aims to evaluate the ability of accelerometer data from WFTD to diagnose frailty in patients with liver cirrhosis.
Method: From 03/2022 to 11/2024, patients with liver cirrhosis were prospectively enrolled in the study. All patients performed frailty assessment by LFI and walking of a predefined distance while wearing the standardized WFTD. Laboratory and clinical data were collected at the study time point. A random forest model was employed with model evaluation conducted using weighted F1 scores and five-fold cross-validation. Prior to model fitting, the data was scaled, and the dataset was split into 70% training and 30% test subsets. In addition to the WFTD data, Model of endstage liver disease (MELD) Score, MELD 3.0 and the Freiburg index of post-TIPS survival (FIPS) were added to the random forest analysis. Due to the unequal size of the frail and not-frail group, a weighted F1 score was used to evaluate the model.
Results: 121 datasets of 115 individual patients qualified for final analysis after exclusion of patients without representative walking distance or insufficient baseline data on LFI, with Budd-Chiari syndrome or HCC outside the Milan criteria. The majority of patients were male (59%) at a median age of 61 years (IQR 54–66). Median MELD, MELD 3.0 and FIPS were 10 (IQR 8–14), 13 (IQR 9–16) and −0.28 (IQR −0.97–0.25), respectively. Based on the LFI, the majority of patients were classified as pre-frail (69.4%, n = 84/121), while only 24.8% (30/121) of patients were frail and 5.8% (7/121) robust at the time point of assessment. With the addition of MELD, the model achieved a weighted F1 score for the random forest analysis on the test data of 0.67. The model further improved when including MELD 3.0 (weighted F1 score: 0.69) or FIPS (weighted F1 score: 0.74). In order to analyze a cohort-adjusted classification of the LFI, the LFIs of the total cohort were divided into quartiles and the lowest quartile representing the most robust patient subset was compared to the remaining three. In doing so, weighted F1 scores for the random forest analysis further improved with the combination of accelerometer data and MELD 3.0 achieving the most accurate results (weighted F1 score: 0.837).
Conclusion: This proof-of-concept study demonstrated that predicting LFI from WFTD data is not only feasible but a time- and personnel-efficient approach to diagnose frailty in patients with liver cirrhosis. Training and testing in larger cohorts is ongoing and certainly needed to further evaluate its accuracy and ability to predict clinical outcomes.

SAT-241
Over the years, diagnostic problems in cirrhosis continue, but its etiology changes: chronic viral hepatitis is decreasing, steatotic liver disease is increasing

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Background and aims: To investigate the characteristics of cirrhosis etiology, diagnostic methods, and complications with a 1-decade interval.
Method: The clinical and demographic characteristics of patients with cirrhosis at the time of diagnosis at a tertiary university hospital between 2005–2009 (first period) and 2019–2023 (second period) were retrospectively investigated.
Results: A total of 1068 patients (64.5% men, mean age 55.5 ± 12.6 years) were diagnosed with cirrhosis (709 (66.4%) patients in the first period, and 359 (33.6%) in the second period). In the first period, patients were younger ($p = 0.000$). The mean MELD-Na was 12 ± 5.2. MELD-Na was not different between the periods ($p = 0.061$). In the first and second periods, 57.7% and 61.3% of the patients were in Child-Pugh A, 31.6% and 32.4% in B, 10.7% and 6.3% in C, respectively. While there was no difference in Child-Pugh stages A and B between the periods, the rate of patients diagnosed in stage C was significantly less in the second period ($p = 0.025$). In the first period 191 (26.9%) patients, and in the second period 95 (26.5%) patients were diagnosed with complications in the emergency department. The

others were diagnosed in the outpatient clinic under elective conditions. There was no difference in where cirrhosis was diagnosed between periods (p = 0.868). 587 (55%) patients were decompensated at diagnosis. There was no difference between periods (p = 0.109), but the patients diagnosed in the emergency clinic had a higher rate of decompensated cirrhosis (p = 0.000). The causes of cirrhosis were, in order, 246 (23%) HBV, 196 (18.4%) cryptogenic, 188 (17.6%) MASLD, 143 (13.4%) alcohol, 126 (11.8%) HCV, 83 (7.8%) autoimmune liver diseases, 45 (4.2%) HDV, 23 (2.2%) other causes, and 18 (1.7%) genetic diseases. In the second period, while the frequency of cirrhosis caused by HBV, HCV, and HDV decreased (p = 0.000, p = 0.000, and p = 0.022, respectively), the frequency of MASLD and alcohol-related liver disease (ALD) increased (p = 0.000, and p = 0.023). In respect to the clinical stage 251 (23.5%) patients were diagnosed as stage 1, 260 (24.3%) as stage 2, 114 (10.7%) as stage 3, 402 (37.6%) as stage 4, 36 (3.4%) as stage 5, and 5 (0.5%) as stage 6. The frequency of diagnosis in stage 1 was higher in the second period (p = 0.000). While the frequency of using clinical features in the diagnosis of cirrhosis was higher in the first period (p = 0.000), the frequency of using the radiological methods and fibroscan was higher in the second period (p = 0.000, and p = 0.000). 120 (11.2%) patients had hepatocellular carcinoma at the time of diagnosis, there was no difference between periods (p = 0.494).

Conclusion: There is still a problem with diagnosing cirrhosis, as most patients are diagnosed after decompensation and in the emergency clinic. Over the years, viral factors in the etiology of cirrhosis have gradually decreased, however MASLD and ALD have progressively increased.

Cirrhosis and its complications – Portal Hypertension

TOP-168

Endoscopic ultrasound-guided portal pressure gradient predicts hepatic decompensation in compensated cirrhosis

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Background and aims: Endoscopic ultrasound guided-portal pressure gradient (EUS-PPG) has emerged as an alternative method for obtaining direct portal pressure measurements for assessing portal hypertension. Transjugular hepatic venous portal gradient (HVPG) is the gold standard for measuring portal hypertension and is the basis for defining clinically significant portal hypertension, defined as ≥ 10 mmHg. Though EUS-PPG has been shown to correlate with HVPG, clinical parameters, FIB4 score, and fibrosis staging, associations with downstream clinical outcomes such as hepatic decompensation are lacking. We aimed to evaluate the utility of EUS-PPG in predicting new hepatic decompensation in patients with compensated cirrhosis.
Method: This was a single-center retrospective study at a tertiary endoscopy center of patients who had EUS-PPG measured from 2014 to 2023. Subjects with cirrhosis without a prior decompensating event were included. A new decompensating event defined as variceal bleeding, ascites, or hepatic encephalopathy was the primary endpoint. Baseline characteristics were compared between patients with and without new decompensation. Univariate and multivariate logistic regression analyses were conducted to determine potential associations between predictors including MELD-Na, Child-Pugh score, platelet count, and PPG, with new decompensation. Receiver operating characteristic curve was constructed with PPG as predictor for hepatic decompensation and Kaplan-Meier curve was constructed according to cut-off level of PPG ≥ 10 mmHg. Post hoc analysis was done to establish optimal PPG cut off with maximal negative predictive value.
Results: 202 patients had EUS-PPG, of which 103 had a diagnosis of cirrhosis. 65 of these had no prior hepatic decompensation at time of EUS-PPG and were included in the study. Median age was 62.0 (IQR 56.0–68.0). 46% were male. Median MELD-Na was 9 (7–11) and 87.7% were Child-Pugh Class A. Liver disease etiologies included viral hepatitis (16.9%), MASLD (44.6%), ALD (15.4%), and others (23.1%) which included AIH, PSC, and PBC. 13 patients (20%) developed new hepatic decompensation. Median PPG in the decompensated group was 9.6 mmHg (6.6–13.6) compared to 6.0 mmHg (3.2–10.0) in the compensated group. 46% of the decompensated group had PPG ≥10 mmHg, compared to 26.9% in the compensated group. In crude and adjusted analyses, PPG was significantly associated with decompensation (OR 1.12, 95% CI 1.01–1.23; aOR 1.17, 95% CI 1.02–1.35). PPG ≥10 mmHg trended towards an association with new decompensation (OR 2.33, 95% CI 0.67–8.13) but was not statistically significant. Post hoc analysis identified PPG value of <8 mmHg as having the greatest negative predictive value of 89% for developing decompensation.
Conclusion: In patients with compensated cirrhosis, higher EUS-PPG had a greater likelihood of new hepatic decompensation. This study supports EUS-PPG as a reliable tool for assessing portal hypertension and possibly predicting clinical decompensation.

TOP-169

Impact of physical exercise and protein-enriched nutritional support on the development of post-TIPS hepatic encephalopathy

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Background and aims: TIPS is a highly effective treatment for complications of portal hypertension but carries a substantial risk (20–40%) of hepatic encephalopathy (HE) post-TIPS. Sarcopenia has been also identified as a contributing factor to HE given the role of skeletal muscle in ammonia metabolism. We aimed to evaluate whether a 12-week intervention (2 weeks pre-TIPS and 10 weeks post-TIPS) consisting of physical exercise and protein-enriched oral nutritional supplements reduces sarcopenia and lowers HE incidence within 6 months post-TIPS.
Method: Prospective, open-label, randomized study including cirrhotic patients scheduled for elective TIPS in two centers. Patients were randomized 1:1 to control group or intervention group. The primary endpoint was the development of HE within 6 months post-TIPS. The secondary endpoint was the intervention's impact on sarcopenia. This is an interim analysis focused on the primary endpoint.
Results: Forty-five patients were included (23 control, 22 intervention). Baseline characteristics, including sex, age, Child-Pugh score, MELD, prior HE, HE treatments, baseline ammonia levels, Liver Frailty Index (LFI), and TIPS indications, were similar between groups. Portal pressure gradients at 24 hours and 1 month post-TIPS were comparable among the two groups. No post-TIPS variceal bleeding occurred, and ascites control was equivalent also in the control and intervention group. Nineteen patients (86%) in the intervention group adhered to >50% of prescribed sessions. 18 patients (40%) developed HE: 14 (77%) in the control group and 4 (22%) in the intervention group. Cumulative HE incidence at 1, 3, and 6 months was 44%, 60%, and 65% in controls versus 14%, 20%, and 20% in the intervention group (log-rank 8.7, $p < 0.01$). Per-protocol analysis revealed an even greater benefit (log-rank 15.4, $p < 0.001$). Among 24 patients with baseline and 6-month LFI assessments (12 per group), 5 intervention patients improved LFI compared to none in the control group ($p = 0.04$).
Conclusion: A 12-week intervention of physical exercise and nutritional support effectively reduces post-TIPS HE incidence and improves frailty parameters, highlighting the value of targeting sarcopenia in cirrhotic patients undergoing TIPS.

TOP-188-YI
Incidence and clinical implications of abstinence-induced hepatic recompensation in decompensated alcohol-related cirrhosis

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Background and aims: Sustained alcohol abstinence improves the prognosis of patients with alcohol-related cirrhosis (ArLD) and may even facilitate hepatic recompensation in decompensated patients. However, more evidence is needed on the incidence, predictors and prognostic implications of recompensation in ArLD.
Method: This Baveno Cooperation-endorsed multicentre study included patients with decompensated ArLD who achieved alcohol abstinence between 2001 and end of 2022. Following Baveno VII criteria, recompensation was defined as (i) the resolution of ascites and encephalopathy (including cessation of medical therapy) and absence of variceal bleeding and (ii) improved hepatic function (Child-Pugh A or MELD < 10). Patients were censored upon alcohol relapse or liver transplantation.
Results: A total of 418 patients with decompensated ArLD from 13 centres were included at the time of alcohol abstinence (median age: 55 years; 71.1% male). The median MELD at inclusion was 19 (IQR: 13–24) and 68.2% had experienced further decompensation prior to abstinence. The median duration from first decompensation to abstinence was 1.0 month (IQR: 0.0 – 11.7). Over a median follow-up of 34.3 months (IQR: 15.7 – 63.2), 101 patients achieved recompensation with a cumulative incidence of 7.5% after 1 year, 18.9% after 2 years and 27.2% after 5 years. With regard to predictors of recompensation (including centre as random effect), recompensation probability decreased with a longer duration to alcohol abstinence after first decompensation (subdistribution hazard ratio [SHR] per month: 0.97; p = 0.004). Neither MELD (SHR: 0.98; p = 0.353) nor albumin (SHR per mg/dL: 0.98; p = 0.145) at abstinence significantly impacted subsequent recompensation. However, there was a higher likelihood in patients with a higher platelet count (SHR per 10 G/L: 1.03; p < 0.001) and in patients presenting with alcohol-related hepatitis at abstinence (SHR: 2.05; p = 0.095). Liver-related death (LRD) occurred in 59 patients (14.1%) and de novo hepatocellular carcinoma (HCC) was diagnosed in 7 patients (1.4%). Not a single patient who had recompensated and remained abstinent progressed to LRD or HCC over a median follow-up of 22.3 months after recompensation. In contrast, the cumulative incidence of LRD/HCC in abstinent patients who remained decompensated was 11.8%/1.2% after 1 year, 16.5%/2.1% after 2 years and 21.1%/2.8% after 5 years. Of note, of the 16 patients who relapsed to alcohol consumption after recompensation (15.8% of recompensated cohort), 4 progressed to LRD and 1 to HCC.
Conclusion: Hepatic recompensation can be achieved in a significant proportion of decompensated ArLD patients, particularly when abstinence is achieved early after decompensation and platelet count is higher. Recompensation in ArLD cirrhosis significantly improves clinical outcomes, with a negligible risk of liver-related mortality.

TOP-189-YI

Vibration-controlled transient elastography of the liver and the spleen for hepatic decompensation risk stratification in a european multicentre study of contemporary cACLD patients

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Background and aims: The recently introduced Non-**I**nvasive Clinically Significant Portal Hypertension (CSPH) Estimated Risk ('NICER') model comprising liver (LSM) and spleen stiffness measurement (SSM; at 100 Hz) by transient elastography, platelet count (PLT), and body mass index (BMI) outperformed ANTICIPATE ± NASH (LSM & PLT ± BMI) for the non-invasive diagnosis of CSPH in compensated advanced chronic liver disease (cACLD).

Herein, we present follow-up data from the Baveno Cooperation study leading to the NICER model, and compare the prognostic utility of non-invasive strategies and hepatic venous pressure gradient (HVPG).

Method: Child-Pugh stage A cACLD (LSM ≥10 kPa and/or F3/4) patients from 16 specialized European centres who underwent paired assessment of HVPG, SSM (at 100 Hz), and LSM from 2020–2023 and had lab and follow-up data available were included into the study.

Results: 393 cACLD patients (MASLD: 40.7%, MetALD/ALD: 32.1%) with CSPH (HVPG ≥ 10 mmHg) prevalence of 59.3% were included. Patients were followed for a median of 1.3 (0.8–1.9) years until the occurrence of hepatic decompensation, hepatocellular carcinoma, liver transplantation, death, or last visit. Hepatic decompensation incidence rates were 8.3% (n = 28, 95% CI: 5.0–10.7%) and 13.4% (n = 37, 95% CI: 8.7–17.8%) at 1 and 2 years of follow-up, respectively. HVPG (AUC: 0.755, 95% CI: 0.662–0.849), ANTICIPATE ± NASH (AUC: 0.751, 95% CI: 0.654–0.848), and NICER (AUC: 0.739, 95% CI: 0.635–0.844) conferred similar time-dependent discriminative ability for hepatic decompensation at 2 years. The presence/absence of CSPH (Y1 decompensation rate: 10.9% vs. 3.4%, Y2: 20.0% vs. 3.4%, log-rank test: $p < 0.001$), or a non-invasively predicted CSPH probability of ≥60%/<60% according to ANTICPATE ± NASH (Y1: 11.6% vs. 4.3%, Y2: 19.9% vs. 7.2%, $p = 0.003$) or NICER (Y1: 10.1% vs. 5.0%, Y2: 18.0 vs. 7.4%, $p = 0.010$) all similarly distinguished high-risk cACLD patients from those with a more favourable prognosis. In Cox regression analysis, serum albumin level was identified as a key predictor of hepatic decompensation (hazard ratio [HR]: 0.83 per g/L, $p < 0.001$) besides portal hypertension as evaluated by either HVPG (albumin-adjusted HR [aHR]: 1.10 per mmHg, $p = 0.002$) or by ANTICIPATE ± NASH (aHR: 1.13 per 10% CSPH probability, $p = 0.049$) or NICER (aHR: 1.14 per 10% CSPH probability, $p = 0.042$). Consideration of albumin increased discrimination in comparison to HVPG/NICER/ANTICIPATE ± NASH alone ($p < 0.001$ for all; Harrel's C: 0.764–0.775 for albumin-containing models).

Conclusion: In our multicentre study of contemporary European cACLD patients, non-invasively estimated CSPH risk was similarly predictive for hepatic decompensation as HVPG. Consideration of serum albumin increased the discriminative ability, while the addition of SSM-100 Hz *per se* did not improve hepatic decompensation risk stratification.

TOP-190

Biomarkers of pathophysiological mechanisms identify stage-specific divers of disease progression in ACLD

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Background and aims: Our prospective study (VICIS; NCT03267615) investigated biomarkers of key pathophysiological mechanisms involved in advanced chronic liver disease (ACLD) progression throughout different clinical stages and evaluated their stage-specific ability of identifying progressive disease.
Method: 464 ACLD patients with portal hypertension (PH; hepatic venous pressure gradient [HVPG] >5 mmHg) were characterized at the time of HVPG measurement from 2017–2021 and prospectively followed. Clinical stages were defined as cACLD, first decompensation, further decompensation, ACLF, liver-related death, and recompensation. The following pathophysiological mechanisms were assessed: PH/endothelial dysfunction (HVPG/von Willebrand Factor [VWF]), extracellular matrix (ECM) remodeling/fibrogenesis (enhanced liver fibrosis score [ELF]), systemic inflammation (SI; C-reactive protein [CRP], interleukin-6 [IL-6], and procalcitonin), circulatory dysfunction (proBNP, copeptin), hepatic impairment (MELD, albumin, and bile acids [BA]). Endpoints: First decompensation in cACLD, further decompensation/ACLF in first decompensation, and liver-related death in further decompensation.
Results: All biomarkers showed significant differences between cACLD and decompensated cirrhosis. Interestingly, HVPG reached a plateau with first decompensation, while VWF, CRP & IL-6, copeptin, and albumin & BA were significantly increasing between patients with first and further decompensation. During a median follow-up of 28.8 months, 35/179 (19.6%) cACLD patients developed first decompensation; 60/168 (35.7%) first decompensation patients developed further decompensation/ACLF; 40 (34.2%) of further decompensated patients experienced liver-related death. Investigating differences between progressors and non-progressors within 24 months (cACLD) and 12 months (first/further decompensation) in sub-stages, the most profound differences were found for PH/endothelial dysfunction (HVPG/VWF), ECM remodeling/fibrogenesis (ELF), and liver function (MELD, albumin, and BA) in cACLD, while SI (CRP, PCT, and IL-6) was the key driver of progression after first decompensation. Profound systemic inflammation (PCT & IL-6) and circulatory dysfunction (copeptin) were hallmarks of adverse outcomes among those with further decompensation.
Conclusion: PH/endothelial dysfunction are the main druggable targets (i.e., HVPG-lowering medications & statins) in cACLD, while modulating SI (e.g., antibiotics & albumin) seems key for preventing progression from first to further decompensation. In those with further decompensation, improving circulatory dysfunction (e.g., albumin) is becoming increasingly relevant. Notably, even within these stages, there was profound interindividual variation of pathophysiology-related biomarkers that can be visualized by spider diagrams and may help to guide personalized therapy in future trials.

WEDNESDAY 07 MAY

WED-157
A prospective multicenter study for comparison of standard-dose repeated bolus injection vs. low-dose continuous intravenous infusion of terlipressin for acute esophageal variceal bleeding in patients with liver cirrhosis

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Background and aims: Acute esophageal variceal bleeding (AVB) is one of the most serious complications of liver cirrhosis. For the emergent management of variceal bleeding, administration of a vasoconstrictor is essential for hemostasis together with endoscopic variceal ligation (EVL). Standard-dose repeated bolus injection (SDRBI) of terlipressin 4–6 times daily is most widely employed before and after EVL, but the adverse effects of terlipressin cannot be overlooked. To minimize the ischemic side effect, low-dose continuous infusion (LDCI) of terlipressin has been proposed for hepato-renal syndrome in patients with liver cirrhosis. However, data from prospective comparisons between the two methods for AVB are sparse. This study aims to compare the safety and efficacy of the two methods for the management of AVB.
Method: This study is a randomized controlled trial to compare SDRBI and LDCI of terlipressin in patients with AVB. A total of 125 patients were enrolled and randomly assigned to the SDRBI group (n = 63, 1 mg bolus injection every 6 hours after initial 2 mg of terlipressin) or LDCI group (n = 62, 2 mg/day of terlipressin infusion) after EVL. Patients with gastric varices on the fundus, failure of initial endoscopic therapy, or advanced hepatocellular carcinoma were excluded.
Results: The baseline characteristics of the patients were not significantly different. Re-bleeding incidence after initial successful EVL was observed for 5 days. The success rate of maintaining hemostasis was 98.4% in both groups (Crude odd ratio = 0.98 [0.06–6.09], P = 0.991). One patient died in the SDRBI group. Decrease of Hb more than 3 g/dL or adjusted blood requirement index over 0.75 to maintain Hb>8.0 g/dL were observed in 7 patients (11.1%) in the SDRBI and 9 (14.5%) in the LDCI group (P = 0.763), respectively, without newly developed hematemesis or melena. The overall incidence of gastrointestinal, cardiovascular, metabolic, or neurologic adverse events was significantly higher in the SDRBI group than in the LDCI group during 5 days (P < 0.05).
Conclusion: Compared with SDRBI, LDCI of terlipressin shows comparable efficacy and better safety for managing AVB in patients with liver cirrhosis.

WED-158
A metabolomic model based on portal venous functional metabolites for predicting post-TIPS overt hepatic encephalopathy using machine learning methods

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Background and aims: The occurrence of overt hepatic encephalopathy (OHE) after transjugular intrahepatic portosystemic shunt (TIPS) is associated with poor outcomes but cannot be predicted accurately. The identification of serum biomarkers from portal vein for predication and patient risk stratification remains underexplored. We aimed to determine the portal venous functional metabolites to predict the development of OHE after TIPS establishment.
Method: Prospective TIPS cohorts including 332 patients underwent preoperative serum collection and follow-up evaluation. Serum metabolomics was analyzed to predict OHE on random forest analysis. A training cohort (n = 221) was used to build the prediction model and a validation cohort (n = 111) was used to test the model. Cell experiments were conducted to test the functions of the selected metabolites.
Results: A total of 71 patients (21.4%) developed OHE after TIPS. By metabolomic profiling, 668 portal venous plasma metabolites are identified. Our machine learning analysis reveals a 7-metabolite OHE predictive model, which is validated in a test set, yielding an area

under the receiver operating characteristic (AUROC) of 0.911. We stratified patients into high-risk and low-risk groups based on the predictive model cutoff. The hazard ratio for the occurrence of post-TIPS OHE in the high-risk group was 16.82 times that of the low-risk group (95% confidence interval 4.02–70.33, $p < 0.001$). Moreover, we individually applied these metabolites from the model to stimulate the astrocyte and found that citrate and taurolithocholic acid could inhibit cell proliferation and promote astrocyte senescence.
Conclusion: Collectively, our findings reveal the metabolic landscape of post-TIPS OHE and identify a distinct biomarker panel that enables prediction, thus facilitating precision prevention for OHE.

WED-159

The role of hepatic venous pressure gradient in patients with porto-sinusoidal vascular disease

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Background and aims: The hepatic venous pressure gradient (HVPG) is commonly used as a surrogate for direct portal pressure gradient (PPG) measurement. However, its suitability in patients with porto-sinusoidal vascular disease (PSVD) remains unclear. This study aims to evaluate the correlation between HVPG and direct PPG in these patients.
Method: We conducted a "proof-of-concept" study to evaluate the HVPG and ultrasound-guided percutaneous portal pressure gradient (US-PPG) measurements in patients with PSVD. Prior to this, we assessed the stability of US-PPG by enrolling 21 patients with decompensated cirrhosis who underwent both US-PPG and pre-transjugular intrahepatic portosystemic shunt (TIPS) PPG measurements on the same day. Agreements between HVPG and US-PPG in PSVD patients, as well as US-PPG and pre-TIPS PPG in decompensated cirrhotic patients, were analyzed using the intra-class correlation coefficient (ICC) and the Bland-Altman method.
Results: Among the 21 patients, US-PPG demonstrated a good correlation with pre-TIPS PPG ($R = 0.85$, 95% CI: 0.65–0.94), with an ICC of 0.85 (95% CI: 0.67–0.94). Similarly, a good agreement was observed between ultrasound-guided portal pressure (PP) and pre-TIPS PP ($R = 0.91$, ICC = 0.88; $p < 0.001$). For the primary evaluation, 8 patients with biopsy-proven PSVD were included. Among them, only one patient was decompensated, and HVPG measurement failed in this case due to extensive hepatic venous-to-venous communications; the US-PPG in this patient was 34 mmHg. In the remaining 7 patients, the median US-PPG was 9.0 mmHg (IQR: 9.0–24.0), while the median HVPG was 8.0 mmHg (IQR: 4.0–9.0). However, the agreement between US-PPG and HVPG was poor, with an ICC of 0.73 (95% CI: 0.06–0.95) and a correlation coefficient (R) of 0.75 (95% CI: 0.07–1.0). Similarly, a poor agreement was observed between ultrasound-guided portal pressure (PP) and Wedge hepatic vein pressure ($R = 0.53$, ICC = 0.63). The median platelet count was 95.0×10^9/L (IQR: 46.3–238.0), the median liver stiffness measurement was 9.7 kPa (IQR: 5.6–13.4), and the median spleen stiffness measurement was 43.5 kPa (IQR: 23.9–73.9).
Conclusion: HVPG demonstrated poor accuracy in reflecting portal pressure values in patients with PSVD. Further studies are warranted to explore non-invasive tools for evaluating portal hypertension in PSVD individuals.

WED-160

Long-term outcome of interventional radiological management of Budd-Chiari syndrome: a retrospective, multicenter survey of 10 years

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Background and aims: Large cohort study on radiological interventional management, including percutaneous angioplasty recanalization (PTA)/thrombolysis, transjugular intrahepatic portosystemic shunting (TIPS), for symptomatic patients with Budd-Chiari syndrome (BCS) are lacking. We aimed to depict characteristics and treatment allocation of BCS patients, and intensively assess its long-term outcomes and complications.
Method: Consecutive patients diagnosed as BCS from 6 Chinese tertiary centres were retrospectively screened for eligibility between Jul-2010 to May-2019. Unadjusted, propensity score match (PSM) adjusted, and competing risk analyses with death as a competing event were conducted.
Results: A total of 997 patients were enrolled, including inferior vena cava (15.7%), hepatic vein (16.2%), and combined (68.1%) types. All patients received anticoagulation. Medical treatment alone sufficed in 117 (11.7%) patients, and 22 (2.2%) patients received thrombolysis for acute thrombosis. PTA was used in 834 (83.7%) patients, 268 with and 566 without initial stenting. Initial stenting reduced competing risk adjusted restenosis rate in patients underwent PTA, but not improved survival before and after PSM in all three types of BCS, and patient with unsolved restenosis had a worse prognosis, compared to these solved restenosis or non-restenosis (hazard ratio: 3.0 [1.14–7.63], $p < 0.001$). TIPS was performed in 90 (0.9%) patients (46 initial and 44 converted TIPS). Overall, the 3-year shunt dysfunction and 3-month hepatic encephalopathy rates were 52.3% (40.8%–63.8%) and 20% (11.7%–28.3%), respectively, with no differences between initial TIPS and converted TIPS. Anticoagulation-related, PTA-related, and TIPS-related complications occurred in 152/997, 11/834, and 1/90 patients. The 5-year orthotopic liver transplantation (OLT)-free survival rate was 90.2% (88.2%–92.3%) in the whole cohort with 103 (10.5%) patients died after a median follow-up of 57.3 months, which was similar among different BCS types patients.
Conclusion: With predominantly IVC-obstruction presented and angioplasty used, interventional radiological treatment could also achieve a good long-term outcome in Chinese patients with BCS.

WED-161

Dedicated stent decreases the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients

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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive interventional procedure to relieve the symptomatic complications of portal hypertension, and HE is the most common and often severe complication following TIPS, previous research had found that polytetrafluoroethylene (ePTFE) stents and bare stents had a comparable post-TIPS HE rates. The Fluency (Bard, Murray Hill, USA) and the Viatorr (W.L. Gore & Associates, Flagstaff, AZ, USA) are two types of ePTFE-covered stents, Despite the ePTFE-covered stent was widely recommended by the guidelines, the effect of different ePTFE-covered stents on patients` outcomes remains controversial. This study aimed to investigate the incidence of hepatic encephalopathy (HE) following transjugular intrahepatic portosystemic shunt (TIPS) using different types of stent grafts in patients with cirrhosis.
Method: Consecutive patients with cirrhosis who underwent TIPS from January 2012 to December 2022 in our center were considered to be included in the study. Patients were divided into the Viatorr group and Fluency group. Case-control matching was performed to control potential confounding variables at baseline. Kaplan-Meier and Cox regression analyses were used to identify the cumulative rates and independent risk factors of post-TIPS HE.
Results: 1077 patients were included in this study, 340 patients in the Viatorr group and 737 in the Fluency group. The 2-year cumulative incidence of HE was significantly lower in the Viatorr group compared with Fluency group (26.4% vs. 34.3%, p = 0.018). The 2-year cumulative rate of shunt dysfunction was also lower in the Viatorr group (2.2% vs. 7.5%, p = 0.037). However, the 2-year cumulative rate of transplant-free survival (93.4% vs. 90.1%, p = 0.428) was comparable between two groups.
Conclusion: TIPS creation using the Viatorr stent-grafts showed a lower risk of HE and better patency compared with the Fluency stent-grafts. Therefore, dedicated stent-graft should be preferred for the TIPS creation in patients with cirrhosis.

WED-162

Cardiac failure following transjugular intrahepatic portosystemic shunt patients with cirrhosis

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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is effective in alleviating the complications of portal hypertension. Post-TIPS cardiac failure has become one of the main concerns recently. It is as high as 20% after TIPS insertion in the Western population. This study was designed to evaluate the incidence of post-TIPS cardiac failure and predisposing factors in patients with cirrhosis.
Method: Between September 2022 and April 2024, consecutive cirrhotic patients who underwent elective TIPS were prospectively screened for inclusion. Patients were excluded if they had (1) a history of previous TIPS or surgical shunt; (2) medium to severe pulmonary hypertension; (3) heart failure; (4) End-stage renal disease requiring hemodialysis; (5) respiratory failure; (6) malignancies with a life expectancy of less than 6 months. A systematic cardiac assessment was conducted in each patient, including biological parameters and transthoracic echocardiography. The primary endpoint was the incidence of cardiac failure.
Results: 238 patients underwent TIPS during the study period, 210 met inclusion criteria [aged 54.0 (47.0–61.0) years, 68.0% man]. Etiologies of cirrhosis were hepatitis B viral infection in 120 (57.1%) patients, and the indication for TIPS was secondary prophylaxis in 166 (79.0%) patients. Baseline echocardiography showed the ejection fraction was 68.0% (63.0%–72.0%), E/A was 1.0 (0.8–1.3), and Pro-BNP was 103.0 (48.0–194.3) respectively. After a median follow-up of 12.0 (8.0–17.0) months, only one patient (0.47%) experienced post-TIPS cardiac failure. 104 (49.6%) patients had post-TIPS echocardiography, end-systolic diameter (ESD), left ventricle (LV) diameter, and stroke volume (SV) were slightly increased after TIPS (ESD, 30.0 vs 31.0, p = 0.001; LV diameter, 48.0 vs 50.0, p = 0.000; SV, 72.0 vs 82.0, p = 0.000). Diastolic function parameters, including left atrial volume index (LAVI), left ventricular mass index (LVMI), and Mean E/e' also showed a slight increase after TIPS (LAVI, 36.7 vs. 41.1, p = 0,000; LVMI, 91.4 vs. 98.5, Mean E/ e', 8.9 vs. 9.5, p = 0.014). However, 155 (73.8%) patients had edema, and 13(6.2%) patients needed liver transplantation or died.
Conclusion: Post-TIPS cardiac failure is rare in the current Chinese cohort. The following echocardiography revealed that despite diastolic function being impaired, patients with cirrhosis can increase cardiac contractility to compensate for the increased volume load shunted to the heart after TIPS.

WED-163

Prevention of hepatic encephalopathy following transjugular intrahepatic portosystemic: lactulose plus rifaximin vs. lactulose monoprophylaxis

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Background and aims: Hepatic encephalopathy (HE) is the most common complication after transjugular intrahepatic portosystemic shunt (TIPS). Rifaximin and lactulose are effective in preventing HE in patients with cirrhosis and TIPS. There is a lack of evidence concerning whether a combination of rifaximin and lactulose is better than lactulose monoprophylaxis. The present aims to compare the efficacy of lactulose plus rifaximin with lactulose monoprophylaxis in preventing post-TIPS HE.
Method: Consecutive patients with cirrhosis who underwent TIPS successfully from May 2019 to May 2024 in our center were included in the study. Patients were divided into group A and group B (A: lactulose monoprophylaxis; B: lactulose plus rifaximin). Propensity score matching (PSM) was performed to control potential confounding variables at baseline, and the Child-Pugh score, MELD score, PT and age were defined as covariates. Patients were prescribed rifaximin 600 mg two times daily and lactulose 15 ml three times daily (the starting dose) or lactulose 15 ml three times daily for six months after TIPS placement.
Results: 608 patients were included in this study, 527 patients treated with lactulose, and 81 patients treated with lactulose plus rifaximin. After PSM, there were 74 fuzzy-matched patients in group A and group B. The Child-Pugh score was 10.5, and MELD score was 7.0 in group A versus 9.8 and 7.0, respectively, in group B (p = 0.943; p = 1.000). The median follow-up was 22 (12–35) and 7 (6–9) months in groups A and B, respectively. The 1-year cumulative rate of overt HE was comparable between the two groups (22.0% vs. 22.4%, Grays test, p = 0.537). 58.0% and 64.2% of patients had only one episode of overt HE in groups A and B. No statistically significant difference was found in the 1-year cumulative rate of transplant-free survival (80.6% vs. 90.0%, Grays test, p = 0.269).
Conclusion: Our data show that adding rifaximin to lactulose monoprophylaxis is not effective in the prevention of overt HE following TIPS.

WED-164

Cirrhotic patients with acute variceal bleeding and an indication for preemptive-TIPS: real-life results

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Background and aims: Acute variceal bleeding is a severe complication of portal hypertension in patients with cirrhosis. Patients who had a Child-Pugh C (<14 points) or child B >7 points with active bleeding at endoscopy were at high risk of treatment failure and mortality. Pre-emptive transjugular intrahepatic portosystemic shunt (pre-emptive TIPS) is indicated in these patients and widely recommended by guidelines. However, the actual implementation of pre-emptive TIPS varied significantly between different centers. The present study was designed to assess the application of pre-emptive TIPS in real clinical practice.
Method: This was a retrospective cohort study. From December 2019 to November 2022, cirrhotic patients with acute variceal bleeding admitted to West China Hospital who met the indication of pre-emptive TIPS were included. Those treated with TIPS were included in group A, and the remaining patients were included in group B. The primary outcomes were 5-day treatment failure and 6-week mortality.
Results: A total of 709 patients with cirrhosis and acute variceal bleeding were admitted to our hospital, among whom 126 patients (17.77%) met the criteria of high-risk. Twelve patients were child B >7 points with endoscopic active bleeding, and 114 patients were child C (<14 points). TIPS was performed in only 37 patients (29.37%). TIPS was not carried out due to refusal by the patient or the relatives (n = 42), hepatic encephalopathy (HE) (n = 6) and poor liver function (n = 10), hemodynamic instability (n = 2), prior TIPS (n = 2), hepocellular carcinoma (HCC) (n = 22) and balloon-occluded retrograde transvenous obliteration therapy (n = 5). Patients' characteristics such as age, sex ratio, etiology, ascites, and the proportion of patients with HE, ascites, and portal vein thrombosis were similar in the two groups. Chronic viral infection was the main cause of cirrhosis, accounting for 65.87% of all patients. Child-Pugh class varied significantly between these two groups, with the proportion of child B patients being 21.62% in group A and 7.87% in group B (P = 0.03), but there was no significant difference in Child-Pugh scores between the two groups (P = 0.19). The proportion of patients with HCC is higher in group B (18.92% vs 41.57%, P = 0.02). The 5-day treatment failure were 24.32% in group A and 21.35% in group B (P = 0.82), and 6-week mortality were 10.81% and 33.71% in group A and B respectively (P = 0.00). Multivariate analysis was performed in 104 non-HCC patients, which found that TIPS (OR = 0.08, 95% CI: 0.01–0.86, P = 0.04), viral cirrhosis (OR = 8.72, 95% CI: 1.36–55.80, P = 0.02) and the 5-day treatment failure rate (OR = 19.54, 95% CI: 2.30–165.97, P = 0.00) were related to 6-week mortality.
Conclusion: The proportion of patients with high risk of treatment failure and mortality who received pre-emptive-TIPS was relatively low in our cohort and TIPS can improve short-term survival in non-HCC patients.

WED-165

Baveno VII algorithm was able to stratify the risk of portal hypertension-related events in patients with HBV-related cirrhosis

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Background and aims: Baveno VII algorithm has been proposed and validated for avoiding endoscopy screening in cirrhosis patients, however, its prognostic value lacks prospective validation.
Method: HBV-related compensated cirrhosis were prospectively enrolled from April 2019 to April 2022 and followed until July 2023. All patients underwent liver stiffness measurement (LSM), spleen stiffness measurement (SSM) and esophagogastroduodenoscopy (EGD) screening for esophageal varices (EV) and some were reassessed during follow-up.
Results: Overall 1253 patients were enrolled with a median follow-up of 29 months (IQR 20–42). One experienced decompensation from 667 patients identified as low-risk by the Baveno VII algorithm, compared to 31 cases among 586 high-risk patients (0.6 vs. 20.8 per 1,000 person-years, p = 0.0004). The Baveno VII algorithm identified more patients (53.2%) into low-risk for decompensation than Baveno VII single cutoff model (47.2%, p = 0.003) and than Baveno VI criteria (33.8%, p < 0.0001) did. Patients with high-risk varices diagnosed via endoscopy following Baveno VII algorithm assessment had greater probability of decompensation compared to those identified by the Baveno VII single cutoff model (43.2 vs. 21.3 per 1,000 person-years, p = 0.0093). Additionally, among the 499 patients who underwent endoscopic re-assessment, 242 consecutively identified as low-risk had much lower incidence of EV progression (2.6 vs. 106.3 per 1,000 person-years, p = 0.0003) and lower risk of decompensation compared to 144 consecutively identified as high-risk by the Baveno VII algorithm (0 vs. 33.5 per 1,000 person-years, p = 0.0266).
Conclusion: Baveno VII algorithm could identify HBV-related cirrhosis patients at low risk of decompensation, which was greatly improved upon Baveno VII algorithm reassessment.

WED-166

Prophylactic antibiotics cannot prevent infection in patients undergoing trans jugular intrahepatic portosystemic shunt or plug assisted retrograde transvenous obliteration electively for portal hypertension complications- a double-blind pilot randomized controlled trial

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Background and aims: Trans jugular (Direct) intrahepatic portosystemic shunt (T(D)IPSS) and Plug assisted retrograde transvenous obliteration (PARTO) are widely utilized interventional procedures to manage the complications of portal hypertension. The role of prophylactic intravenous antibiotics in patients undergoing these procedures electively is unclear, which we aimed to assess.
Method: In this double-blind, placebo-controlled, pilot randomized controlled trial, we included consecutive patients with portal hypertension undergoing T(D)IPSS or PARTO electively from 21/02/2024 to 15/11/2024. Patients were randomized to receive the drug (ceftriaxone 1 g twice daily till discharge) or placebo in a 1:1 ratio. The objectives were to assess the incidence of clinically significant infection (defined as fever >38C and quick SOFA $\geq$ 2) during the hospital stay, the duration of the hospital stay, in-hospital mortality, and adverse events related to the drug.
Results: Seventy patients (age 49.7 ± 15 years: women 32.9%; cirrhosis 85.7%; Among cirrhosis, Child Pugh class B 70% and MELD Sodium 12.4 ± 3.3) were included. 63% underwent PARTO, and 37% underwent T(D)IPSS, which were equally distributed between the two groups. The most common indication for PARTO was fundal varices and/or hepatic encephalopathy and the most common indication for T(D)IPSS was hepatic venous outflow tract obstruction. A total of 13% (9/70; 95% CI, 6–23) developed infection in hospital. The incidence was 11.4% (4/35; 95%CI, 3.2–26.7) in the antibiotic arm and 14.3% (5/35; 95% CI, 4.8–30.2) in the placebo arm (p = 0.72) in the hospital. However, only one patient in each group had a culture-positive infection with Gram-negative bacteria and one died in the hospital in the antibiotic group due to pneumonia. The duration of hospital stay was similar in both groups (Antibiotic: 4 ± 2.2 days vs. Placebo: 4.4 ±

1.7 days; p = 0.47). One patient in the placebo group complained of itching, while none in the drug arm had adverse events.
Conclusion: Prophylactic antibiotics cannot prevent infection in patients undergoing T(D)IPSS/PARTO electively for complications of portal hypertension.

WED-167
The efficacy of HCP407 in reducing dysphagia and chest pain following esophageal variceal ligation in patients with cirrhosis. Preliminary results of a prospective randomized study
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Background and aims: Endoscopic band ligation (EBL) is the preferred endoscopic treatment for esophageal varices (EV), owing to its effectiveness and safety profile. However, it often results in adverse effects such as dysphagia and chest discomfort. An over-the-counter medication containing hyaluronic acid, chondroitin sulfate, and poloxamer 407 (HCP407/ Esoxx One®), commonly used for treating gastroesophageal reflux, may offer therapeutic benefits in this context. This study aims to evaluate the efficacy of HCP407 in alleviating dysphagia and chest discomfort associated with EBL and to assess its effect on the healing of post-EBL ulcerations.
Method: All patients undergoing EBL at Hospital Clinic of Barcelona from October 2021 to May 2024 were prospectively included in this study. Participants were randomized into two groups: one group received HCP407 treatment following EBL, while the control group did not receive any treatment. Dysphagia was assessed using the validated Brief Esophageal Dysphagia Questionnaire (BEDQ) questionnaire on days 3 and 7 post-procedure. Baseline and follow-up endoscopies (conducted at 3–4 weeks) provided additional clinical data for analysis.
Results: Of the 31 patients initially enrolled and randomized, 29 completed the study and were analyzed. Most participants were male (82.8%), with a mean age of 63.3 years, and alcohol-related cirrhosis as the primary cause of EV. The HCP407-treated group reported lower dysphagia scores (mean BEDQ total score) on both day 3 (5 vs. 10.46 points) and day 7 (0.75 vs. 2.23 points) compared to the control group; however, these differences were not statistically significant. No significant differences were observed in the resolution rate of post-EBL ulcerations between groups.
Conclusion: Post-EBL treatment with HCP407 reduces the incidence and severity of dysphagia and chest discomfort, potentially benefiting patient comfort. However, a larger sample size is necessary to determine statistically significant effects.

WED-170
Descriptive study of the impact of using non-cardioselective beta-blockers in cirrhotic patients after a first episode of ascites
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Background and aims: Non-selective beta-blockers (NSBB) are the only non-etiological treatment with a proven positive impact on advanced chronic liver disease (ACLD). They are indicated in compensated ACLD with clinically significant portal hypertension and in decompensated ACLD with esophagogastric varices. However, their role in decompensated ACLD with ascites but no varices remains unclear. This study aimed to compare the progression of patients with ACLD treated or not treated with NSBB after a first ascitic episode.
Method: This retrospective single-center study included ACLD patients admitted to the General Hospital of Valencia for a first ascitic decompensation (2013–2023). Patients already on NSBB or with prior decompensation were excluded. Demographics, clinical progression, and mortality were compared between NSBB and non-NSBB groups using Chi-square, Mann-Whitney U, or Student's *t*-test. $P < 0.05$ was considered significant.
Results: We analyzed 92 patients (mean age 59.2 ± 9.9 years; 86% male). Predominant etiologies were alcohol-related liver disease (75%) and hepatitis C (16%). After the first ascitic episode, 54.9% did not initiate NSBB, while 45.1% did (56% propranolol, 44% carvedilol). No differences were found between groups in age, sex, ACLD etiology, or Child-Pugh/MELD scores. During follow-up, the non-NSBB group showed a higher probability of new hepatic decompensation (75% vs. 63%, $p = 0.25$), which occurred earlier (9.0 ± 10.7 vs. 13.2 ± 19.1 months, $p = 0.3$). They also experienced more recurrent events (67% vs. 49%, $p = 0.08$) and hospitalizations (2.3 ± 2.3 vs. 1.6 ± 1.8, $p = 0.14$). More patients in this group required therapeutic paracentesis (33% vs. 15%, $p = 0.039$). Mortality rates after the first ascitic event were similar (57% vs. 51%, $p = 0.66$), but death occurred earlier in the non-NSBB group (22.5 ± 23.2 vs. 37.7 ± 31.6 months, $p = 0.046$).
Conclusion: After a first ascitic decompensation, patients treated with NSBB had fewer hepatic decompensations, a reduced need for therapeutic paracentesis, and longer survival. NSBB may benefit patients following their first ascitic episode, regardless of varices.

WED-171
Safety of seladelpar in primary biliary cholangitis patients with cirrhosis and clinical signs of portal hypertension: data from the ENHANCE and RESPONSE studies
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Background and aims: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, cholestatic liver disease that can cause cirrhosis and portal hypertension (PHT). Seladelpar is a first-in-class delpar (selective PPAR-delta agonist) approved for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients (pts) unable to tolerate UDCA. In two Phase 3, placebo-controlled studies (ENHANCE [NCT03602560] and RESPONSE [NCT04620733]), seladelpar significantly reduced cholestatic markers of disease and pruritus with a safety profile similar to placebo (primary analyses at month 3 in ENHANCE and month 12 in RESPONSE). Here, we present pooled safety data from these studies in a subgroup of patients with cirrhosis and clinical signs of PHT.
Method: Pts with PBC who received UDCA for ≥ 12 months or were UDCA intolerant with alkaline phosphatase (ALP) ≥ 1.67 × upper limit of normal (ULN) and total bilirubin (TB) ≤ 2 × ULN were randomised 1:1:1 to daily placebo, seladelpar 5 mg, or seladelpar 10 mg for up to 52 weeks in ENHANCE and 2:1 to daily seladelpar 10 mg or placebo for 52 weeks in RESPONSE. Cirrhosis was defined by medical history, liver biopsy, transient elastography, laboratory findings, radiological features, or clinical determination by the investigator. Pts with cirrhosis were identified as having signs of PHT at baseline (BL) if they had thrombocytopenia (platelet count < 140×10^3/μL), low albumin, elevated TB, or medical history of varices or ascites. Data are reported for the seladelpar (5 mg and 10 mg) and placebo groups.
Results: Among 56 pts with a diagnosis of cirrhosis at BL across the two studies, 27 had signs of PHT at BL (21 pts on seladelpar [15/21 on

10 mg] and 6 placebo). The majority of pts were female (85%) and White (89%), with a mean (range) age of 55.6 (33–74) years, and BL mean ALP and TB levels of 319.9 U/L and 1.2 mg/dL. Mean (SD) liver stiffness was 17.4 (3.5) kPa with placebo and 21.0 (11.8) kPa with seladelpar. In total, 5/6 (83%) pts on placebo and 15/21 (71%) pts on seladelpar experienced an adverse event (AE); 2/6 (33%) pts on placebo and 1/21 (5%) pts on seladelpar discontinued treatment due to AEs. Serious AEs occurred in 1/6 (17%) pts on placebo and 1/21 (5%) pts on seladelpar and deemed unrelated to study drug. Liver-related AEs by a predefined search strategy were similar across pts on placebo (2/6, 33%) or seladelpar (3/21, 14%) and included hepatomegaly, ascites, hyperbilirubinaemia, and portal hypertensive gastropathy. Liver-related laboratory abnormalities by predefined categories occurred in 2/6 (33%) placebo-treated pts and 1/21 (5%) seladelpar-treated pts.

Conclusion: In this pooled analysis of pts with PBC and cirrhosis with clinical signs of PHT from the ENHANCE and RESPONSE studies, safety outcomes were overall similar between seladelpar and placebo, with no new safety signals.

WED-172

Outcomes following transjugular intrahepatic portosystemic shunt in patients with hepatorenal syndrome and acute-on-chronic liver failure

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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) has a proven role in the management of variceal bleeding and refractory ascites. However, the role of TIPS in special populations, i.e., patients with hepatorenal syndrome-acute kidney injury (HRS-AKI), acute-on-chronic liver failure (ACLF), and chronic kidney disease (CKD) is less known, which we aimed to assess.

Method: In this retrospective multicenter study from India and Singapore, we included patients who had undergone TIPS. We aimed to assess the transplant-free survival (TFS) of patients with HRS-AKI, ACLF, splenoportal (SP) axis thrombosis and CKD following TIPS. ACLF was defined as per APASL criteria.

Results: Two hundred and seven patients who underwent TIPS for various indications were included. Approximately 36.4% (71/195) had a history of HRS-AKI in the previous three months and had received vasoconstrictor with albumin for treatment. Patients with HRS-AKI had lower platelets (101.31 ± 57.7 vs. 129.5 ± 84.2; P = 0.01), indicating a greater degree of portal hypertension. Similarly, the portal pressure gradient was higher in HRS-AKI patients (25.35 ± 7.4 in HRS group vs 21.6 ± 6.3 mmHg in non-HRS group; P = 0.008). Most common indication was refractory ascites/hydrothorax (67%) in HRS-AKI group, while bleed (41.1%) was common indication in non-HRS group. On Kaplan Meier analysis, TFS was 52.1% (37/71; 95%CI, 40–64.1) in HRS group compared to 73.4% (91/124; 95%CI, 64.7–81) in non-HRS group (P < 0.001). Of the twelve patients with ACLF pre-TIPS, TFS was only 33.3% compared to 67.2% in those without ACLF (P < 0.001). Thirteen percent (27/207) of patients had SP axis thrombosis and seven percent (15/207) had CKD. TFS was similar among those with SP axis thrombosis (66.7%) and those without (65%). TFS was comparable among patients with CKD (53.3%) and those without CKD (66.1%; P = 0.31). However, the incidence of HE was 67% in CKD group compared to 34.4% in non-CKD group (P = 0.01).

Conclusion: TIPS may not be optimal therapy in improving survival in those with antecedent HRS-AKI or concomitant ACLF.

WED-173

Machine and deep learning for non-invasive detection of esophageal varices in hepatocellular carcinoma patients

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Background and aims: Portal hypertension (PH) screening in advanced hepatocellular carcinoma (HCC) remains challenging. As current Baveno criteria lack sensitivity, endoscopy is required to detect esophageal varices (EV) to determine need for variceal bleeding prophylaxis. We aim to develop and validate a non-invasive classifier for EV status in HCC patients to avoid systematic endoscopy, utilizing deep learning (DL-imaging model) on contrast-enhanced CT scans (CECT) alongside clinical-biological data and imaging findings at baseline (baseline model).

Method: Data from 223 HCC patients eligible for Atezolizumab-Bevacizumab (AtezoBev) from three French hospitals with arterial phase CECT and no prior liver transplant were collected. Endoscopy for EV assessment was conducted within six months before starting AtezoBev. Patients were divided into training (AVC, PSL) and validation (SAT) cohorts. Abdominal axial CT features were extracted for DL-imaging model training and validation for EV classification. For the baseline model, a logistic regression model with LASSO-selected signature was trained and validated. Model performance was assessed by area under the receiver operator curve (AUROC).

Results: Median patient age was 65.6 years (84% male). Cirrhosis was present in 83.8% of patients, 49% had viral infection, alcohol consumption was present in 46% and metabolic syndrome in 37% (74% had mixed cause of liver disease). 74% were Child-Pugh A (MELD 8, 14% ALBI score 3). Median platelet count was 164,000/mm^3, total bilirubin was 14.0 uM/dL, INR was 1.14, albumin was 35.0 g/dL and creatinine was 72.0 uM. 53% had EV and 21% had history of ascites. Collaterals at imaging were present in 55%. HCC was multinodular in 77% of cases, with median size of 60 mm for largest lesion, 38% had infiltrating HCC and 41% vascular invasion, 60.5% were BCLC-C and 50% were treatment-naive for HCC. The DL-imaging model was able to classify EV status with AUROCs (median [95% confidence interval]) of 0.76 [0.57–0.91] in validation. For the baseline model, the signature was composed of 6 features: platelet count with log-odds ratio (LOR) of −0.22, total bilirubin (LOR: 0.40), presence of collaterals (LOR: 2.74), albumin (LOR: −0.19) and creatinine levels (LOR: −0.29) and INR (LOR: 0.09), showing an AUROC of 0.95 [0.84–1.00] in validation.

Conclusion: The baseline model classified EV status with very good performance, outperforming the DL-imaging model. High

importance for collateral vessel presence on CECT-scan was observed in the baseline model, suggesting that patients with collaterals may benefit from AVB prophylaxis with beta-blockers, potentially eliminating the need for endoscopy.

WED-174

Utility of spleen elastography in predicting transjugular intrahepatic porto-systemic shunt dysfunction in patients with liver cirrhosis

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Background and aims: Transjugular Intrahepatic porto-systemic shunt (TIPS) dysfunction (defined as portocaval pressure gradient (PPG) > 12 mmHg) is a situation that can be associated with the recurrence of serious complications of portal hypertension (PHrC). The gold standard for its diagnosis is PPG measurement through TIPS catheterization. Doppler ultrasound (US) used as a screening test has a sensitivity of 90% but specificity of 45%, resulting in a significant number of normally functioning TIPS revisions. The aim of the study was to evaluate whether spleen stiffness measurement (SSM) by transient elastography, alone or in addition to US, is effective in detecting TIPS dysfunction.

Method: we retrospectively reviewed a prospective cohort of patients with liver cirrhosis treated with TIPS that underwent a routine/elective TIPS revision and SSM one month after TIPS, between 2019 and 2024. Patients with portal vein and/or TIPS thrombosis were excluded. US criteria considered indicative of TIPS dysfunction were the presence of echographic ascites, a mean of maximum portal flows velocities <28 cm/s together with hepatofugal flow at the intrahepatic portal vein branches or <39 cm/s if the flow at the intrahepatic portal vein branches was hepatopetal flow.

Results: 57 patients were included, 44 (75.9%) of them were men with a median age of 57.5 (49–66) years. At monthly catheterization, 12 (21%) patients had TIPS dysfunction and 45 (79%) did not. The mean SSM in patients with dysfunction was significantly higher than in patients without dysfunction (51 ± 14 Kpa vs 36 ± 10 KPa; p < 0.000). SSM has an AUROC of 0.805 to identify TIPS dysfunction. The most sensitive (sensitive 100%) cut-off point was 30 Kpa, although the specificity was low (36%). Thus, applying this value, 41 patients would have undergone TIPS revision but only 12 of them were dysfunctional. Of the entire cohort of 57 patients, 50 had screening US and 22 of them (38.6%) had US criteria suggesting TIPS dysfunction, which was only confirmed in 7 (all of them with an SSM >30 Kpa). The strategy of applying SSM to the 22 patients with US suggesting dysfunction and only reviewing those with SSM>30 Kpa (n = 15) would avoid unnecessary TIPS revision (reduction by 32% in the number of hemodynamic revisions; from 22 to 15 patients). We evaluated an additional group of 8 patients submitted to a TIPS revision due to a follow-up US suggesting TIPS dysfunction: 3 were dysfunctional and all of them had SSM > 30 KPa. Again, using SSM after US-Doppler would reduce from 8 to 4 patients (by 50%) the numer of TIPS revision for suspicion of TIPS dysfunction.

Conclusion: SSM alone appears to be less predictive of TIPS dysfunction than US-Doppler. However, the evaluation of SSM in the subgroup of patients in whom US suggests dysfunction allows avoiding unnecessary TIPS revisions (around 30–50% of patients), in patients with SSM < 30 KPa. These preliminary data must be confirmed in larger series of patients.

WED-175

Anemia following portal hypertension-related bleeding in liver cirrhosis: incidence and impact on prognosis

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Background and aims: Approximately 50% of patients with liver cirrhosis have anemia, usually multifactorial and its presence is associated with worse prognosis. Restrictive transfusion policies in the context of upper gastrointestinal bleeding (UGIB) could aggravate this anemia or determine its appearance if not previously present. The objective of the study was to evaluate the incidence of anemia at discharge after UGIB due to portal hypertension (PHT) in patients with cirrhosis and its impact on prognosis.
Method: Retrospective multicenter observational study of a prospective cohort of cirrhotic patients hospitalized for UGIB-PHT between 2017 and 2019. Patients were followed up to 1-year, death or liver transplant (LT) whatever occurred first.
Results: 844 episodes of UGIB-PHT were registered in 14 referral centers. 377 patients were excluded for different reasons (116 death during episode; 62 receiving TIPS, among other reasons) and finally 467 patients were included. 353 (75.6%) were men with a median age of 60 (IQR:52–69) years. The most frequent etiology was related to alcohol (42%). 62% of patients received red blood cell (RBC) transfusion during admission, with a median of 3 (2–5) units. At discharge, Child-Pugh score and MELDNa scores were 7 (6–8) and 13 (10–17) points. The median Hb at discharge was 9 (8.4–9.7) g/dl. 73 patients (15.6%) had Hb ≤ 12 g/dL (mild anemia); 310 (66.4%) Hb ≤ 10 (moderate) and 67 (14.8%) Hb ≤ 8(severe). In 373 patients (80%) an Hb value within the 6 previous months was available and 23% had moderate/severe anemia. At discharge, 81.2% of these patients had moderate/severe anemia. 259/467 (55.4%) patients received intravenous/oral iron during admission or at discharge (40% of those having mild anemia, 59% moderate and 60% severe). At 1 year, 69 (15%) patients died, 34 (7%) underwent LT, and 210 (44.9%) suffered PHC. The probability of LT-free survival without PHC was 85.6%, 72.6%, and 43.6% at 1, 3, and 12 months, and was associated at univariate analysis with male sex, older age, higher Child and MELDNa, lower Hb at discharge, and non being treated with iron. At multivariate analysis, male sex, higher MELDNa, and lower Hb at discharge were independently associated with this event. When analyzing those patients with moderate/severe anemia (Hb<10 g/dl), MELDNa and no receiving iron were independently associated with LT-free survival without PHC. Higher MELDNa and no receiving iron treatment were also independent predictive factors when survival without LT was considered (96.9%, 93.2%, and 67.5% at 1, 3, and 12 months).
Conclusion: Current transfusion-restrictive policies are associated with a high incidence of moderate/severe anemia at discharge of a UGIB-PHT, which is linked to a poor prognosis. Iron administration improves prognosis, but a high percentage of patients do not receive this treatment.

WED-176

Role of splenic stiffness in predicting outcomes in decompensated cirrhosis: an ambispective cohort study

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Background and aims: Liver and splenic stiffness have emerged as promising non-invasive markers of portal hypertension. Studies have observed the utility of splenic stiffness in predicting high risk esophageal varices and decompensation in patients with compensated cirrhosis, but there is lack of data on its utility in predicting further decompensation and outcomes in more advanced stages of cirrhosis with pre-existing decompensation. This study evaluates the role of splenic stiffness measurement (SSM) in predicting outcomes in decompensated cirrhosis and compares its performance to liver stiffness measurement (LSM).
Method: This single center ambispective cohort study included consecutive adult patients with decompensated cirrhosis attending the liver clinic of a tertiary care hospital in India, whose liver and splenic stiffness values had been measured. Patients with valid measurements were included, while those with hepatic vein outflow tract obstruction, grade III ascites, or unreliable readings were excluded. Patients were followed up for further decompensation [new onset or refractory ascites, variceal bleed, hepatic encephalopathy, or acute-on-chronic liver failure (ACLF)]. Statistical analysis was done using Cox proportional regression analysis.
Results: Two hundred and fourteen patients were included: median age 46 years (IQR: 38–52) with 172 (80.37%) being male. The underlying etiology of cirrhosis was alcohol-related (83, 38.8%), chronic HBV (49, 22.9%), MASLD (24, 11.21%), chronic HCV (19, 8.9%), autoimmune hepatitis (20, 9.35%) and cryptogenic in the remaining patients. The most common pre-existing decompensation was ascites (90.1%) followed by variceal bleed (55.5%) and hepatic encephalopathy (25.3%). Baseline LSM and SSM values were 40.9 kPa (IQR: 22.7–63) and 58.1 kPa (IQR: 44.7–79.8), respectively. Further decompensation occurred on 41 (19.2%) patients over a follow up of 6 (3–16) months. The most common decompensation events were hepatic encephalopathy in 22 (10.3%) patients, ascites in 15 (7%), variceal hemorrhage in 9 (4.2%), and ACLF in 8 (3.7%) patients. Baseline Child-Turcotte-Pugh (CTP) score (HR 1.37, p 0.03), but not baseline SSM (HR 1.25, p 0.5), LSM (HR 1.01, p 0.06), change in SSM (HR 0.99, p 0.7), or SSM/LSM ratio (HR 0.88, p 0.2) was a significant predictor of further decompensation in survival analysis.
Conclusion: Splenic stiffness measurement does not predict further decompensation in decompensated cirrhosis.

WED-177-YI

Cirrhotic cardiomyopathy in patients underwent transjugular intrahepatic portosystemic shunt (TIPS): clinical impact of the updated diagnostic criteria for diastolic dysfunction

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Background and aims: Cirrhotic cardiomyopathy (CCM) is a clinical syndrome characterized by functional and structural cardiac abnormalities in patients with cirrhosis, manly defined by the impaired ventricular relaxation (diastolic dysfunction - DD) in the absence of known cardiac disease. It is largely subclinical until significant haemodynamic stress, such as transjugular intrahepatic portosystemic shunt (TIPS), occurs. CCM criteria were recently refined and consisted of echocardiographic parameters. However, the clinical significance of these new criteria of DD in cirrhotic patients underwent TIPS is poorly understood.
Method: We conducted a retrospective, monocentric study aimed at evaluating the impact of DD, using 2005 and 2019 criteria for CCM and the Toulouse algorithm, on post-TIPS outcomes defined as major cardiovascular events (MACE) and liver transplant (LT) - free survival at 6-month after TIPS.
Results: Overall, 200 patients were included in the study. Of those, 144 (72%) were male and the median age at TIPS was 59 years (IQR 53–65). Considering only patients (127/200) with DD certainly definable through the 2019 CCM criteria, the prevalence of DD was 26%. These patients were significantly older (63 vs 57 years; p < 0.001) and with higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (178 vs 90 pg/ml; p 0.04). With regards to 6-month outcomes after-TIPS, they did not show a higher rate of MACE (11% vs 3%; p = 0.29) nor of composite outcome LT and death (14% vs 18%; p = 0.55). We also observed that 2005 and 2019 DD criteria and Toulouse algorithm failed to predict MACE and LT – free survival at 6-month after TIPS. According to our results, only NT-proBNP value showed a significantly association with MACE (HR 1.07, CI 1.00–1.14, p 0.04) and severity of liver disease, defined by Model for End-Stage Liver Disease (MELD) and portal pressure gradient (PPG) pre-TIPS, was the only independent risk factor for mortality or LT (HR 1.32, CI 1.18–1.48, p < 0.001 and HR 1.12, CI 1.02–1.22, p 0.02, respectively).
Conclusion: Our findings suggest that while DD on echocardiography should not preclude the clinical benefits of TIPS, a comprehensive cardiac evaluation remains essential for patient selection. However, echocardiography parameters alone should not be used to predict cardiac decompensation or mortality risk after the procedure.

WED-178
Dynamics in hepatic venous pressure gradient (HVPG) during the course of recompensated alcohol-related cirrhosis

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Background and aims: Alcohol abstinence may lead to recompensation in decompensated alcohol-related cirrhosis. However, the proportion of patients resolving clinically significant portal hypertension (CSPH) during recompensation and the utility of non-invasive tests for CSPH in this setting are unclear.
Method: Patients with recompensated alcohol-related cirrhosis and same-day hepatic venous pressure gradient (HVPG), liver stiffness (LSM) and spleen size (on ultrasound) measurement at the Vienna General Hospital were analysed. Recompensation was defined as resolution of all decompensation-defining complications and improvement in hepatic function following abstinence (Baveno VII criteria).
Results: Among 26 patients with recompensated alcohol-related cirrhosis undergoing HVPG measurement after a median of 3.5 months after recompensation (all Child-Pugh A5; median MELD: 9.5), median HVPG was 11 mmHg (IQR: 8–16) and CSPH resolved in 11 patients (42%). LSM was reliable (IQR/median < 30%) in 23/26 patients (median 20.7 kPa), performing well for diagnosing CSPH as a standalone marker (AUROC 0.833) and within the ANTICIPATE model (AUROC 0.788). Baveno criteria (LSM ≥ 25 kPa) showed excellent diagnostic accuracy for ruling-in CSPH (PPV and specificity 100%; CSPH in n = 8/8). In contrast, rule-out criteria (LSM ≤ 15 kPa & platelets ≥ 150 G/L) were less accurate (NPV 60% and sensitivity 84%; CSPH in n = 2/5), due to the limited diagnostic utility of platelet count (AUROC 0.461), with thrombocytopenia in 7/11 patients (64%) with resolved CSPH. In contrast, the AUROC of von Willebrand factor (vWF) antigen for CSPH was excellent (0.794) and applying a cut-off of < 170% to rule-out CSPH yielded an NPV and sensitivity of 100% (CSPH in n = 0/6). Splenomegaly (≥ 13 cm) persisted in 3/11 patients (27%) with resolved CSPH vs. 9/15 (60%) with CSPH persistence (p = 0.130). A paired prior HVPG in a decompensated stage was available in 17 patients (median 37 months between measurements). Median decompensated HVPG was 19 mmHg (IQR: 16–20), with a relative decrease of 44% (IQR: 19–53) following recompensation (p < 0.001). Similarly, MELD decreased by a median of 36%, C-reactive protein by 58%, interleukin-6 by 56% and von Willebrand factor (vWF) by 39% (p < 0.05 for all), with no significant change in platelets (–7%; p = 0.932) or spleen size (–5%; p = 0.210). While HVPG decrease showed no correlation with the increase in platelets (Spearman's r: 0.23; p = 0.381), its correlations with decreases in spleen size (r: 0.75; p = 0.001), vWF (r: 0.58; p = 0.025) and MELD (r: 0.50; p = 0.042) were statistically significant.
Conclusion: CSPH resolves in a considerable proportion of patients with alcohol-related cirrhosis achieving recompensation following abstinence. While Baveno criteria with LSM ≥ 25 kPa accurately ruled in CSPH persistence, rule-out criteria were inaccurate and may be improved by incorporating vWF.

WED-179
CT-based imaging indices predict hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients

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Background and aims: The transjugular intrahepatic portosystemic shunt (TIPS) is a critical therapeutic intervention for patients with

decompensated cirrhosis. Despite its benefits, hepatic encephalopathy (HE) is a prevalent postoperative complication that significantly impairs patients' quality of life and prognosis. Current research on imaging-based prediction models for HE development following TIPS is limited. This study aimed to determine the incidence of HE in patients with decompensated cirrhosis within six months post-TIPS and to evaluate the predictive value of liver volume and the third lumbar vertebral level skeletal muscle area (SMA) for the development of HE six months after TIPS.

Method: We enrolled 126 patients with decompensated cirrhosis treated at the Third Central Hospital of Tianjin, China, from April 2020 to July 2023, who underwent TIPS and had an enhanced computed tomography (CT) scan. These patients were followed for six months post-TIPS. Patients were stratified into two groups based on the development of HE within six months post-TIPS: those who developed HE and those who did not. The volumes of the liver and the L3 SMA were delineated using 3D Slicer software.

Results: We included 95 cirrhotic patients who met the inclusion criteria. The mean age of the patients was 57.7 ± 10.6 years, with 56 males (59.0%). The causes of cirrhosis were viral in 31 patients (32.6%), alcohol-related in 26 patients (27.4%), and other etiologies in 38 patients (40.0%). The median volumes of the liver lobes were as follows: left lobe 449.46 cm^3 (IQR 349.97, 540.22), right lobe 509.74 cm^3 (IQR 416.63, 679.80), and caudal lobe 26.60 cm^3 (IQR 21.55, 36.98). The median total hepatic volume was 1,000.94 cm^3 (IQR 843.81, 1284.77), and the median L3 SMA was 207.72 cm^2 (IQR 170.34, 243.46). Within six months post-TIPS, hepatic encephalopathy developed in 11 patients (11.58%). The left lobe volume, L3 SMA, and Child-Pugh scores significantly differed between groups ($p < 0.05$). Multivariate logistic regression analyses identified the left lobe liver volume (OR = 0.991, 95% CI 0.983–0.998) and the L3 SMA (OR = 0.979, 95% CI 0.959–0.999) as independent predictors of hepatic encephalopathy occurrence in cirrhotic patients within six months post-TIPS. A predictive model for hepatic encephalopathy within six months post-TIPS was developed, with the following characteristics: AUC = 0.839, sensitivity = 0.909, specificity = 0.774, and cutoff value = 0.161.

Conclusion: The incidence of HE among patients with decompensated cirrhosis within six months post-TIPS was 11.58%. The CT-derived volume of the left liver lobe and the L3 SMA were identified as independent predictors for the development of HE in these patients within six months post-TIPS. Consequently, a predictive model for HE development was established. A model score exceeding 0.161 indicated a lower likelihood of HE development in cirrhotic patients within six months following TIPS.

WED-180

Rate of recurrent gastrointestinal bleeding and outcomes in patients undergoing balloon-occluded retrograde obliteration (BRTO) versus transjugular intrahepatic portosystemic shunt (TIPS) for gastric variceal bleeding

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Background and aims: Gastroesophageal varices are a complication of cirrhosis and are associated with significant morbidity and mortality[1]. There is published guidance on the management of esophageal varices (EV), however less is known regarding the treatment of gastric varices (GV). Options are institution dependent and include transjugular intrahepatic portosystemic shunts (TIPS) or balloon-occluded retrograde transvenous obliteration (BRTO)[2]. The aim of our study is to compare outcomes for patients with GV bleeding treated with BRTO versus TIPS.

Method: This is a single center retrospective study conducted at a suburban health network in Pennsylvania. Patients older than 18 years with a diagnosis of cirrhosis and history of GV bleeding treated with BRTO or TIPS were included. The study time period was 2015 through 2022, with 1 year follow-up. Primary endpoint was rate of recurrent gastrointestinal bleeding (GIB). Secondary endpoints were rate of complications related to portal hypertension, time to recurrence of GIB, and overall mortality and survival.

Results: A total of 67 patients (n = 22 BRTO, n = 45 TIPS) were included. The average age was 58, 70% were male, and 92% were white. The etiology of cirrhosis was alcohol related in 58%, followed by metabolic dysfunction-associated steatohepatitis in 25%. The majority were Child-Pugh class B (72%) with a median MELD of 15. Recurrent GIB occurred in 10 patients with an overall incidence of 15% and a median length time of 3.5 days. The incidence of recurrent GIB for patients who had BRTO (n = 4) and TIPS (n = 6) was 18% and 13% respectively, and was not statistically significant ($p = 0.72$). Time to recurrent GIB was not statistically significant ($p = 0.75$). EV were found in 41 patients pre-procedurally (n = 8 BRTO, n = 33 TIPS) and 18 patients post-procedurally (n = 8 BRTO, n = 10 TIPS). The incidence of hepatic encephalopathy (HE) increased from 18% to 56% and ascites decreased from 64% to 56%, and this difference was not statistically significant ($p = 0.13$ and $p = 0.66$). Overall incidence of mortality was 46%, with median time to death of 131 days. 50% of patients in the BRTO group experienced death compared to 44% in TIPS group, and this was not statistically significant ($p = 0.67$). The median survival time was 2315 days versus 1931 days in the TIPS versus BRTO groups, and this was not statistically significant ($p = 0.71$).

Conclusion: TIPS and BRTO are performed for GV bleeding, and our study found that outcomes between the two groups were similar. The incidence of recurrent GIB was ~15%, occurred within one week of the procedure, and did not differ significantly between the groups. While a main concern with BRTO is worsening portal hypertension, our study did not show an increase in EV or ascites. Our data did not show a statistically significant difference in survival and overall mortality. Findings suggest that both treatments have comparable outcomes; therefore, the decision on procedure remains dependent on multiple factors including the patient, facility, and the expertise available.

WED-181-YI

Role of spleen stiffness measurement by vibration-controlled transient elastography at 100 Hz in guiding invasive hemodynamic reassessments after underdilated TIPS

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Background and aims: Underdilated Transjugular Intrahepatic Portosystemic Shunt (udTIPS) effectively manages portal hypertension complications while minimizing shunt-related adverse events. Spleen Stiffness (SS) measured by vibration-controlled transient elastography has shown high accuracy in detecting clinically significant portal hypertension when compared to the gold standard hepato-venous pressure gradient. The aim of this study is to evaluate SS as a non-invasive tool for identifying patients with Porto-Caval Pressure Gradient (PCPG) <12 mmHg after udTIPS.

Method: We prospectively enrolled patients with cirrhosis undergoing udTIPS at our referral center (January 2023–September 2024). Both invasive PCPG assessment and SS measurement with the spleen-dedicated 100 Hz probe by FibroScan® were performed at three time-points: before TIPS, immediately post-TIPS, and one-month after the procedure.

Results: The study included 51 patients (mean age 62 ± 12 years, 63% male) with preserved liver function [median Child-Pugh score 7 (IQR

3), MELD-Na 13 (IQR 6)]. TIPS indications were secondary prophylaxis for variceal bleeding (65%) and refractory ascites (35%). Median udTIPS dilation diameter was 6 (IQR 1) mm. PCPG progressively decreased from 22 (IQR 7) pre-TIPS to 15 (IQR 4) immediately post-TIPS and 11 (IQR 5) mmHg at one-month. Correspondingly, SS decreased from 74.5 (IQR 5) to 55.5 (IQR 21) and 41.6 (IQR 19) kPa. All SS measurements strongly correlated with PCPG values ($\rho = 0.72$, $p < 0.0001$). SS demonstrated an excellent diagnostic discrimination for PCPG <12 mmHg [AUC = 0.90 (95% CI 0.84–0.96)]. The cut-off of <35 kPa accurately ruled in patients with post-TIPS PCPG <12 mmHg (97.8% specificity, 88.2% PPV, 21.3 positive likelihood ratio).
Conclusion: SS measured with the spleen-dedicated 100 Hz probe strongly correlates with PCPG over time and reliably identifies patients achieving PCPG <12 mmHg after udTIPS. If validated in larger cohorts, SS may become a non-invasive tool for tailoring invasive hemodynamic reassessments in post-TIPS monitoring protocols.

WED-182
Predicting post-TIPS hepatic encephalopathy risk in patients with cirrhosis and refractory ascites: a proof-of-concept study using a 4D MRI perfusional model
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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is a well-established treatment for refractory ascites (RA) in patients with cirrhosis. However, a major drawback is the development of post-procedural hepatic encephalopathy (HE), which results from the diversion of blood from the portal vein. According to the first-pass effect, this diversion reduces the liver's capacity to metabolize substances from the gut, leading to an accumulation of toxic compounds in the brain. Given that liver perfusion relies on arterial compensation (hepatic arterial buffer), it is plausible that effective compensation, which also depends on cardiac function, may reduce the risk of encephalopathy by detoxifying the blood during the second-pass metabolism. The aim of this study is to evaluate by Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI) the changes in liver perfusion induced by TIPS in patients with RA and their relationship with the risk of HE.
Method: Twenty-nine consecutive patients underwent DCE-MRI, cardiac and hepatic hemodynamic evaluation before and after TIPS. MRI images were processed by a homemade software using the Dual Input Dual Compartment (DIDC) model, focusing on perfusion parameters.
Results: The DIDC model showed that total hepatic perfusion decreased by 24% after TIPS (248 ml/min/100 ml vs 189 ml/min/100 ml, p 0.095). As expected, a significant reduction in portal perfusion (decreased by 67%; 128.6 ml/min/100 ml vs 42.4 ml/min/100 ml, p 0.004) and an increase in hepatic arterial fraction post-TIPS (48% vs 77%, p 0.001) was observed. Post-TIPS residual total hepatic perfusion inversely correlated with one-year HE risk: patients with perfusion ≤130 ml/min/100 ml had a HE risk of 67.6% vs 36.4% for those >130 ml/min/100 ml (HR: 2.1, p 0.039).
Conclusion: Perfusion MRI is able to elucidate the impact of TIPS on liver perfusion, quantifying the extent of hepatic perfusion and its correlation with the development of post-TIPS HE.

WED-183
Cardiopulmonary hemodynamics and liver stiffness changes in predicting cardiac decompensation after TIPS: a prospective study
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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) can induce significant cardiovascular distress in patients with cirrhosis. Despite its therapeutic benefits, post-TIPS cardiac decompensation (CD) remains a serious concern, with early predictive factors still incompletely characterized. The aim of this study is to identify reliable predictive factors of post-TIPS symptomatic CD (AHA stage C-D).
Method: We prospectively enrolled consecutive patients with cirrhosis undergoing TIPS between May 2022 and May 2024 at our tertiary referral center. Baseline clinical and biochemical parameters were recorded. Right-heart catheterization was performed at three time points: pre-TIPS, immediately post-TIPS, and one-month post-procedure. Liver stiffness measurement (LSM) by vibration-controlled transient elastography was performed at corresponding intervals.
Results: Among 53 patients treated with TIPS for secondary prophylaxis of variceal bleeding (59%) or refractory ascites (41%), with a median Child-Pugh score of 7 (IQR 3) and a MELD-Na score of 12 (IQR 6), CD developed in 20% of patients, with a median onset of 3.3 months (IQR 5.8). At univariable Cox regression analysis, factors associated with CD were advanced age (71 vs. 59 years; HR 1.10, p = 0.010), presence of post-capillary pulmonary hypertension (pcPH) at one-month (82% vs. 26%; HR 6.33, p = 0.018), and the evidence of increased LSM at one-month follow-up (73% vs. 19%; HR 6.42, p = 0.006). The median LSM increased by +22% in patients who developed CD, in contrast to a – 23% decrease observed in those who did not (p = 0.012).
Conclusion: Presence of pcPH and increase of LSM at one-month follow-up are strongly associated with the development of post-TIPS CD. This is the first demonstration that gold-standard diagnosis of pcPH few weeks after TIPS can predict evolution towards CD. Further studies are required to investigate the relationship between LSM changes and cardiac adaptation following TIPS.

WED-184
Assessment of impact of ascitic fluid polymorphonuclear count on development of spontaneous bacterial peritonitis and survival in patients with liver cirrhosis and ascites
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Background and aims: Spontaneous bacterial peritonitis (SBP) is defined by ascitic fluid polymorphonuclear (A-PMN) cells count higher than 250 cells/microliter in the absence of an intraabdominal source of infection or any other explanation for an elevated A-PMN count. The clinical implications of SBP in terms of morbidity and mortality, have been well established however, knowledge about clinical implications of non SBP cirrhotic patients defined by A-PMN counts less than 250 cells/ microliter is limited. Aim of this study was to determine the development of SBP and survival in non–SBP cirrhotic patients with high A-PMN counts and compare it with low A-PMN count patients.

Method: In this prospective observational study, liver cirrhotic patients with ascites were stratified into 3 categories based on ascitic fluid PMN counts: 1) SBP group (PMN ≥ 250 cells/ microliter, number = 25 patients), 2) Intermediate ascitic fluid PMN group (I-PMN) (PMN counts in between 60 and 249 cells/ microliter, number = 50 patients), 3) Low ascitic fluid PMN group (L-PMN) (PMN counts less than 60 cells/ microliter, number = 81 patients). All patients were followed periodically up to 6 months for development of SBP and mortality.
Results: All the demographic profile of patients including Child Turcotte Pugh (CTP) and model for end stage liver disease sodium (MELD sodium) scores were similar among all the three groups. Median baseline PMN counts (25–75% IQR) was 819 cells/microliter (385–1490), 91 cells/microliter (76 – 110) and 24 cells/microliter (18–34) ($p < 0.001$) in SBP, I-PMN and L-PMN groups respectively. During follow up ascites resolved or reduced to become grade 1 ascites in 44%, 61% and 74% respectively in SBP, I-PMN and L-PMN group. Interval ascitic fluid examination was done in 59 patients (SBP group – 16 patients, I-PMN – 18 patients, L-PMN – 25 patients) during follow up period of 6 months. Respective median (IQR) interval PMN count in SBP, I-PMN and L-PMN group was 260 (142–397) cells/ microliter, 147 (88–256) cells/ microliter and 72 (47–88) cells/ microliter ($p < 0.001$). 11 patients (44%) in SBP and 5 patients (10.5%) in I-PMN group developed SBP whereas none of the patients in L-PMN group developed SBP ($p < 0.001$). 6 (24%), 4 (8.7%) and 5 (5.9%) patients died during follow up in SBP, I-PMN and L-PMN group respectively. Death in SBP group was significantly higher than L-PMN group, but difference of death rate between SBP and I-PMN group did not reach up-to statistical difference ($p = 0.08$). Death rate in I-PMN group was similar to L-PMN group.
Conclusion: Patients of I-PMN group are associated with significantly higher rate of development of SBP and rehospitalisation at month 6 as compared to L-PMN group. Both groups have similar mortality.

WED-185
Exploring point-of-care ultrasound for diagnosis of spontaneous bacterial peritonitis in patients of decompensated cirrhosis - proof of concept study

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Background and aims: Ascitic fluid examination is required to diagnose spontaneous bacterial peritonitis (SBP) in patients of decompensated cirrhosis. Being an invasive procedure, it is not only associated with a risk of bleeding in patients who often have coagulopathy, but may also introduce infection due to repeated need for paracentesis. Inflammation and transmigration of bacteria associated with SBP may lead to changes in peritoneum, omentum, bowel wall thickness and vascularity which if detected using ultrasonography, may help to diagnose SBP. We conducted this study to evaluate the utility of Ultrasonography (POCUS) as a non-invasive, point-of-care modality to diagnose SBP in patients of decompensated cirrhosis.
Method: Patients with decompensated cirrhosis with ascites were included. At baseline, all patients underwent ascitic fluid examination to diagnose SBP, as well as POCUS to assess bowel wall thickness, stratification, vascularity, peristalsis, peri-colonic and mesenteric lymph nodes and fat stranding. Amount of ascites, grading, internal echoes, septations, peritoneal and omental thickening and vascularity were also noted. POCUS findings were compared between SBP and no SBP groups.
Results: A total of 69 patients, aged 48 ± 13.8 years were included in the study of which 63 (91%) were males. The most common aetiology of cirrhosis was alcohol in 38 (55%) followed by metabolic dysfunction associated steatotic liver disease (MASLD) in 12 (18%) patients. SBP diagnosed on ascitic fluid examination was present in 34 (49.3%) patients. The SBP and no SBP patients were comparable in terms of age, gender distribution and aetiology of cirrhosis. The caecal bowel wall thickness ($p < 0.05$) and small bowel thickness ($p < 0.05$) were significantly higher in SBP group as compared to no SBP group. On logistic regression analysis increased caecal wall thickness (> 3 mm) had 3.1 times higher odds of having SBP in comparison to the thickness < 3 mm. The difference in bowel wall thickness at ascending, transverse, descending and sigmoid colon was statistically non-significant in SBP and no SBP group. There was no evidence of bowel wall five-layer stratification loss in any of the patients in both the groups. Increase in bowel wall vascularity was observed in SBP group, however it did not reach statistical significance as compared to the no SBP group ($p > 0.05$). There was a significant difference in internal echoes and septations in SBP versus no SBP group ($p < 0.05$). Peritoneal thickening, omental thickening and vascularity were comparable in both the groups.
Conclusion: This study demonstrates that POCUS can serve as a valuable diagnostic tool for the detection of SBP in patients of decompensated cirrhosis particularly in settings where rapid clinical decision-making is critical.

WED-186
TIPS for hydropic decompensation improves short-term outcome: a case-control study

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Background and aims: Portal hypertension characterizes decompensated cirrhosis and may trigger acute-on-chronic liver failure (ACLF) which carries the highest mortality. Transjugular intrahepatic portosystemic shunt (TIPS) is the most efficient therapy for portal hypertension-related complications including hydropic decompensation (HD) defined as refractory or recidivant ascites, hepatorenal syndrome and/or hydrothorax. However, TIPS for HD in ACLF is questioned.
Method: In this case-control study, patients from the prospective cohorts CANONIC (n = 1324) and German TIPS-Registry (n = 724) were screened for cases of HD and matched 1:1 by gender, age, MELD-score and presence and grade of ACLF. The total population was 118 ACLF patients of whom 59 received TIPS and 59 did not. Clinical parameters, ACLF status and mortality were assessed.
Results: There were no significant differences between the two groups regarding general characteristics. The main indication for TIPS was hepatorenal syndrome (61.0%). ACLF patients who did not receive TIPS had a higher 28-day cumulative mortality rate (22.0% vs. 5.1%, $p = 0.009$). At 28 days TIPS insertion in ACLF associated with a 78% mortality reduction (HR 0.22 [0.06–0.77]). It further led to improvement of ascites, hepatic encephalopathy, MELD and CLIF-C OF scores. Additionally, ACLF resolution occurred in 61% of TIPS ACLF patients.

The presence of coagulation and circulatory organ failures as well as higher bilirubin, INR, MELD and CLIF-C OF were associated with 28-day mortality. The survival benefit of TIPS was no longer observed after 90 days.
Conclusion: TIPS decreased the 28-day mortality of patients with hydropic decompensation and ACLF. Nevertheless, the role of TIPS is a bridging strategy to liver transplantation rather than a definitive therapy.

WED-187
Shunt cross-sectional area is a better predictor of overt hepatic encephalopathy than minimal hepatic encephalopathy
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Background and aims: Predicting overt hepatic encephalopathy (OHE) is critical. Psychometric tests for minimal hepatic encephalopathy (MHE) do not significantly increase post-test OHE probability. Portal hypertension causes spontaneous portosystemic shunts (SPSS), influencing OHE risk. This study investigates the link between SPSS total cross-sectional area (TCA), MHE, and OHE risk, hypothesizing that larger shunts prevalent in MHE patients may identify those at increased risk for OHE.
Method: We enrolled cirrhosis patients for contrast-enhanced abdominal CT and psychometric testing to identify MHE using a portosystemic hepatic encephalopathy score (PHES ≤−4 = MHE). Two hepatologists measured SPSS TCA, with discrepancies resolved by a senior radiologist. A large TCA was defined as >83 cm². We followed patients for 297 days (range 13–758), monitoring hospital admissions for OHE.
Results: The study included 102 patients (age 63, 68% male, 65% Child-Pugh A, 30% on lactulose and/or rifaximin). MHE patients (n = 34) had a mean shunt diameter twice that of non-MHE (261 cm² vs. 108 cm², p = 0.02), with higher ammonia (47 vs. 36, p = 0.02) and CRP levels (17 vs. 5, p = 0.002). Large-TCA patients (n = 27) showed higher ammonia (53 mg/L vs 35 mg/L, p = 0.003), with 40% having MHE. Sixteen patients (15%) developed OHE: 69% had MHE, 93% had large TCA, 55% had both, and 56% were on lactulose/rifaximin. OHE was more frequent in patients with both MHE and large TCA compared to MHE with smaller/no shunts (55% vs. 11%, p < 0.0001), and 73% (8/11) of MHE + large TCA patients developed OHE while on lactulose and/or rifaximin. Regression analysis showed Child-Pugh class, MELD, MHE status, and shunt TCA as risk factors (OR 2.6, 2.1, 5.7, 3.5; p < 0.001). MHE and SPSS TCA remained significant in multivariate analysis (OR 6.2, 1.1; p < 0.01). AUROC values for shunt diameter, CP class, and PHES were 0.71, 0.70, and 0.55, respectively.
Conclusion: MHE correlates with larger SPSS, significantly increasing OHE risk despite anti-HE treatment. Nearly all patients developing OHE had large SPSS TCA. Systematic SPSS assessment may be crucial for OHE prevention, potentially more so than MHE screening. Further research in larger cohorts is warranted.

WED-191
De novo decompensation and portal vein thrombosis are both linked to similar pathophysiologic alterations associated with advanced liver disease
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Background and aims: Portal vein thrombosis (PVT) and decompensation are major complications in chronic liver disease (CLD) but their temporal and pathophysiologic relationships remain poorly understood. We aimed to determine the sequence of these events and characterize their underlying pathophysiological patterns and to explore the overlap in the underlying mechanisms in a prospective cohort of patients with compensated advanced chronic liver disease (cACLD).
Method: From 2011 to 2021, we prospectively enrolled 545 patients with cACLD without HCC. At enrollment, these patients underwent upper gastrointestinal endoscopy, liver ultrasonography and elastography, hepatic venous pressure gradient measurement, and a series of laboratory tests, including 28 serum biomarkers related to inflammation, immunity, hypoxia, coagulation, and angiogenesis using the Ella ELISA method (Bio-Techne).
Results: At baseline, 45 patients (8.3%) had portal vein thrombosis (PVT) and 141 patients had experienced decompensation in the past despite being compensated at enrollment. Therefore, they were excluded from the prospective PVT and decompensation analysis. Over a median follow-up of 7 years, 58 patients (11.6%) developed PVT, corresponding to a yearly incidence of 1.16% and 131 (32.4%) developed decompensation, with a yearly incidence of 3.25%. Decompensation and PVT occurred concurrently in 7 of 131 cases (5.3%). In 12 cases (9.1%), PVT preceded decompensation, whereas in 16 cases (12.2%), PVT occurred afterward. In 98 cases (73.2%), decompensation was not associated with PVT. Median MELD was significantly higher in patients who developed decompensation with/without PVT than in 10 patients who developed PVT without decompensation. Baseline biomarkers associated with angiogenesis, inflammation, coagulation, and hypoxia were similarly and greatly altered in cases of newly developed decompensation, whether occurring alone or alongside PVT. However, inflammatory biomarkers were significantly more elevated in patients who experienced decompensation without PVT. In contrast, biomarkers in cases of isolated PVT primarily indicated endothelial alterations.
Conclusion: De novo decompensation and PVT both reflect similar pathophysiologic changes associated with advanced liver disease. They are linked to the extensive remodeling of liver tissue, representing two facets of the same underlying phenomenon. (supported by AIRC IG 2020-ID. 24858 project-P.I. Villa Erica).

WED-192
Real-world outcomes and treatment response to terlipressin in patients with hepatorenal syndrome - acute kidney injury: a multicenter study from the German cirrhosis/Terli-CKD study group
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Background and aims: Real-world data on patients with the acute form of hepatorenal syndrome (HRS-AKI) are currently lacking, particularly taking into account the new diagnostic criteria (Acute Disease Quality Initiative (ADQI)-International Club of Ascites (ICA)). This multicenter, retrospective study aimed to evaluate treatment strategies and outcomes in patients with HRS-AKI.
Method: This study analyzed 490 patients with HRS-AKI treated with albumin/terlipressin at 12 tertiary care centers in Germany (2018–2022). The primary endpoint was a complete response to terlipressin treatment (ICA criteria). Baseline and follow-up data on HRS-AKI diagnosis, treatment initiation, duration, and response, as well as mortality, liver transplantation (LTX), and the need for renal replacement therapy were collected.
Results: The median age was 59 years and 62% of patients were male with a predominant etiology of alcohol-related liver disease (63%). Median duration of albumin therapy was 48 hours (IQR 0, 96) with a median albumin dose of 40 g/day (IQR 0, 100). Interestingly, terlipressin treatment was already initiated after 24 hours, instead of 48 hours in 194 (40%) patients. AKI-stages at time of treatment initiation with terlipressin were: AKI 1A 11%, AKI 1B 21%, AKI 2 31%, AKI 3 37% with a median serum creatinine (SCr) of 2.3 mg/dl, respectively. Overall, the mean initial dose of terlipressin was 2.6 mg/day, administered via continuous infusion in 85% of patients and was increased in 45% of patients to a maximum dose of 3.65 mg/day. 42% of patients showed complete response after a median of 11 days (IQR 9, 13). Partial and no response were achieved in 25% and 33% of patients, respectively. Interestingly, there was no difference in response rates when terlipressin was initiated after 24 hours compared to 48 hours (complete response: 41.8% vs. 42.5% ($p = 0.923$), partial response: 23% vs. 28% ($p = 0.280$), no response: 35% vs. 30% ($p = 0.263$)). Importantly, patients with AKI stage 3 had lower rates of treatment response (28.4% vs. 65.4% for AKI stage 1A, 47.6% for AKI stage 1B, and 46.7% for AKI stage 2, $p < 0.001$) but similar 12-month LTX-free survival ($p = 0.157$). Patients without treatment response to terlipressin, independent of AKI stage, had significantly lower 12-months LTX-free survival compared to patients with partial or complete response. In multivariable regression analysis, complete response to terlipressin therapy (HR 0.61 [0.48–0.77], $p < 0.001$), female sex (HR 0.74 [0.58–0.94], $p = 0.013$) and alcohol-related etiology (HR 0.70 [0.53–0.84], $p < 0.001$) were independently associated with better LTX-free survival.
Conclusion: Approximately two-thirds of patients with HRS-AKI responded to terlipressin in this real-world cohort, which is higher than in published clinical trials. However, the prognosis remains poor, especially in patients without any response to terlipressin at all.

WED-193

Resolution of portal hypertension by transjugular intrahepatic portosystemic shunt (TIPS) implantation reverses markers of gut-barrier dysfunction, systemic inflammation and anti-inflammatory monocyte alterations in patients with decompensated liver cirrhosis

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Background and aims: Decompensation of cirrhosis is accompanied by gut-barrier dysfunction, higher blood levels of *pathogen-associated molecular patterns* (PAMPs), *systemic inflammation* (SI), and functional immune cell alterations, leading to the syndrome of *cirrhosis associated immune dysfunction* (CAID). We hypothesize that *portal hypertension* (PH) is the functional driver of these immunological alterations, which can be reversed by its resolution via TIPS.
Method: 75 patients with ascitic decompensated cirrhosis undergoing TIPS-placement were included in our prospective cohort study, along with 15 patients with compensated cirrhosis as controls. The following markers were measured pre- and post-TIPS and once in controls: I-FABP (gut-barrier function), LBP (PAMP), sCD14 (monocyte activation), and 18 cytokines as a surrogate for SI. A phenotype profiling of monocytes was carried out by assessing the impact of patient serum on LPS-activated monocyte-derived macrophages from healthy donors using flow cytometry along with core monocyte/macrophage functions such as efferocytosis and cytokine secretion. RNA bulk sequencing analysis on CD14+ monocytes isolated from patients with compensated or decompensated cirrhosis pre- and post-TIPS was also carried out. Last, we analyzed the changes in all markers in correlation with the incidence of bacterial infections and transplant-free survival.
Results: Patients with decompensated cirrhosis pre-TIPS showed elevated levels iFABP, LPB and sCD14, as compared to controls. SI was present pre-TIPS, as indicated by elevated levels of e.g. IL-6 and C-reactive protein (CRP). Phenotypic profiling revealed a high expression of cell surface molecules normally associated to an anti-inflammatory monocyte/macrophage, resulting in an enrichment of a $MerTK^{high}CD163^{high}$ population. RNA bulk sequencing results further indicated the anti-inflammatory/suppressive signature in decompensated cirrhosis. Resolution of PH by TIPS lead to a decrease in all measured markers, finally reaching similar levels as in compensated controls. These changes were also observed at a transcriptional and phenotypic level in monocytes. Efferocytosis remained intact pre- and post-TIPS, whereas we observed an altered response to bacterial stimuli, as mirrored by an increased IL-6 secretion post-TIPS. The correlation with clinical data revealed that patients with further ascitic decompensation post-TIPS showed no improvement in SI or the monocyte phenotype, translating into a three-fold higher incidence of bacterial infections requiring hospitalization and a strongly decreased transplant-free survival.
Conclusion: Resolution of PH by TIPS is associated with a reversal of gut-barrier dysfunction, SI and monocyte alterations associated with a blunted immune response. Recompensation by TIPS translates into less bacterial infections and an improved transplant-free survival, most likely by altering the cytokine milieu and the macrophage polarization status.

WED-194-YI

Treatment response to terlipressin in patients with acute kidney injury - hepatorenal syndrome and preexisting chronic kidney disease – the german liver cirrhosis/CKD-Terli study group

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Background and aims: The previous definition of hepatorenal syndrome - acute kidney injury (HRS-AKI) excluded patients with signs of structural kidney injury. The recent update in the Acute Disease Quality Initiative (ADQI) - International Club of Ascites (ICA) consensus guidelines acknowledged that HRS-AKI might also occur in the presence of chronic kidney disease (CKD). However, no data are currently available on efficacy of treatment with terlipressin and its impact on outcome in patients with HRS-AKI and CKD. This multicenter, retrospective, observational study aimed to investigate treatment response of albumin and terlipressin in patients with HRS-AKI and CKD compared to patients without CKD.
Method: A total of 490 patients admitted between 2018 and 2022 with AKI-HRS who received albumin/terlipressin at 12 tertiary centers in Germany were retrospectively analyzed. Patients were stratified according to: (i) no CKD; (ii) suspected CKD: baseline glomerular filtration rate (GFR) < 60 ml/min *and* no evidence of structural kidney damage; (iii) proven CKD: GFR < 60 ml/min *and* history of primary nephropathy *or* evidence of structural kidney damage *or* known cardiovascular risk factors. The primary endpoint was a complete response to terlipressin treatment according to ICA recommendations (decrease of serum creatinine to a value within 0.3 mg/dl of baseline). Secondary endpoints included need for renal replacement therapy (RRT) and 12-month transplantation (LTx) - free survival.
Results: In total, 339 patients (69.2%) had no CKD, 35 patients (7.1%) suspected CKD and 116 patients (23.7%) proven CKD at baseline. 206 patients (42%) reached the primary endpoint of complete treatment response to terlipressin; 14 (40%) with suspected CKD, 43 (37.1%) with proven CKD and 149 patients without CKD at baseline (44%) (p = 0.435). The median time to partial or complete treatment response did not differ between patients without CKD or with proven CKD at baseline (6.0 [5.04–6.96] vs. 7.0 days [5.11–8.89], p = 0.775). Furthermore, the need for RRT during follow-up was similar between patients with or without CKD at baseline (31.4% vs. 24.1% vs. 25.1%, p = 0.408). The 12-month LTx-free survival was 35.2% (LTx in 17.5% and death in 47.3% of patients), with a median LTx-free survival time of 3 month (1.7–4.3) in the overall cohort. When adjusting for age, etiology, treatment response and liver function parameters (INR, bilirubin, albumin) with LTx as competing event, preexisting suspected and proven CKD did not impact survival in patients with AKI-HRS (sHR 1.40 [0.90–2.15], p = 0.132).
Conclusion: Suspicion or even presence of CKD does not seem to influence treatment response to terlipressin in patients with HRS-AKI and patients show comparable outcome irrespective of CKD. This study supports initiation of vasopressor treatment in patients with AKI-HRS independent of pre-existing structural kidney injury.

WED-195-YI
Frequency and impact of early and sustained hepatic recompensation after TIPS

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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is a highly effective treatment for patients with decompensated liver cirrhosis and may lead to recompensation in numerous cases. This study aimed to investigate determinants and clinical relevance of hepatic recompensation after TIPS insertion in a large prospective cohort.
Method: All consecutive patients with liver cirrhosis undergoing TIPS insertion between 07/2019 and 04/2024 at Hannover Medical School were prospectively enrolled. Prescheduled follow-ups were conducted at 1, 3, 6, 12, and 24 months post-TIPS. First and further decompensation were defined according to the Baveno VII criteria considering TIPS insertion as new baseline. For hepatic recompensation modified criteria were applied: Absence of any hepatic decompensating event until month 3 irrespective of the use of HE prophylaxis or diuretic treatment was considered as modified early recompensation (mER). Absence of hepatic decompensation until month 12 post-TIPS was defined as modified sustained recompensation (mSR). Competing risk analyses evaluated survival (with liver transplantation (LTx) as a competing event) and hepatic decompensation (with death and LTx as competing events). Landmark analyses at 3 and 12 months mitigated immortal time bias. All analyses were adjusted for MELD. Multivariable binary logistic regression analysis including age, MELD, CRP and IL-6 were performed to identify baseline predictors of mER and mSR.
Results: A total of 220 patients (median MELD: 12, 53% alcohol-related cirrhosis, 75% underwent TIPS for refractory ascites) were analysed. Overall, 38% and 23% achieved mER and mSR, respectively, while 1% of patients fulfilled the original Baveno VII criteria for hepatic recompensation. Only baseline IL-6 levels were significantly linked to mER (asHR: 0.93; p = 0.04) and mSR (asHR: 0.89; p = 0.03) in the multivariable analysis. Overall, mER (asHR: 0.41; p = 0.03) was linked to lower mortality. Of note, negative prognostic impact of early decompensation events was independent of fulfilling the first or further decompensation criteria. In contrast, mER was not associated with the risk of any hepatic decompensation (asHR: 0.83; p = 0.51), while there was a numerically lower risk for developing a further hepatic decompensating event thereafter (asHR: 0.55; p = 0.09). Surprisingly, achieving mSR did not lead to an improved survival (asHR: 1.13; p = 0.84). However, those with mSR after TIPS had a significantly lower risk of any decompensation (asHR: 0.13; p = 0.01) during longer follow-up and not a single mSR patient progressed to further hepatic decompensation (asHR: < 0.001; p < 0.001).
Conclusion: A significant number of patients achieve hepatic recompensation after TIPS. While mER indicates an improved survival, sustained recompensation month 12 after TIPS may identify patients with permanent symptom control.

WED-196-YI
Validation of the blood-based Vienna 3P/5P portal hypertension risk models in patients with compensated advanced chronic liver disease

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Background and aims: Clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, identifies patients at risk for hepatic decompensation with risks escalating at HVPG ≥16 mmHg. While invasive HVPG measurement remains the gold standard for CSPH diagnosis, non-invasive alternatives are critically needed. We assessed the Vienna 3P and 5P models, machine learning tools based on three or five routine blood parameters, for non-invasive portal hypertension (PH) severity estimation as well as risk prediction and stratification capabilities in patients with compensated advanced chronic liver disease (cACLD). Their performance was benchmarked against HVPG, liver stiffness (LSM), and the ANTICIPATE ± NASH model, which incorporates LSM, platelet count ± body mass index (BMI).
Method: Patients with cACLD undergoing HVPG measurement, LSM and a blood withdrawal within the prospective VICIS study (NCT03267615) were included. Detection of CSPH and severe PH (i.e. HVPG ≥ 16 mmHg) were evaluated using area under the receiver operating characteristic curves (AUROC). Multivariate risk regression analysis was performed to predict hepatic decompensation (variceal bleeding, ascites, or hepatic encephalopathy), accounting for hepatocellular carcinoma (HCC) and non-liver-related death as competing risks. Additionally, the models' risk stratification capabilities were assessed.
Results: Among 266 patients with cACLD, the leading etiologies were viral hepatitis (27.8%) and alcohol-related liver disease (23.7%). The median HVPG was 11 mmHg (IQR: 8–16), with a prevalence of CSPH and severe PH of 62.8% and 25.6%, respectively. During a median follow-up of 23.9 months (IQR: 14.4–32.6), hepatic decompensation occurred in 48 patients (18%). The 3P and 5P models correlated with HVPG (p < 0.001), achieving AUROCs of 0.704 (5P) and 0.672 (3P) for CSPH, and 0.800 (5P) and 0.704 (3P) for severe PH prediction. The 5P model showed comparable time-dependent AUROCs to HVPG for predicting first hepatic decompensation at 6 months and 1 year (0.753–0.822), outperforming ANTICIPATE ± NASH (0.689–0.691) and LSM (0.621–0.636). In multivariate analysis, the 5P (adjusted subdistribution hazard ratio [aSHR]: 1.261, p = 0.002) and 3P (aSHR: 1.098, p = 0.032) models were independent risk factors for decompensation. Risk stratification by 3P/5P (<60%, 60–79%, ≥80%) effectively identified low- and high-risk patients (Gray's test p < 0.001), with the 5P model performing comparably to HVPG (<10, 10–15, ≥16 mmHg).
Conclusion: The blood-based 3P/5P models demonstrate strong prognostic value for predicting hepatic decompensation and stratifying cACLD patients in high and low risk groups. The 5P model performed comparably to invasive HVPG measurement, supporting its applicability in selecting "at-risk" cACLD patients for preventive therapies.

WED-197
Prognostic performance of the enhanced liver fibrosis (ELF) test in patients with advanced chronic liver disease in tertiary care

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Background and aims: The enhanced liver fibrosis test (ELF) is a blood-based biomarker developed for liver fibrosis staging but also reflects the dynamic process of matrix remodeling. We assessed the prognostic performance of ELF in a diverse cohort of patients with compensated (cACLD) and decompensated (dACLD) advanced chronic liver disease.
Method: Patients of the prospective VICIS (NCT03267615) study with measurements of hepatic venous pressure gradient (HVPG), liver stiffness (LSM) and ELF were included and grouped as cACLD and dACLD (ascites, overt hepatic encephalopathy, variceal bleeding). For cACLD patients, the event of interest was first decompensation (with HCC and non-liver-related death as competing events), for dACLD patients the liver-related events (LREs) of interest were either further decompensation, acute-on-chronic liver failure (ACLF) or liver-related death (with HCC, liver transplantation and non-liver-related death as competing risks). Multivariate competing risk regression models were adjusted for age, sex, HVPG and body-mass-index.
Results: Among 573 patients (n = 230 cACLD, n = 343 dACLD) alcohol-related liver disease (ALD) was the predominant etiology (44.7%). Median ELF (12.00 vs. 10.79; p < 0.001) and HVPG (19 vs. 11 mmHg; p < 0.001) were significantly higher in dACLD compared to cACLD. During a median follow-up of 18.7 months, first decompensation occurred in 51 (22.2%) cACLD and LRE in 168 dACLD patients (49.0%). In cACLD, ELF demonstrated time-dependent area under the receiver operating characteristic curves (td-AUROCs) of 0.765 and 0.754 for predicting first decompensation at 1 and 2 years, respectively, and was independently associated with first decompensation (adjusted subdistribution hazard ratio [aSHR]: 1.351; p = 0.002). Risk stratification was effective with balanced allocation in 3 distinct cACLD risk groups and robust identification of high-risk patients (high-risk ≥11.1 vs. low-risk <10.1, Gray's test p < 0.001; medium-risk: 10.1–11.09 vs ≥11.1, p = 0.006). In dACLD, ELF showed td-AUROCs of 0.585 and 0.649 for LREs at 1 and 2 years, comparable to HVPG (0.593 and 0.630, p = 0.886 and p = 0.712). ELF was an independent risk factor for LRE (aSHR: 1.150, p = 0.008) and effectively identified patients at high risk for LREs (high-risk: ≥14.0 vs. low-risk: <12.5, p < 0.001; medium-risk: 12.5–13.9 vs. ≥14.0, p = 0.004). However, risk group allocation was less balanced than in cACLD.
Conclusion: The ELF score demonstrates robust prognostic value in tertiary care cohorts, particularly in cACLD, where it effectively predicts first decompensation and stratifies risk. In dACLD, moderate predictive performance and less effective risk stratification reduce its clinical utility. Nevertheless, ELF remains an independent risk factor for LRE in dACLD and identifies high-risk patients who should be prioritized for intensified treatments.

WED-198
Incidence and clinical significance of recompensation after HCV-cure

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Background and aims: Baveno VII has proposed criteria for cirrhosis recompensation. However, their prognostic significance in decompensated patients cured from hepatitis C virus (HCV) remains incompletely studied. Thus, we investigated the incidence and impact of recompensation after HCV-cure as well as its predictors.
Method: 2570 patients with advanced chronic liver disease (ACLD) from 10 European centers, including 2209 with compensated advanced chronic liver disease (cACLD) and 361 patients with decompensated cirrhosis, who achieved sustained virologic response to direct-acting antivirals (DAAs) were retrospectively included. The association between achieving recompensation according to Baveno VII and clinical outcomes (hepatocellular carcinoma [HCC], portal vein thrombosis [PVT], and [liver-related] death [LRD]) was investigated.
Results: 158 (43.8%) had a history of variceal bleeding and 330 (91.4%)/147 (40.7%) patients had previous or current ascites/hepatic encephalopathy; median MELD was 11 [IQR: 9–14] before DAA-treatment. During a median follow-up of 8.4 years, 132 patients (36.6%) achieved recompensation. Lower albumin levels and diabetes were negatively associated with achieving recompensation. The incidence-rates (IR) of LRD (4.2 vs. 8.8/100 patient-years) and PVT (2.7 vs. 5.4/100 patient-years) were substantially lower after recompensation vs. in the non-recompensated state, while HCC incidence remained high (3.9 vs. 5.5/100 patient-years). Compared to decompensated cirrhosis, achieving recompensation was independently associated with decreased risks of subsequent LRD (adjusted hazard ratio [aHR]: 0.38 [95%CI: 0.23–0.66]) and of PVT (aHR: 0.42 [95%CI: 0.22–0.76]), but both risks remained higher than in cACLD. Importantly, HCC incidence was not reduced as compared to decompensated cirrhosis.
Conclusion: Recompensation after HCV-cure is associated with substantially decreased risks of (liver-related) mortality and PVT, but not of HCC.

WED-199

Advanced chronic liver disease in the context of further decompensation & recompensation – a multistate analysis of a contemporary prospective study

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Background and aims: Despite the recent introduction of further decompensation and recompensation in advanced chronic liver disease (ACLD), most research still relies on a unidirectional time to first event framework, which neglects the medical reality of a multidirectional patient journey. Notably, previous multistate analyses were based on historical natural history data, which may no longer be generalizable in the present era of effective etiological therapies. We aimed to investigate the multistate trajectories of ACLD in a contemporary prospectively characterized cohort.
Method: ACLD patients with portal hypertension (n = 464; hepatic venous pressure gradient [HVPG] >5 mmHg) were prospectively recruited from 2017 to 2021 (VICIS; NCT03267615). Clinical disease stages at baseline and during follow-up were defined as compensated (c)ACLD, first decompensation, further decompensation/ACLF (combined), liver-related death (LRD), and recompensation. A multistate model using Nelson-Aalen estimator of cumulative hazards was employed to study stage transitions. Recompensation and non-liver-related death were treated as absorbing states (i.e., patient censoring).
Results: The predominant etiologies were ALD/MetALD in 217 (46.8%), followed by viral hepatitis in 81 (17.5%), and MASLD in 40 (8.6%). At baseline, 179 (38.6%) were classified as cACLD, 168 (36.2%) as first decompensation, while 117 (25.2%) had further decompensation/ACLF. Median HVPG was 17 (12–21) mmHg. During a median follow-up of 28.8 months, 35 (19.6%) of cACLD patients developed first decompensation, 134 (28.9%) of all patients developed further decompensation/ACLF, and 83 (17.9%) experienced a LRD, while 75 (16.2%) achieved recompensation. For cACLD patients, the probability for remaining compensated at 24 months was 81.3% (95%CI: 75.0–87.6), for first decompensation 12.0% (7.4–16.7), further decompensation/ ACLF 2.8% (1.3–4.2), LRD 2.2% (0.3–4.1), and recompensation 1.7% (0.7–2.7). Among patients with first decompensation, 63.7% (56.2–71.3) remained decompensated at 12 months, 15.1% (10.4–19.8) transitioned to further decompensation/ ACLF, 6.3% (3.7–8.9) LRD, and 14.9% (10.0–19.8) achieved recompensation. In those with further decompensation/ACLF, 45.7% (37.4–54.1%) remained decompensated at 12 months, 32.2% (24.3–40.1%) had LRD, and 22.1% (15.1–29.0%) achieved recompensation.
Conclusion: In the era of etiological therapies, achieving recompensation is more likely than LRD after first hepatic decompensation. Further decompensation/ ACLF substantially worsens the prognosis, with a nearly five-fold increase in LRD risk, however, recompensation may still be achieved (similarly likely as after first decompensation), emphasizing the universal effectiveness of etiological therapies.

WED-200

Non-invasive prediction of clinically significant portal hypertension in patients with compensated advanced chronic liver disease of different aetiologies

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Background and aims: Patients with compensated advanced chronic liver disease (cACLD), defined according to the Baveno VI criteria based on a liver stiffness measurement (LSM) ≥10 kPa, are at risk of developing clinically significant portal hypertension (CSPH). Identifying cACLD patients with CSPH is essential for implementing personalized therapeutic strategies. We aimed to non-invasively stratify the CSPH risk in patients with cACLD of different etiologies and to predict the probability of liver decompensation (LD) using the Baveno VII criteria, the Baveno VII criteria implemented with spleen stiffness measurement (SSM), and the NICER model (PMID 39326431).
Method: Monocentric retrospective observational study including 191 consecutive cACLD patients, who underwent vibration-controlled transient elastography (VCTE) examination for LSM and SSM between December 2022 and April 2024. The Baveno VII criteria were applied, along with the Baveno VII-SSM criteria using a single cut-off (SSM ≤40 kPa and SSM >40 kPa) and dual cut-offs (SSM ≤25 kPa and SSM ≥55 kPa). Additionally, the NICER model was computed as published: Logit = –6.40032480 + ln(SSM) × 1.96952565 + ln(LSM) × 1.83093447 - BMI × 0.12882190 – platelets (PLT) × 0.01850461. Esophagogastroduodenoscopy (EGD) was performed per Baveno VI recommendations and proposed to all patients with SSM >40 kPa.
Results: Among the 191 patients (57.6% male, median age 65.87 years, median BMI 25.8 kg/m²), the median LSM was 19.1 kPa (IQR 13.4–32.2), SSM 42 kPa (IQR 28.1–52.8), PLT 139 × 10³/mmc (IQR 100–181). Applying the Baveno VII criteria: 36 patients (18.8%) were at low risk for CSPH (rule-out CSPH), 66 (34.5%) at high risk (rule-in CSPH), 89 (46.6%) in the grey zone. Using the Baveno VII-SSM criteria with a single cut-off: 71 patients (37.2%) were at low risk, 94 (49.2%) at high risk, 26 (13.6%) in the grey zone. Using the Baveno VII-SSM with dual cut-offs: 71 patients (37.2%) were classified as low risk, 66 (34.5%) as high risk, and 54 (28.3%) in the grey zone. Based on the NICER model, the median CSPH risk in the 191 patients was 65%. CSPH risk distribution was: <25% 80 patients (41.9%), >75% 92 patients (48.2%). Among the 152 patients who underwent EGD, esophageal varices were found in 11.5% of patients with a CSPH risk <25% and in 82% of patients with a CSPH risk >75% ($p < 0.0001$). During follow-up (median 8.4 months), 4 patients developed LD. In patients with CSPH risk >75% calculated using NICER, the probability of LD at 12 and 15 months was 2.5% and 7.6%, respectively, compared to 1.1% at both time points in patients with a CSPH risk ≤75% ($p = 0.27$).
Conclusion: The addition of SSM to the Baveno VII criteria reduces the diagnostic grey zone, enabling improved risk stratification for CSPH in cACLD patients. CSPH risk estimation using the NICER model provides additional non-invasive support for predicting CSPH.

WED-205-YI

A pan-elastographic machine learning model for non-invasive diagnosis of clinically significant portal hypertension

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Background and aims: Clinically significant portal hypertension (CSPH) is the main driver of complications in patients with advanced chronic liver disease (ACLD). While hepatic venous pressure gradient (HVPG) measurement remains the diagnostic gold standard, its invasiveness and limited availability hinder widespread use. Non-invasive tests such as liver (LSM) and spleen (SSM) stiffness measurement, and platelet count (PLT) are capable to reflect CSPH risk and are recommended by Baveno guidelines. However, they are limited by significant diagnostic gray zones and suboptimal performance in diverse etiologies and elastography modalities. This study aimed to develop a machine learning model (MLM) incorporating elastography and clinical parameters to predict CSPH across multiple elastography modalities.
Method: We analyzed 1,218 patients with ACLD across 17 Centers, who underwent HVPG and elastography with vibration-controlled transient elastography (n = 668), 2D-shear-wave elastography (n = 274) or point-shear-wave elastography (n = 276). Variables included LSM, SSM, PLT, age, gender, etiology, and Child-Pugh (CP) score (≤6 vs. >6). Elastography values were harmonized using Z-scores. We evaluated several MLMs with a 1,068–150 train-test split, targeting proportional representation across elastography modalities and balanced CSPH ratio. We evaluated MLM cut-offs for 100% Negative Predictive Values (NPV) in ruling-out CSPH and 100% Positive Predictive Values (PPV) in ruling-in CSPH (training set) and evaluated their performance in the test set. Clinical performance was evaluated against Baveno VII criteria, including standard (without SSM), dual (SSM<21 kPa/SSM>50 kPa), and single (SSM≤40 kPa/SSM>40 kPa) cut-off criteria.

Results: Random Forest (RF) outperformed other MLMs (AUC = 0.93, Brier Score = 0.11). Regarding CP score, only 2.6% of patients had CP>7 in test set. MLM output ranges 0.0–1.0. In test set, cut-offs of ≤0.45 for ruling-out and ≥0.60 for ruling-in CSPH achieved sensitivity of 0.97 (95%CI:0.95–1.00), NPV of 0.97(95%CI:0.93–1.00), specificity of 0.91 (95%CI:0.80–0.96), and PPV of 0.93(95%CI:0.87–0.97). The MLM significantly reduced the diagnostic gray zone to 10.6% versus 44.0%, 39.3%, and 23.3% for standard Baveno VII, dual cut-off, and single cut-off criteria (all $p < 0.001$). This improvement was consistent across all elastography techniques and etiologies. In patients with alcohol-related disease, the model reduced the gray zone to 6.9% compared to 48.2% with standard Baveno VII criteria ($p < 0.001$). Similarly, in metabolic dysfunction-associated steatotic liver disease the gray zone reached 2.1% from 51.3% ($p < 0.001$).
Conclusion: Our pan-elastography MLM based on LSM, SSM, PLT significantly improves CSPH prediction while reducing diagnostic uncertainty across liver disease etiologies and elastography techniques. This approach offers reliable tool for CSPH diagnosis and non-invasive guidance for non-selective beta-blocker treatment.

WED-206-YI
Influence of low-dose acetylsalicylic acid on renal function in patients with liver cirrhosis and ascites

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Background and aims: Non-steroidal anti-inflammatory drugs are not recommended in patients with cirrhosis and ascites due to acute kidney injury (AKI) risk. Nowadays, with the increasing prevalence of metabolic dysfunction-associated steatotic liver disease, more patients require low-dose acetylsalicylic acid (ASA) for cardiovascular prophylaxis. This study aims to evaluate the impact of low-dose ASA on transplant (LT)-free survival, renal function, and further decompensation in patients with cirrhosis and ascites.
Method: This is a retrospective unicentric analysis of consecutive patients with cirrhosis and ascites from 01/2019 to 12/2022. Baseline data included medical history, liver disease severity, complications, cardiovascular comorbidities, co-medications, and laboratory values. Follow-up was extended until 12/2023. Endpoints were LT-free survival, changes in serum creatinine (sCr), incidence of AKI, and further decompensation. Variables were compared with T-student and Mann-Whitney U test. Propensity score matching (PSM), Cox regression analyses, and competing risk analyses were performed.
Results: 303 patients [194 (64%) men, median age 59 (53–66) years], of whom 53 (17.5%) were on low-dose ASA, were included and followed for a median of 350 (150–406) days. Thirteen (31.0%) ASA patients and 59 (29.1%) controls died or underwent LT. There was no difference in LT-free survival (HR 1.13, 95% CI 0.62–2.07) or death (HR 0.77, 95% CI 0.33–1.80) (with LT as competing risk) in patients who took ASA. Seven (16.7%) ASA patients developed AKI, of which three (42.9%) were hepatorenal syndrome (HRS-AKI), compared to 23 (11.4%) AKI cases [7 (30.4%) HRS-AKI] in controls, with no significant differences in their incidence (AKI: HR 1.47, 95% CI 0.63–3.42; HRS-AKI: HR 1.96, 95% CI 0.51–7.57). Although ASA patients had significantly higher sCr levels at baseline (100 µmol/l vs. 77 µmol/l, $p = 0.006$), they decreased slightly in ASA patients (−4 µmol/l) and worsened in controls (+10 µmol/l) during follow-up ($p = 0.052$). Further decompensation occurred in 14 (33.3%) ASA patients and 70 (34.5) controls, with no significant effect of ASA (HR 0.90, 95% CI 0.51–1.60). This observation was maintained in the competing risk analysis (death and LT as competing risks), (HR 0.85, 95% CI 0.36–2.02). After PSM (1:1), no differences were observed in LT-free survival (HR 1.18, 95% CI 0.52–2.64), the incidence of AKI/AKI-HRS (AKI: HR 1.83, 95% CI 0.53–6.29; AKI-HRS: HR 2.79, 95% CI 0.29–26.84), and further decompensation (HR 0.84, 95% CI 0.41–1.72).
Conclusion: Intake of low-dose ASA does not affect LT-free survival, renal function and the incidence of AKI or further decompensation in patients with cirrhosis and ascites.

WED-207-YI
Effectiveness of carvedilol plus variceal band ligation compared to carvedilol alone in primary prophylaxis of variceal bleed in cirrhosis with high-risk oesophageal varices

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Background and aims: Portal hypertension is a major complication of liver cirrhosis, frequently leading to the development of oesophageal varices. Variceal bleeding accounts for significant morbidity and mortality among cirrhotic patients. Non-selective beta-blockers (NSBBs) and endoscopic variceal ligation (EVL) are commonly employed as prophylactic measures to prevent initial variceal bleeding. Aim of this study was to assess the effectiveness of combination therapy of carvedilol and EVL compared to carvedilol alone for primary prophylaxis of variceal bleed in cirrhosis with high-risk oesophageal varices.
Method: A randomized controlled trial was conducted in which 80 cirrhotic patients with high-risk oesophageal varices (large varices or varices with positive red color sign) without a prior history of variceal bleeding were prospectively enrolled. Participants were randomized into two groups: 40 received combination therapy of carvedilol plus EVL, and 40 received carvedilol alone. Patients were followed for one year, with regular clinical assessments, biochemical evaluations, and endoscopic surveillance. 8 Patients lost during follow up (4 in each group). Total 72 patients were analysed at the end of 1 year. The primary outcome was the incidence of first variceal bleed. Secondary outcomes included overall mortality, bleeding-related mortality and adverse events related to interventions.
Results: The mean age was slightly higher in the EVL plus carvedilol group (59.7 ± 12.9 years) compared to the carvedilol alone group (56.1 ± 11.9 years), with a p value = 0.222, indicating no significant difference. Gender distribution showed more males in both groups, with 63.9% in the EVL plus carvedilol group and 77.8% in the carvedilol alone group. Intention-to-treat analysis showed that the combination group had a significantly lower incidence of first variceal bleed compared to those in the carvedilol-alone group after 1 year (22.2% vs. 50%, $p = 0.014$). Overall mortality after 1 year was lower in combination group although without a statistically significant difference (11.1% vs. 19.4%, $p = 0.325$). Mortality due to bleeding after 1 year was also lower in combination group but without a statistically significant difference (5.6% vs. 13.9%, $p = 0.232$). Variceal bleeding was the most common cause of death in both group (5.6% vs. 13.9%, $p = 0.232$). Both groups had similar adverse event profiles. No significant differences were found in baseline demographic or clinical parameters, including age, ensuring comparability between the groups.
Conclusion: The combination of EVL and carvedilol is superior to carvedilol alone for primary prophylaxis of variceal bleeding in cirrhosis patients with high-risk oesophageal varices and there is no significant difference in adverse events between two groups.

WED-208
The GEMA score predicts mortality in patients undergoing TIPSS for ascites

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Background and aims: The GEMA and GEMA-Na scores were recently derived in patients awaiting liver transplantation and performed better than MELD-Na and MELD 3.0 for predicting waiting list mortality [1]. We evaluated the predictive ability of GEMA and GEMA-Na in a cohort of patients who underwent transjugular intrahepatic portosystemic shunts (TIPSS) for the management of ascites.
Method: Data was collected for patients undergoing TIPSS procedures at the Royal Free between 2010 and 2022. Statistical analyses used included *t*-tests and Mann-Whitney tests for comparison of continuous variables and the Cox proportional hazards model to identify predictive factors for mortality. Patients were censored at the point of death, last known follow up or the date of transplantation.
Results: 279 TIPSS were performed. 62.7% of the patients were male with a mean age of 56.7 years. Alcohol was the most common aetiology (63.4%), followed by metabolic dysfunction- associated steatotic liver disease (14.3%) and hepatitis C infection (8.6%). The median baseline MELD was 11 (IQR 9–14). Following TIPSS, a total of 14% of patients were transplanted, 5 within 90 days and 24 within one year. Of the remaining patients, survival at 90-days and 12-months was 91.5% (237/259) and 74.5% (175/235) respectively. Of the documented causes of death, 68.1% were due to liver related causes and 13.9% due to sepsis. Baseline variables predictive at univariate analysis for 90-day mortality included hypertension, diabetes, previous cardiac history and smoking histories but only hypertension (aHR 3.780, 95% C.I. 1.628–8.776) remained so at multivariable analysis. MELD (aHR 1.083, 95% C.I. 1.022–1.148), MELDNa (aHR 1.056, 95% C.I. 1.008–1.106) and GEMA (aHR 1.071, 95% C.I 1.007–1.139) scores (in separate models) were independent predictors of 12-months mortality alongside previous cardiac disease (aHR 2.561, 95% C.I 1.206–5.437). For overall mortality, although all prognostic scores were significant at univariate analysis only MELD (aHR 1.073, C.I 1.025–1.122), MELDNa (aHR 1.043, 95% C.I. 1.007–1.079) and GEMA (aHR 1.050, 95% C.I. 1.004–1.099) remained independently predictive at multivariable analysis. Additional clinical factors included age (aHR 1.022, 95% C.I 1.004–1.041), diabetes (aHR 1.448, 95% C.I. 1.005–2.086) and platelet count (aHR 0.998, 95% C.I. 0.995–1.000).
Conclusion: In this cohort of patients undergoing TIPSS for ascites, GEMA (and other prognostic scores) were predictive of 12 month and overall mortality. This study provides proof-of-concept that GEMA has prognostic utility outside a transplant setting.

WED-209-YI
Early need for paracentesis after TIPS is linked to further ascitic decompensation and impaired survival

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Background and aims: Clinically significant portal hypertension (CSPH) in cirrhosis can result in recurrent/refractory ascites (RA). Aside from liver transplantation (LT), a transjugular intrahepatic portosystemic shunt (TIPS) remains the most effective treatment for RA. However, some patients may still require large-volume paracentesis (LVP) after TIPS. An early need for LVP (i.e., within ≤30 days after TIPS) is often considered clinically insignificant, based on the assumption that TIPS requires some time to achieve adequate ascites control. We aimed to evaluate the impact and timing of post-TIPS LVP requirement on patient prognosis.
Method: A total of 1,509 patients undergoing TIPS implantation between 2000 and 2023 at three European centers (Hannover, Vienna, Hamburg) were screened. Patients with TIPS indication other than RA, vascular liver disease, hepatocellular carcinoma, or insufficient follow-up data were excluded. Outcomes were recorded until one year after TIPS. Competing risk analyses were performed, considering LT or death as competing events for LVP outcomes, and LT as a competing event for survival analysis. Cox proportional hazards regression with time-dependent covariates and landmark analyses at 30- and 90-days post-TIPS were utilized to mitigate immortal time bias.
Results: A total of 729 patients (median MELD: 13 [IQR 10–16], 66% male, 65% alcohol-related liver disease) were included in the final analysis. In the 30-day landmark analysis, patients requiring LVP within the first 30 days post-TIPS demonstrated an elevated risk of requiring LVP beyond 30 days (subdistribution hazard ratio (sHR): 2.95 [2.18–4.01]; $p < 0.001$) and worse LVP-free (sHR: 3.66 [2.82–4.76]; $p < 0.001$) as well as worse overall survival (sHR: 2.43 [1.74–3.39]; $p < 0.001$). Similarly, patients requiring LVP between 30–90 days post-TIPS exhibited a higher risk of requiring LVP after 90 days (sHR: 1.93 [1.42–2.63]; $p < 0.001$) worse LVP-free (sHR: 3.84 [2.84–5.2]; $p < 0.001$) and overall worse survival (sHR: 1.83 [1.24–2.71]; $p < 0.001$). Time-dependent analysis, treating LVP as a time-varying covariate, also showed significantly impaired survival of patients requiring LVP during follow-up (HR: 3.99 [2.86–5.12]; $p < 0.001$). These findings remained consistent after adjustment for MELD or the Freiburg Index of post-TIPS survival.
Conclusion: Early LVP – regardless if required within 30 or within 30–90 days – after TIPS is a strong predictor of survival, the need for subsequent post-TIPS LVP, and LVP-free survival – indicating that post-TIPS LVP requirement should not be dismissed as clinically insignificant. Caregivers should consider prompt and decisive action, such as optimizing diuretics or considering TIPS revision, whenever LVP occurs, regardless of the timing.

WED-210
Growth differentiation factor 11 increases after TIPS insertion, correlates with muscle mass and is an independent predictor of survival

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Background and aims: Growth differentiation factor 11 (GDF11), a member of the TGF-beta family, has been implicated in tissue regeneration and fibrosis. Experimental studies suggest elevated GDF11 levels in patients with fibrosis, though its role in clinical outcomes and muscle mass remains controversial. Thus, we investigated GDF11 as a potential biomarker for sarcopenia and clinical outcomes following transjugular intrahepatic portosystemic shunt (TIPS).
Method: We prospectively recruited 199 consecutive patients with cirrhosis undergoing TIPS insertion at two German centers. Structured follow-up visits, including biosampling and frailty assessment using the liver frailty index (LFI), were conducted at one, three, six, and 12 months post-TIPS. GDF11 levels were measured pre-TIPS and at each follow-up using enzyme-linked immunosorbent assay. Analyses included Spearman rank correlation coefficients, competing risk analysis for outcome data with liver transplantation as competing event, and linear mixed models (LMM) to assess GDF11 kinetics after TIPS. Additionally, we used maximally selected rank statistics to determine a predictive GDF11 cut off for survival.
Results: Among the 199 patients, 54% had alcohol-related cirrhosis, median MELD score was 12 (IQR: 9–16), and 78% underwent TIPS for refractory ascites. Before TIPS, median GDF11 levels were 1,905 pg/mL (IQR: 893–3,158). GDF11 correlated significantly with muscle mass (skeletal muscle index, $r = 0.51$, $p < 0.001$) and frailty (LFI, $r = -0.31$, $p < 0.001$). GDF11 levels before TIPS were associated with reduced mortality (subdistribution hazard ratio (sHR): 0.34 [0.15–0.79]; $p = 0.012$) after TIPS, an association that remained significant after adjusting for MELD (adjusted sHR: 0.33 [0.14–0.76]; $p < 0.001$). Using maximally selected rank statistics, a GDF11 cutoff of 1,069 pg/mL stratified survival ($p = 0.03$), with patients below this threshold showing significantly increased mortality (sHR: 2.60 [1.41–4.67]; $p = 0.002$, MELD adjusted: $p = 0.002$, asHR: 2.64 [1.44–4.85]; $p = 0.002$). GDF11 levels increased significantly post-TIPS (LMM baseline vs. follow-ups: BL–FU1 $p = 0.15$; BL–FU3 $p < 0.001$; BL–FU6 $p < 0.001$; BL–FU12 $p < 0.001$). Notably, GDF11 levels did not correlate with MELD.
Conclusion: GDF11 levels increased significantly following TIPS and effectively stratified survival outcomes. Furthermore, GDF11 correlated with muscle mass and frailty and emerged as an independent predictor of post-TIPS survival, highlighting its potential utility for risk stratification.

WED-211

Non-invasive evaluation of portal hypertension in patients with advanced chronic liver disease undergoing major abdominal surgery

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Background and aims: In patients with advanced chronic liver disease (ACLD) undergoing major surgery, the presence of clinical decompensation (Child-Pugh B/C) increases mortality. In patients with compensated disease, the presence of severe portal hypertension (SPH) defined by a hepatic venous pressure gradient of 16 and especially 20 mmHg [Reverter E (J Hepatology, 2019)], is associated with higher postoperative mortality. Studies are needed to evaluate the impact of this diagnosis using non-invasive techniques. The aim was to compare postoperative mortality based on the presence or absence of non-invasive variables suggestive of preoperative severe portal hypertension.
Method: A retrospective, single-center study was conducted on patients with ACLD undergoing major abdominal surgery between 2010 and 2019. ACLD was defined as: 1) transient elastography (TE) >15 kPa; 2) abdominal ultrasound with signs of chronic liver disease, 3) data on portal hypertension. The SPH was considered by non-invasive methods (ni-SPH) according to previously published parameters [Jindal (Am J Gastroenterol, 2020)]: 1) splenomegaly (>13 cm) and thrombocytopenia <100,000/uL; 2) TE >42.8 kPa; 3) large varices. Patients were categorized into 3 groups: without ni-SPH (group A), without ascites with ni-SPH (group B), and with ascites (group C). Baseline characteristics were compared using univariate analysis (X^2 and U-Mann Whitney) and survival using mortality curves (Kaplan-Meier) and proportional hazards model (Cox regression).
Results: A total of 197 patients were included: median age 65 years, 68% male, and 53% with ACLD due to alcohol. Abdominal surgery was open in 57% (n = 113). Emergency surgery was performed in 44.2% (n = 87). There were 111 (56.4%) patients in group A, 62 (31.5%) in group B, and 24 (12.2%) in group C. In the 181 patients with Child-Turcotte-Pugh (CTP), the prevalence of CTP ≥ B7 was 12.6% (13/103), 29% (16/55) and 100% (23/23), respectively ($p < 0.01$). Patients in Group B vs. A had a higher proportion of ASA-IV (12.9% vs. 9%; $p = 0.03$), and worse liver function according to CTP ≥ B7 (29.1% vs. 12.6%, $p = 0.01$); without differences in MELD-Na (12 vs. 11 points, $p = 0.14$). The 90-day postoperative mortality was 4.5% (5/111) in group A, 12.9% (8/62) in group B, and 41.7% (10/24) in group C, respectively ($p < 0.01$). The increase in mortality [HR (95% CI), p] associated with ni-SPH among compensated patients (B vs. A) was 3.0 (1.0–9.2), $p = 0.05$. Moreover, ascites compared to compensated patients (A+B vs. C) were associated with an increased mortality of 6.8 (3.0–15.5); $p < 0.01$. The greatest difference was observed between patients without ni-SPH and those with ascites of 11.5 (3.9–33.8), $p < 0.01$.
Conclusion: Patients without hepatic decompensation but with non-invasive parameters suggestive of severe portal hypertension have three times higher 90-day postoperative mortality. Preoperative identification of these parameters can facilitate early initiation of treatments and more selective perioperative management.

WED-212

Determining the optimal portal pressure gradient after small-diameter TIPS for ascites: a cohort study

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Background and aims: The transjugular intrahepatic portosystemic shunt (TIPS) is a well-established therapeutic strategy for refractory and recurrent ascites. However, the optimal hemodynamic threshold for portal pressure gradient (PPG) following TIPS placement remains uncertain. This study aimed to elucidate the relationship between post-TIPS PPG and clinical outcomes in patients undergoing small-diameter (8-mm) cover TIPS for ascites.

Method: From July 2015 to June 2023, consecutive patients receiving small-diameter (8-mm) TIPS for ascites were considered for inclusion retrospectively. The impact of PPG on clinical outcomes—including ascites response, overt hepatic encephalopathy (OHE), further decompensation, and mortality—was evaluated using Fine and Gray competing risk regression models, both unadjusted and adjusted for potential confounders.
Results: A total of 143 patients were included in the analysis. Patients with persistent or recurrent ascites after TIPS exhibited significantly higher post-TIPS PPG than those without ($P < 0.001$). While patients who developed OHE had significantly lower post-TIPS PPG ($P < 0.001$). Receiver operating characteristic (ROC) curve analysis identified post-TIPS PPG as a reliable predictor of both ascites (AUC: 0.733, $P < 0.001$; cutoff: 10.5 mmHg) and OHE (AUC: 0.716, $P < 0.001$; cutoff: 7.5 mmHg). Univariate and multivariate Fine and Gray competing risk regression analyses further revealed that patients with PPG between 8 and 10 mmHg had favorable outcomes, including a lower incidence of ascites (>10 mmHg vs. 8–10 mmHg, adjusted SHR: 5.74, 95% CI: 1.11–15.58, $P < 0.001$), a reduced risk of OHE (<8 mmHg vs. 8–10 mmHg, adjusted SHR: 2.87, 95% CI: 1.29–6.35, $P = 0.010$), and a decreased risk of further decompensation after TIPS placement (>10 mmHg vs. 8–10 mmHg, adjusted SHR: 2.78, 95% CI: 1.43–5.41, $P = 0.003$; <8 mmHg vs. 8–10 mmHg, adjusted SHR: 2.42, 95% CI: 1.20–4.90, $P = 0.014$).
Conclusion: This study revealed post-TIPS PPG was associated with clinical outcomes in patients with refractory and recurrent ascites undergoing small-diameter TIPS. A post-TIPS PPG of 8–10 mmHg emerges as the optimal range, effectively controlling ascites without significantly increasing the risk of shunt-related hepatic encephalopathy, while also reducing the risk of further decompensation.

WED-213-YI
Right heart function on hemodynamic alterations and survival outcomes after transjugular intrahepatic portosystemic shunt

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Background and aims: To assess the right heart function in patients with decompensated cirrhosis and further analyze the impact of right heart function and right ventricular to pulmonary artery vascular coupling on hemodynamic regulation and prognosis after transjugular intrahepatic portosystemic shunt (TIPS).
Method: A prospective study included patients with decompensated cirrhosis underwent TIPS from January 2022 to January 2023. Patients underwent a comprehensive echocardiographic evaluation of cardiac function within 24 hours before the TIPS. The pressures of the portal vein, inferior vena cava, and right atrium were measured immediately before the TIPS, immediately after TIPS, and 2–4 days later. The primary endpoint of the study was all-cause mortality post-TIPS.
Results: Fifty-eight patients were enrolled, among which right heart dysfunction was primarily characterized by enlargement of the right atrial volume (RAV: 40.97 ± 13.19 ml). Nine patients (15.5%) exhibited right ventricular to pulmonary artery vascular uncoupling (TAPSE/PASP: 0.78 ± 0.13 vs 0.43 ± 0.16 mm/mmHg, $p < 0.001$), with worse right atrial strain and right ventricular free wall longitudinal strain (RVFWLS) indicating impaired right atrial and ventricular myocardial function in these patients. However, there were no significant differences in portal vein, inferior vena cava, right atrium pressures, and portal pressure gradients between the two groups at different measurement point. Additionally, patients with right ventricular to pulmonary artery vascular uncoupling showed more severe postoperative peripheral venous congestion at three months (71.4% vs 10.4%, $P < 0.001$) and six months (66.7% vs 6.4%, $P < 0.001$), with a poorer response to diuretic monotherapy. The median follow-up period was 11 months (range 1–17 months), during which six patients (10.3%) died. Elevated right atrial pressure (Log-rank test, $p = 0.0379$) and right ventricular to pulmonary artery vascular uncoupling (Log-rank test, $p = 0.007$) before TIPS significantly affected postoperative survival.
Conclusion: In patients with decompensated cirrhosis, the presence of right ventricular to pulmonary artery vascular uncoupling indicates relatively poorer overall right heart function which does not impair short-term post-TIPS hemodynamic regulation. But it significantly increased rate of postoperative lower extremities edema and mortality.

WED-214
The safety and efficacy of trans-splenic portal vein recanalization-assisted TIPS for the treatment of portal vein obliteration: a multicenter retrospective study

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Background and aims: Trans-splenic portal vein recanalization-assisted transjugular intrahepatic portosystemic shunt (Trans-splenic PVR-TIPS) may be an effective treatment for patients with portal vein obliteration. However, due to the technological complexity, current studies are limited to case reports or small-sample research, and its safety and efficacy require further validation. In this context, we conducted a multicenter retrospective study to assess the safety and efficacy of Trans-splenic PVR-TIPS.
Method: We conducted a multicenter retrospective study of patients who underwent Trans-splenic PVR-TIPS from June 2018 to June 2023, including a total of 67 patients. The procedural success rate, complications, and long-term portal vein recanalization rate(percentage of remnant lumen of the main portal vein $\geq$ 50%) were evaluated. Patients were classified into two groups based on the assistance technique: the balloon-assisted Trans-splenic PVR-TIPS group and the snare-assisted Trans-splenic PVR-TIPS group. Radiation exposure and complications were analyzed to assess which guidance technique is more optimal for the procedure.
Results: In the 67 patients included in the study, the surgical success rate was 95.5% (n = 64). Apart from one case of sepsis due to bacterial colonization within the stent, no other severe surgery-related complications were observed. The median follow-up was 37 months, with a 1-year portal vein patency rate of 90.6% and an overall stent patency rate of 81.3% during the entire follow-up period. Among patients with portal vein occlusion, 75% occurred within the first 2 years after the procedure. Compared to the balloon-assisted group, the snare-assisted group had shorter overall procedure time (155.2 ± 32.8 min vs 134.0 ± 34.5 min, $p = 0.015$) and fluoroscopy time (68.9 ± 19.3 min vs 59.4 ± 17.95 min, $p = 0.045$), but no statistically significant difference was observed in the incidence of splenic-related complications(9.7% vs 3.0%, $p = 0.347$).
Conclusion: Trans-splenic PVR-TIPS appears to be a safe and effective approach for managing portal vein obliteration, demonstrated by its high success rate, low incidence of surgical complications, and favorable long-term portal vein patency. Furthermore, the application of a snare-assisted technique during the procedure may help reduce both complications and radiation exposure.

WED-215-YI
Factors associated with clinical deterioration in patients with ascites that may be preventable by TIPS

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Background and aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment of cirrhotic patients with recurrent/refractory ascites. However, the benefit of TIPS may be more evident in patients with more preserved liver function, while poor liver function and refractory ascites reduced the disease-modifying effect. The aim of the current study was to identify risk factors for portal hypertension (PH)-related complications potentially preventable by TIPS occurring within 12 months in patients with cirrhosis who developed ascites as first decompensating event – to potentially prioritise them for TIPS.
Method: We included 451 patients from two tertiary care centres (Vienna and Padua) with ascites as single first decompensating event between 2003 and 2021 and who had no obvious contraindications for TIPS placement (age >75 years, heart failure, hepatic encephalopathy, hepatocellular carcinoma, MELD ≥20, bilirubin ≥5 mg/dL). Multivariable logistic regression analysis was used to identify variables independently associated with a composite endpoint of PH-associated complications (spontaneous bacterial peritonitis, refractory ascites, HRS-AKI, variceal bleeding), liver transplantation, or liver-related death – but excluding encephalopathy (that could be induced/aggravated by TIPS). Absolute risk was validated in a temporal validation cohort from Vienna (2021–2024, n = 84).
Results: Mean age in the derivation cohort was 56 ± 11years, 69% were male, and the most common aetiology of liver disease was alcohol-related (51.4%). While 252 (56%) presented with ascites grade 2, 199 (44%) presented with ascites grade 3. Median Child-Pugh-score was 8 (IQR: 7–9), and median MELD was 12 (IQR: 9–15). Within 12 months, 152 (34%) patients developed the composite endpoint. A model including ascites grade (odds ratio [OR]: 6.5 [95%CI, 4.12–10.41], p < 0.001), sodium (OR per mmol/L: 0.9 [95%CI, 0.85–0.95], p < 0.001) and MELD (OR per point: 1.1 [95%CI, 1.03–1.19], p = 0.007) predicted best the occurrence of the composite endpoint within 12 months (AUROC: 0.792 [95%CI: 0.748–0.836]). Applying a recursive partitioning classification tree, the following patients were selected with a high risk of PH-related complications potentially preventable by TIPS: ascites grade 3 with either sodium <135 mmol/L or MELD ≥12 points. These patients had an absolute risk of 64.3% (derivation cohort) and 68.9% (validation cohort) to develop the composite endpoint within the first 12 months.
Conclusion: Patients with first decompensation due to ascites grade 3 and either sodium <135 mmol/L or MELD ≥12 are at high risk for PH-related complications that can potentially be prevented by early TIPS placement without waiting for recurrent/refractory ascites. Prospective trials assessing the effectiveness of early TIPS placement in patients with 'high-risk' ascites index decompensation are encouraged.

WED-216
Inter-assay/inter-laboratory comparison of von Willebrand Factor antigen as diagnostic and prognostic biomarker in advanced chronic liver disease

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Background and aims: Von Willebrand factor antigen (VWF:Ag) is an inexpensive lab test that is broadly available in routine laboratories, primarily due to its role in the diagnosis of VWD, the most common bleeding disorder. Moreover, VWF:Ag is the most promising blood-based NIT for CSPH in compensated advanced chronic liver disease (cACLD) and a prognostic biomarker in ACLD. The VITRO score (ratio of VWF:Ag and platelet count) may replace elastography as a NIT for CSPH or reduce the diagnostic grey zone of the Baveno VII criteria. However, the vast majority of published results are based on the Stago VWF:Ag assay. To allow widespread clinical application, we performed a comparative study with the other commonly applied assays (i.e., Werfen & Siemens).
Method: We included citrate plasma samples from 404 ACLD patients undergoing HVPG measurement at the Medical University of Vienna. Frozen samples were provided to centres with expertise in haemostasis/coagulation tests applying different VWF:Ag assays (Stago/Groningen, Werfen/Padua, Siemens/Lausanne). Respective assays were compared and evaluated for diagnostic (CSPH) and prognostic utility in cACLD (endpoint: first hepatic decompensation). Based on previous findings, patients on statins were excluded (n = 51).
Results: 353 patients who predominantly had steatotic liver disease (55%) were studied. Median VWF:Ag levels were: Stago 282 (IQR: 195–358)%, Werfen 256 (IQR: 193–325)%, and Siemens 215 (IQR: 148–298)%, which translated into VITRO values of 2.75, 2.48, and 2.2. Stago and Werfen (intraclass correlation [ICC] 0.911; Pearson's r 0.914) as well as Siemens (ICC 0.921; Pearson's r 0.922) showed near perfect correlation. While the mean difference between Stago and Werfen was small (12.1 [IQR: 5.7–18.5]), there was a substantial difference when comparing Stago with Siemens (49.6 [IQR: 43.9–55.3]), indicating systematically lower values with the Siemens assay. Among 121 compensated patients, the CSPH prevalence was 72.7%. While all assays yielded comparable AUCs, the Stago VWF:Ag assay had the highest discriminative ability for CSPH (0.737; Werfen: 0.719; Siemens: 0.689). When applying VWF:Ag to calculate the VITRO score, all AUCs were >0.8 (Stago: 0.836; Werfen: 0.849; Siemens: 0.817). Using the previously established VITRO score cut-off ≥2.5 to rule-in CSPH, PPV was >90% with all assays, however, the Siemens assay ruled-in CSPH in a lower proportion of patients. Similar findings were observed when applying the Baveno VII-VITRO sequence. VWF:Ag assays as well as respective VITRO scores yielded similar prognostic abilities, with a time-dependent AUC of ~0.65 at 1 & 2 years.
Conclusion: VWF:Ag & VITRO score showed a robust diagnostic and prognostic performance in this inter-assay/inter-laboratory comparison study. The Stago and Werfen assays can be used interchangeably applying established cut-offs. Approaches to incorporate the systematically lower VWF:Ag values of the Siemens assay will be presented at the EASL Congress.

WED-221
Copeptin decrease after TIPS is linked to portal pressure and kidney function

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Background and aims: Arginine-vasopressin (AVP) and the renin-angiotensin-aldosterone system (RAAS) are upregulated in patients

with decompensated cirrhosis (DC). A transjugular intrahepatic portosystemic shunt (TIPS) effectively decreases portal pressure and may impact on AVP and RAAS. We thus investigated plasma levels of copeptin (an AVP biomarker), plasma renin concentration (PRC) and plasma aldosterone concentration (PAC) before and after TIPS implantation.

Method: We assessed copeptin levels in consecutive patients with DC (included in the prospective AUTIPS registry; NCT03409263) undergoing covered TIPS implantation at the Vienna General Hospital between 04/2018–11/2024. Copeptin, PRC and PAC were measured before (i.e., baseline [BL]), as well as 1 (M1), 3 (M3), 6 (M6), 9 (M9) and 12 (M12) months after TIPS implantation.

Results: 96 patients (67.7% male, median age: 57 years) with predominantly alcohol-related liver disease (58.3%) and median MELD of 11 (IQR 9–17) were included. The indication for TIPS implantation was ascites in 68 patients (70.8%) and variceal bleeding in 28 patients (29.2%). Median portal pressure gradient (PPG) was reduced from 18 (IQR 15–22) mmHg to 8 (IQR 6–10) mmHg after TIPS implantation. At BL, copeptin levels were elevated (>11.4 pmol/L) in 57.3% (n = 55/96) of patients. Median copeptin levels significantly decreased from BL to M1 (paired in n = 77; BL: 12.1 pmol/L to M1: 8.8 pmol/L; p < 0.001), while median sodium concentration increased (BL: 136.0 mmol/L to M1: 138.0 mmol/L; p < 0.001). In patients with available copeptin levels at all time points (n = 34), median levels of copeptin showed a significant and sustained decrease after TIPS (from BL: 11.5 pmol/L to M12: 6.9 pmol/L; p = 0.041). In contrast, median PRC (BL: 135.8 µIU/mL to M1: 127.2 µIU/mL; p = 0.366) and median PAC (BL: 219.9 pg/mL to M1: 266.0 pg/mL; p = 0.419) did not decrease after TIPS implantation. Consistently, there was also no decrease of PRC and PAC at later timepoints (PRC n = 34; from BL: 130.3 µIU/mL to M12: 100.1 µIU/mL; p = 0.131/PAC n = 35; from BL: 249.4 pg/mL to M12: 311.0 pg/mL; p = 0.142). In multivariate linear regression analysis (corrected for bilirubin, albumin, sodium and leukocyte count at M1), plasma copeptin at M1 after TIPS implantation was independently linked to post-TIPS PPG (aB: 1.00; 95% CI: 0.24–1.77; p < 0.001) and creatinine at M1 (aB: 16.03; 95% CI: 10.26–21.81; p < 0.001).

Conclusion: The decrease in copeptin, an AVP biomarker, is independently linked to severity of portal hypertension (PPG) and kidney function after TIPS and is associated with improved serum sodium levels. Decreasing AVP activation after TIPS indicates an ameliorated hemodynamic state in patients with DC.

WED-222

Clinical outcomes of cirrhotic patients undergoing balloon-occluded retrograde transvenous obliteration for prevention of gastric variceal rebleeding

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Background and aims: Balloon-occluded retrograde transvenous obliteration (BRTO) is an established treatment for managing gastric varices (GVs). This study evaluated the clinical outcomes of BRTO in preventing rebleeding from gastric varices in patients with cirrhosis.

Method: From May 2015 to May 2024, cirrhotic patients who underwent BRTO at our institution to prevent gastric variceal rebleeding were considered for inclusion. Clinical outcomes, including gastric variceal rebleeding, new or worsening ascites, aggravation of esophageal varices (EV), hepatic encephalopathy (HE), and overall mortality, were assessed using univariate and multivariate logistic regression and Cox proportional hazards models.

Results: A total of 234 patients were included in the analysis. The predominant type of GV was gastroesophageal varices type 2 (GOV2) (51.3%), followed by isolated gastric varices type 1(IGV1) (39.8%). 49.8%/38.0%/12.2% had Child–Turcotte–Pugh A/B/C cirrhosis, respectively, with a median MELD score of 10. During a median follow-up of 31.9 months, worsening of esophageal varices was observed in 38 patients (16.2%), while 29 patients (12.4%) developed new or worsening ascites. Variceal rebleeding occurred in 36 patients (15.4%) (bleeding from GV in 3 and EV in 33). A total of 71 patients died during follow-up. The 1-, 2-, and 3-year survival rates were 91.5%, 86.8%, and 77.3%, respectively. Multivariate Cox regression analysis identified age (HR, 1.045, 95% CI, 1.023–1.066; P < 0.001), Child-Pugh score (HR, 1.306, 95% CI, 1.152–1.481; P < 0.001), and adherence to non-selective beta-blockers (NSBB) (HR, 0.308, 95% CI, 0.132–0.720; P = 0.007) as independent predictors of mortality.

Conclusion: This study demonstrates that BRTO effectively prevents gastric variceal rebleeding, with favorable survival rates. Age, Child-Pugh score, and NSBB adherence are critical predictors of mortality.

WED-223

Colonization with multidrug resistant organisms is associated with poor outcomes in patients with decompensated cirrhosis of liver: a tertiary care center experience

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Background and aims: There is significant morality and morbidity associated with methicillin resistant Staphylococcus aureus (MRSA), carbapenem-resistant enterobacterales (CRE) and vancomycin resistant enterococcus (VRE) infections in patients with cirrhosis of liver. Colonization is associated with increased risk of infections in high risk patients including prolonged hospital stay and organ failures. However, there is limited data on effect of colonization with these organisms on outcomes in liver cirrhosis. We aimed to assess the effect of colonization with MDROs colonization on 28 day mortality in decompensated cirrhosis of liver.

Method: It was a retrospective data analysis done among admitted patients at a tertiary care center from February 2022–September 2024 in patients with decompensated cirrhosis of liver. Inclusion criteria were prior history of hospitalization in last 3 months, multiple co-morbidities, history of any surgeries in last 3 months, history of prolonged antibiotic use in the last 1 month, re-admission in the same hospital. Rectal swab to detect VRE & multi drug resistant organism (MRDO) colonization, CRE screening, nasal swab for MRSA colonization, and axilla and groin swab for candida auris were performed. Necessary contact precautions were taken for those patients positive and were categorized as colonizers.

Results: 240 patients with decompensated cirrhosis of liver were screened and 70 patients with mean age 48.42 ± 12.63 years were included. Mean CTP and MELD were 10.42 ± 2.56 and 21.86 ± 4.73 respectively. Alcohol {28/70 (40%)} was the most common etiology of liver cirrhosis followed by NASH {25/70 (35.7%)}. 37.1% (26/70) were colonizers and out of which 24.2% (17/70) were colonizers with more than one MDROs. MRSA colonization was seen in 14.2% (10/70) and VRE colonization 20% (14/70). The incidence of CRE colonization and candida auris positive screen was 21.4% (15/70) and 11.4% (8/70) respectively. Incidence of pneumonia was seen in {34.6%(9/26) vs 13.6% (6/44); p = 0.03}, urosepsis in {46.1%(12/26) vs 20.4%(9/44); p = 0.02 } in colonizers vs non-colonizers respectively. Mean days of hospitalization were {19.82 ± 5.63 vs 16.32 ± 4.98; p < 0.05}in colonizers vs non-colonizers respectively. 28-day mortality in colonizers was {76.9%(20/26) vs 50%(22/44); p = 0.02 } compared to non-colonizers.

Conclusion: Our study showed that colonization with MDRO is associated with increased incidence of pneumonia and urosepsis and a higher 28-day mortality. Rapid and prompt screening of colonizers is necessary for appropriate management and isolation practices in patients with cirrhosis of liver.

WED-224

The AMMON-OHE model predicts post-TIPS overt hepatic encephalopathy

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Background and aims: Overt hepatic encephalopathy (OHE) occurs in up to 50% of patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), and potentially with recurrent episodes. Due to its impact on health-related quality of life and survival, accurate OHE risk prediction models are needed to allow for adequate management and to ensure favorable outcomes after TIPS. The AMMON-OHE model, a machine learning model that includes 5 clinical and biochemical variables, was recently developed and validated to predict the risk of OHE in outpatients with cirrhosis. The aim of this study was to evaluate the utility of the AMMON-OHE model to predict post-TIPS OHE.
Method: This is an observational cohort study of cirrhosis patients undergoing TIPS in 3 liver units in Europe. The AMMON-OHE model was measured at the time of TIPS insertion and patients were followed-up until OHE development, liver transplant or death, whichever came first. Patients were stratified into low, medium and high-risk groups according to the previously defined AMMON-OHE cut-offs and cumulative OHE incidence curves were constructed. Risk group comparisons were performed using Gray's test. Cox regression models were fitted to study independent risk factors for OHE.
Results: A total of 355 patients were included, 70% males with a median age of 57 (IQR 13) years. The most frequent etiology of cirrhosis was alcohol (54%) and the most common indication for TIPS was ascites (68%) and variceal bleeding (21%). A total of 90 (25%) patients had a history of pre-TIPS OHE episodes and 59 (23%) were on lactulose and 50 (19%) on rifaximin at TIPS implantation. Mean portosystemic gradient before and after TIPS was 18 (5) and 7 (3) mmHg, respectively. During a median of 5.6 (IQR 14) months, 160 (45%) patients developed OHE. There were significant differences in the cumulative OHE incidence between risk groups ($p = 0.022$). At one year, 91 events were observed in the high-risk group with a cumulative incidence of 46% (95% CI: 0.39–0.53), 40 events in the medium-risk group with a cumulative incidence of 40% (95% CI: 0.30–0.49) and 8 events in the low-risk group with a cumulative incidence of 24% (95% CI: 0.08–0.37). Age, diabetes, history of pre-TIPS OHE, MELD, MELD Na, MELD 3.0, Child-Pugh, and creatinine were independently associated with a shorter time to OHE development (all $p < 0.05$).
Conclusion: OHE remains a frequent complication in cirrhosis patients undergoing TIPS. Risk stratification of patients according to the AMMON-OHE model yielded significant differences in the risk of and time to OHE development post TIPS. This novel model could be easily adopted in clinical practice for the selection of candidates who may benefit from intensified OHE prophylaxis.

WED-225

Risk factors of post-banding ulcer bleeding in patients with cirrhosis at a large tertiary center in Switzerland

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Background and aims: Esophageal variceal bleeding is a major complication of liver cirrhosis and portal hypertension, and is related with significant mortality (10–15% at six weeks). Endoscopic band ligation (EBL) is the reference standard procedure for preventing or managing acute variceal bleeding. Post-banding ulcer bleeding (PBUB), which occurs at the sites where ligation bands are placed, is an understudied complication of EBL. This single-center retrospective cohort study, conducted at the University Hospital of Bern (Switzerland) aimed to determine the incidence rate and mortality rates of PBUB; identify factors associated with PBUB; and evaluate strategies used to control PBUB.
Method: The study included patients with cirrhosis who underwent EBL between January 2018 and December 2022. The primary outcome was the overall bleeding secondary to post-banding ulcer (PBU) and risks factors of PBUB. The cumulative incidence of PBUB was visualized for relevant covariates. Associations were assessed using the Cox proportional hazards model with cluster-robust standard errors, first via univariate analysis and then in a multivariate model.
Results: 203 patients underwent 600 endoscopic band ligation procedures, and 900 endoscopies. The main etiologies of cirrhosis were alcohol-related liver disease (59%) and metabolic dysfunction-associated steatotic liver disease (28%). The incidence rate of PBUB was 19% when considering the total number of patients. Several factors were significantly associated with PBUB in the univariate analysis, including the presence of infection (HR 5.26 [1.82; 15.2], $p = 0.002$), high INR (HR 6.25 [2.65; 14.71], $p < 0.001$), anticoagulation therapy (HR 2.21 [1.06; 4.6], $p = 0.035$), and acute variceal bleeding with urgent EBL (HR 3.58 [1.88; 6.83], $p < 0.001$). Treatment with non-selective beta-blockers (HR 0.48 [0.25; 0.93], $p = 0.03$) and platelet count (HR 0.95 [0.89; 1.00], $p = 0.047$) were associated with a reduced risk of PBUB. In the multivariate analysis, only creatinine (HR 1.07 [1.03; 1.11], $p < 0.001$) and anticoagulation therapy (HR 2.47 [1.3; 4.68], $p = 0.006$) were identified as risk factors for PBUB. Treatment for PBUB and refractory ulcer bleeding included pharmacological therapy with proton pump inhibitors and vasoactive drugs. Endoscopic interventions varied and included endoscopic band ligation, hemoclips, hemospray, and self-expandable metallic stents; other interventions included transjugular intrahepatic portosystemic shunt and liver transplantation. The 28-day and 90-day mortality rates after EBL were 6.1% (95% CI 4%–8.1%) and 12% (95% CI 8.3–15.5%).

Conclusion: Although infection, high INR, and urgent EBL were associated with PBUB on univariate analysis, they did not remain significant in the multivariate model. Only renal impairment and anticoagulation therapy were identified as significant independent risk factors for PBUB. The management of this complication was heterogeneous, underlining need of standardization.

WED-226

Unveiling the economic burden of decompensated cirrhosis: a comprehensive cost analysis

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Background and aims: Decompensated cirrhosis has significant clinical and societal impacts, yet comprehensive data on the financial impact is lacking. This study provides in-depth assessment of costs, resource utilization, and outcomes for decompensated cirrhosis, including readmission analysis.
Method: We studied a tertiary-center, retrospective cohort of cirrhosis patients admitted with acute decompensation between October'18-February'21, with six-month follow-up data, extracted from electronic patient records, discharge summaries and clinic letters, capturing demographics, comorbidities, decompensation types and severity, intensive care unit (ICU) interventions, procedures, and outcomes. Follow-up data included readmissions, procedures, and outpatient visits. Costs were estimated using current, UK healthcare resource codes. Statistical analyses included descriptive statistics, multivariate linear regression, and Kaplan-Meier analysis.
Results: 387 patients were included (age 56.7 ± 13.4 years; 67% male); primary aetiology was alcohol (53%), followed by MASLD (11%) and viral hepatitis (10%). The median MELD-Na score at admission was 21, and Child-Pugh 10. Among 533 admissions, the most frequent decompensations were ascites (45%), variceal bleeding (27%), and hepatic encephalopathy (19%). The median length of stay (LOS) was 8 days. Key precipitating factors included alcohol (26%), infection (22%), and variceal bleeding (19%). Readmissions occurred in 100 patients; median time to first readmission of 27 days. Index admission mortality was 15%, increasing to 35% at 180 days. The total cost of inpatient care was £8.2M with a mean cost of £15,334 per admission. ICU stays accounted for £3.25M. Major costs included paracenteses (£1.3M), upper GI endoscopies (£723 K), and TIPS (£356 K). Albumin contributed notably, costing £161 K. Costs varied by decompensation type, with SBP admissions being the most expensive (£27,255/admission), followed by variceal bleeding (£19,838) and ascites (£13,615). Predictors of higher costs included longer LOS (2% increase /day, $p < 0.001$), multi-organ support (140% increase for 3 organs supported, $p < 0.001$), ICU admission (40% increase, $p = 0.014$), paracentesis (1 paracentesis increased costs by 14%, $p < 0.001$, while ≥ 5 led to a 75% increase, $p < 0.001$), TIPS (51% increase, $p < 0.001$), and 20% albumin (0.95% cost increase /100 g, $p < 0.001$). Total follow-up costs were £535 K, with consultant-led visits (£124,866), paracenteses (£121,854), and rifaximin (£120,435) as key contributors.
Conclusion: Cirrhosis acute decompensation imposes significant healthcare costs, especially ICU care, procedures, and albumin and rifaximin use. Mortality and readmission rates remain alarmingly high, underscoring the need for sustained post-discharge care strategies and early intervention, to optimize care and mitigate additional healthcare expenditure.

WED-227

Hormone dysregulation in young people with liver disease and portal hypertension: an unrecognised problem that requires attention

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Background and aims: Hormone dysregulation is described in adults with advanced liver disease but poorly explored in in adolescents and young adults (AYA). The aim of this study was to analyse the hormone profile of AYA with chronic liver disease (CLD) and portal hypertension and its relationship with clinical phenotype, blood tests and radiological features.
Method: Observational study in 72 AYA (22 M), median age 19 (IQR 17–23) years attending a young adult liver clinic. Hormone profiles including serum and urine steroid profile (USP) were analysed and the USP compared with an age and gender matched cohort of healthy controls (n = 67).
Results: 57 AYA had a diagnosis of CLD [20 M] with autoimmune liver disease [n = 24] and biliary atresia [n = 13] were most common; 15 [2 M] were diagnosed with extrahepatic portal vein obstruction (EHPVO). Platelet count $<150 \times 10^9$/l [PLT<150], in keeping with portal hypertension was present in 49 [68%]. Compared to healthy controls, 50% had an abnormal USP and more commonly observed in EHPVO [87%] vs CLD [40%, $p < 0.001$] and in PLT<150 vs PLT>150 group [61% vs 26%, p.005] with no gender difference. An abnormal compared to normal USP was characterised by higher serum bilirubin [23 [14–34] vs 11 [7–19] umol/l, $p < 0.001$], testosterone [4.6 [1.9–16.5] vs 1.2 [0.4–6.7] nmol/l, $p = .011$] and INR [1.1 [1.0–1.3] vs 1.0 [1.0–1.1], $p = .004$] and lower white cell [4.1 [3–5, vs 5.4 [4.0–6.8] $\times 10^9$/l, $p = .011$] and platelet [96 [67–127] vs 150 [89–244] $\times 10^9$/l, $p = .007$] count. The frequency of radiological features in CLD and EHPVO were liver nodules (70%), varices (69%), right lobe atrophy (65%), lieno-renal shunting (45%), umbilical vein patency (34%) and splenic artery aneurysms (20%). The presence of varices, lieno-renal shunting and right lobe atrophy was more common in EHPVO vs CLD [93% vs 62%, $p = .022$, 80% vs 36%, $p = .002$ and 87% vs 59%, $p = .020$ respectively], PLT<150 vs PLT>150 [87% vs 30%, $p < 0.001$, 60% vs 13%, $p < 0.001$, 79% vs 35%, $p < 0.001$ respectively] and abnormal vs normal USP profiles [86% vs 51%, $p = .002$, 64% vs 26%, $p = .001$, 78% vs 51%, $p = .020$ respectively]. Menstrual irregularities including irregular menses ± menorrhagia [n = 22,45%], amenorrhoea [n = 6,12%, primary n = 3] and polycystic ovary syndrome/premature pubarche [n = 7, 14%] were reported by 71% of females. Menstrual irregularities were associated with elevated serum testosterone levels [86% vs 50%, $p = 0.044$] and the presence of varices on imaging [86% vs 51%, $p = .047$]. Nine AYA [8F,1M] had undetectable testosterone levels [<0.4 nmol/l] whilst 11/20 males were had testosterone deficiency [Free androgen index <35]. This group was less likely to have PLT<150 but more likely to have patency of the umbilical vein on imaging when compared with AYA with normal/high testosterone levels.
Conclusion: Hormone dysregulation is prevalent in AYA with EHPVO and CLD and relates to features of portal hypertension and extrahepatic porto-systemic shunting.

WED-228

Frailty, malnutrition, and sarcopenia are prevalent among patients with liver disease and are associated with worse health-related quality of life and complications of cirrhosis

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Background and aims: Chronic liver disease (CLD) has high morbidity and clinical and nutritional complications that affect health-related quality of life (HRQoL). We aimed to quantify HRQoL in patients with CLD and correlate it with clinical and nutritional complications.
Method: Cross-sectional study, response to the Chronic Liver Disease Questionnaire (CLDQ) and nutritional assessment for sarcopenia (bioimpedance – BIA and arm muscle circumference – AMB), frailty (liver frailty index) and malnutrition (subjective global assessment – SGA and specific nutritional assessment for chronic liver disease – SNA-CLD). Statistical analysis used the Mann-Whitney, Kruskal-Wallis, and Chi-square tests.
Results: So far, 277 individuals were included (235 outpatients; 42 inpatients); the mean age was 55.7 ± 13.4 years, 52% women; 62.5% with liver cirrhosis (60% Child A; mean MELD Na 13 ± 5.5). Alcohol-related liver disease was the most prevalent in the total and in-hospital populations (28% and 43%, respectively), and metabolic dysfunction-associated steatotic liver disease among outpatients (29%). Outpatients and inpatients had CLDQ scores of 5.4 ± 1.2 and 4.6 ± 1.1, respectively; $p < 0.000$; the domains with the lowest scores were, respectively, fatigue (5.1 ± 1.7) and activities (4.5 ± 1.6) and worry (4.5 ± 1.7). Patients with more advanced cirrhosis had worse scores than those with Child A, MELD Na < 15, no portal hypertension (PH), and ascites: 4.7 ± 1.2 x. 5.6 ± 1.1 ($p = 0.006$); 4.8 ± 1.3 × 5.5 ± 1.1 ($p < 0.001$); 5.2 ± 1.2 × 5.6 ± 1.1 (p 0.01) and 4.9 ± 1.2 × 5.7 ± 1.1 ($p =$ 0.00), respectively. We detected frailty in 21% of the cases. Sarcopenia (by BIA and AMB) and malnutrition (by SGA and SNA-CLD) were detected in 24.6%, 13.9%, 46.2%, and 53% of cases, respectively. Cirrhosis, its complications, and the use of beta-blockers were associated with frailty ($p < 0.01$). Sarcopenia by AMB was associated with Child B/C, MELD Na ≥ 15, and ascites. More severe degrees of malnutrition by SNA-CLD and SGA were associated with cirrhosis, Child B/C, MELD Na ≥ 15, PH, ascites, and use of beta-blockers ($p <$ 0.001). The HRQoL scores in those with and without sarcopenia by AMB and BIA were 4.6 ± 1.3 × 5.4 ± 1.1 ($p < 0.001$) and 4.6 ± 1.3 × 5.5 ± 1.1 ($p < 0.001$), respectively. The frail and pre-frail groups had lower HRQoL scores when compared to the robust group of individuals: 4.6 ± 1.2 × 5.5 ± 1.1 × 5.6 ± 1.0 ($p < 0.001$). By SGA, severely malnourished patients had worse HRQoL when compared to those moderately malnourished and well-nourished: 4.7 ± 1.0 × 5.0 ± 1.3 × 5.0 ± 1.1 ($p <$ 0.001). According to SNA-CLD, the HRQoL worsened as the patients became increasingly malnourished ($p < 0.001$).
Conclusion: In this population, there was an association between the severity of liver disease (assessed by Child B/C, MELD Na ≥15, PH, and ascites), worse HRQoL, and a higher prevalence of frailty, malnutrition, and sarcopenia (AMB). These nutritional complications were also associated with worse HRQoL.

WED-229-YI

Prognostic performance of MELD 3.0 in patients undergoing transjugular intrahepatic portosystemic shunt placement - a retrospective multicentre study

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Background and aims: The MELD score was initially developed as a means of predicting mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) placement. In 2022, MELD 3.0 was introduced with the objective of improving mortality prediction in patients with liver cirrhosis. Despite having been validated in a number of cohorts, its prognostic value in patients undergoing TIPS remains elusive, particularly in Western cohorts. The objective of this study is to compare the accuracy of MELD 3.0 in predicting mortality with that of the established scores FIPS, MELD-Na and MELD.
Method: This retrospective multicentre study evaluated MELD 3.0 in two cohorts of patients with liver cirrhosis undergoing TIPS placement. Cohort 1 was derived from a single German tertiary hospital, while a multicentre validation cohort 2 included patients from seven German tertiary hospitals. The primary outcome measure was one-year mortality following TIPS placement. The prognostic performance of each score was evaluated using receiver operating characteristic (ROC) analysis and the concordance index (c-index). Furthermore, the c-indices were compared using DeLong's tests. In order to identify risk groups for TIPS placement in each cohort, patients were defined as belonging to a high-risk group if they were above the 85th percentile for each score, and as not belonging to a high-risk group if they were below the 85th percentile. Subsequently, one-year mortality was assessed using log-rank tests and Kaplan-Meier survival curves.
Results: A total of 1828 patients were included in the study (cohort 1: n = 412, cohort 2: n = 1416). The primary indication for TIPS placement in both cohorts was refractory ascites. In cohort 1, the ROC analysis demonstrated a c-index for one-year mortality of 0.701 (MELD 3.0), 0.704 (FIPS), 0.712 (MELD-Na), and 0.670 (MELD). In cohort 2, the corresponding c-indices were 0.633 (MELD 3.0), 0.670 (FIPS), 0.626 (MELD-Na) and 0.629 (MELD). DeLonǵs test revealed no statistically significant differences between MELD 3.0 and the other scores in cohort 1. However, in cohort 2, MELD 3.0 demonstrated superior performance in comparison to MELD-Na ($p = 0.0475$), while FIPS demonstrated superior performance in comparison to MELD 3.0 ($p = 0.0033$). The log-rank tests demonstrated that each high-risk group showed a significantly higher one-year mortality compared to the respective non-high-risk group ($p < 0.05$), with the exception of the patients in cohort 1 stratified by MELD ($p = 0.063$).
Conclusion: The findings of this study indicated that MELD 3.0 demonstrated comparable prognostic accuracy to MELD and MELD-Na in predicting one-year mortality in patients undergoing TIPS placement at high-volume tertiary centres. However, the results also suggested that FIPS might perform slightly better.

WED-230-YI

A novel MELD-copeptin score accurately predicts ACLF and liver-related death in patients with decompensated cirrhosis

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Background and aims: Copeptin, a biomarker for arginine-vasopressin (AVP) activation may improve prognostication in patients with decompensated cirrhosis (DC). We aimed to develop and validate a novel MELD-copeptin score for the prediction of liver-related events in DC patients.
Method: Copeptin levels were determined in consecutive patients with DC undergoing hepatic venous pressure gradient (HVPG) measurement at the Vienna Hepatic Hemodynamic Lab. According to inclusion time period, patients were subdivided into a derivation cohort (01/2017–12/2019; n = 150) and an internal validation cohort (12/2019–04/2023; n = 148). The results were validated in an external cohort including hospitalized patients with DC from Besancon (04/2008–06/2009; n = 125) and patients with acute decompensation (AD) included in the CANONIC study (03/2011–12/2011; n = 646). The MELD-copeptin score was developed with coefficients derived from a competing risk regression model for the prediction of acute-on-chronic liver failure (ACLF) and of liver-related death. Liver transplantation was considered as a competing event. The prognostic utility of copeptin for ACLF and liver-related death (LRD) was investigated by calculating time-dependent areas under the receiver-operating characteristic curve (AUROCs).
Results: The multivariate competing risk regression model revealed copeptin (asHR: 1.45; 95%CI: 1–09–1.93; p = 0.011) and MELD-Na (asHR: 1.07; 95%CI: 1.01–1.13; p = 0.028) as independent risk factors for LRD in the derivation cohort. With these coefficients, the following score was created:.
MELD-copeptin = 0.0637 * MELD-Na + 0.3718 * log (copeptin [pmol/L]). In the internal validation cohort, the MELD-copeptin score showed excellent accuracy for the prediction of LRD at 6 months (AUROC 0.777) and 1 year (AUROC 0.784) of follow-up, while the MELD-Na yielded lower AUROCs (6 months: 0.673; 1 year: 0.661). Similarly, in the external validation cohort, the MELD-copeptin score consistently provided higher AUROCs for the prediction of ACLF (6 months: 0.803 vs. 0.726; 1 year: 0.827 vs. 0.755) and LRD (6 months: 0.765 vs. 0.748; 1 year: 0.761 vs. 0.747) compared to MELD-Na.
Conclusion: The developed and validated MELD-copeptin score shows excellent accuracy for the prediction of ACLF and LRD in patients with DC and refines prognostication as compared to MELD-Na.

WED-231
Ultrasound muscular thickness-based model to identify sarcopenia in patients with portal hypertension (PH): a cross-sectional single-center observational study

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Background and aims: Sarcopenia is a frequent complication of cirrhosis (40–70%) and is an independent prognostic factor of worse outcome. Currently, CT scan is the gold standard to identify this condition, but new user friendly and reliable non-invasive screening tools are needed.
Method: This single center prospective study includes consecutive outpatients with portal hypertension and abdominal CT who underwent US assessment of biceps brachii (BB), rectus abdominis (RA), rectus femoris (RF) and thigh muscle (TM), performed by two blinded trained investigators. The sum of both-side muscle thickness was adjusted for height obtaining an index (mm/m). Sarcopenia was defined using CT by L3-SMI cut-offs prosed by EASL/AASLD. Association between sarcopenia and US parameters, anthropometric, clinical, biochemical and nutritional data was assessed.
Results: 103 patients were enrolled (median age 61 ys, 63% men, 84% cirrhotic, median BMI 25,7 kg/m^2). Prevalence of sarcopenia was high among both cirrhotic and non-cirrhotic portal hypertension patients (54.1% vs 61.5%, p = ns), without statistically significant difference between women and men.
Among US measurements and anthropometric data, RF index and BMI showed the best inverse-correlation with sarcopenia with an OR of 0.79 (95% CI: 0.69–0.91, p < 0.01) and 0.80 (95% CI: 0.63–0.91, p < 0.01), respectively. Based on these findings, a gender specific integrated model to identify sarcopenia was proposed with best results among cirrhotic men and women overall where BMI threshold of 28 and 23.9 kg/m^2 and RF index of 14.8 and 13.4 mm/m showed the highest positive (73% and 78%) and negative (81% and 74%) predictive value, with a ROC of 0.81 and 0.80 respectively. Moreover, US muscular measurements showed high intra/inter-operator reliability.
Conclusion: US can be a bedside, non-invasive and reproducible tool to assess muscle thickness with a good capability in a model with BMI to discriminate patients with sarcopenia.

WED-232
Assessing portal hypertension with endoscopic ultrasound portal pressure gradient (eus-ppg): clinical correlations and procedural outcomes

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Background and aims: Portal hypertension (PH) is a critical complication in chronic liver diseases, notably cirrhosis, and often precedes severe outcomes. Recent advancements have introduced endoscopic ultrasound-guided PPG (EUS-PPG) as a method for directly measuring the portal pressure gradient, potentially overcoming the limitations of traditional indirect measures like the hepatic venous pressure gradient (HVPG). This prospective study aims to evaluate the technical success, safety, and correlation of EUS-PPG with clinical and laboratory indicators of portal hypertension.

Method: The study involved a cohort of patients with suspected or confirmed PH who underwent EUS-PPG using a linear echoendoscope, a 25G fine needle aspiration needle, and a compact manometer with non-compressible tubing. All procedures were performed by the same operator under conscious sedation. For each patient, at least three measurements were taken in the portal vein and three in the hepatic vein or retrohepatic inferior vena cava, with the gradient calculated as the difference between the means of these measurements. Clinical and laboratory data were collected for each patient to assess potential correlations with EUS-PPG values.
Results: A total of 32 patients underwent EUS-PPG. Descriptive analysis of demographic, clinical, and laboratory characteristics, as well as procedural details, is provided in supplemental data. Technical success was achieved in 100% of cases, with only minor complications (9%), such as mild post-procedural abdominal pain. For statistical analysis, a Student's t-test was conducted to compare PPG values between patients with a low probability versus a high probability of PH (defined as the presence of one specific sign of PH or, in its absence, at least two non-specific signs of PH). Results showed significantly higher PPG values in the high-probability group (p 0.0011). Spearman's correlation analysis was performed to evaluate the association between EUS-PPG values and portal hypertension severity, defined as the sum of specific and non-specific signs of PH. This analysis revealed a positive correlation, with an increase in PPG associated with greater PH severity (Spearman's p = 0.6283, p = 0.0003). Similarly, Spearman's correlation was used to assess the relationship between EUS-PPG values and platelet count, liver stiffness, and spleen stiffness. An inverse correlation was observed between PPG and platelet count (p = –0.5323, p = 0.0030), while positive correlations were found with liver stiffness (p = 0.6320, p = 0.0028) and spleen stiffness (p = 0.5812, p = 0.0231).
Conclusion: EUS-PPG demonstrated high technical success and safety in evaluating PH, with meaningful correlations between PPG values and clinical and laboratory indicators of PH severity. These findings support the potential of EUS-PPG as a valuable tool in the direct assessment of portal hypertension, warranting further studies to confirm its clinical applicability.

WED-237
Development and validation of a novel fibrosis digital pathology biomarker to predict portal pressure in patients with MASH cirrhosis

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Background and aims: Primary outcomes in MASH cirrhosis trials include hepatic venous pressure gradient (HVPG), liver histology, and clinical events. Current histologic methods to evaluate liver fibrosis have significant limitations and few data are available regarding their correlation with portal pressure. Using Artificial Intelligence, we report on the development and validation of a continuous fibrosis Digital Pathology score for the prediction of HVPG in patients with compensated MASH cirrhosis and portal hypertension (PH).
Method: The study is based on 164 patients from a belapectin Phase 2 study (NCT 04365868). Patients with PH (HVPG >6 mm Hg) had paired measurements of HVPG and liver histology one year apart. 103 patients had clinically significant PH (HVPG>10 mmHg). Fibrosis was evaluated from Masson's Trichrome stained biopsies scanned at 40X. Quantitative image analysis (FibroNest™) was performed to extract single-fiber quantitative traits (qFTs, N = 336) from the fibrosis composition, morphometric and architectural histological phenotypes. The qFT dataset was mined to identify qFTs that would exhibit a significant (p < 0.05) and meaningful (>20%) relative difference (group average) between a subgroup of 60 patients (training set) with low (4.5–7 mmHg, n = 30) and high HVPG (17.5–23 mmHg, n = 30). Such qFT are assembled into a normalized (0–10 range) fibrosis-based HVPG predictive composite score (HVPG-PS) Composite Score (PBC-FCS). The performance of the HVPG-PCS was then evaluated on 302 images.
Results: From the training dataset, the HVPG-PCS achieved an AUROC of 0.88 to predict Severe HVPG, with a Youden's Index of 0.633 for a HVPG-PCS cutoff score of 4.2. Validation against the entire cohort (n = 302) reduced the AUROC to 0.649 and Youden's Index to 0.244. However, distinguishing low HVPG (<7.5 mmHg, n = 53) from high HVPG (>15.5 mmHg, n = 73) improved the AUROC to 0.754 with a Sensitivity or True Positive Rate (resp. Specify, True Negative rate) of 69% (resp. 56%) for a cutoff of 4.2.
Conclusion: In patients with MASH cirrhosis and PH, our digital pathology AI method exhibits a moderate performance to predict PH but could potentially discriminate between patients with low or very high HVPG.

WED-238
ANT at discharge can predicts further development of overt hepatic encephalopathy after elective TIPS placement

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Background and aims: Overt hepatic encephalopathy (OHE) is the most feared complication after transjugular intrahepatic portosystemic (TIPS) placement. Accurate tools for the prediction of OHE after TIPS are still missing. Minimal HE is a risk factor for OHE, and can be screened thanks to the animal naming test (ANT). One previously published study suggested that ANT, evaluated before TIPS and at different time points after TIPS, had limited predictive value for predicting OHE after TIPS. We aimed to validate this result in an independent cohort of patients.
Method: We prospectively screened patients that were candidates for elective TIPS placement. ANT (1 minute) was evaluated on the day of TIPS placement, at discharge, and then at 1, 3 and 6 months after TIPS.
Results: 88 consecutive patients were included (men 81.8%, age 60 years, cause of cirrhosis MASH/ALD/MetALD/other in 15/41/24/20%, MELD score 11.8, Child-Pugh B/C in 76/6%, TIPS indication ascites/secondary prophylaxis/pre surgery in 62/19/14%, previous OHE in 21.6%, lactulose in 35.2%, rifaximin in 69.3%). Median ANT was 20 (16–25) and 41/88 (46.4%) of patients had a score <20. A poor negative correlation was found between MELD score and ANT before TIPS (ρ = –0.22; r2 = 0.024; p = 0.04). During follow-up, ANT was not statistically modified, neither at discharge, nor at 1, 3 or 6 months. Overall, 29/88 (32.9%) patients developed OHE in a mean delay of 54 days. In multivariate analysis, independent factors associated with further development of OHE were age (HR = 1.04, 95% CI [1; 1.09], p = 0.04), baseline ammonia (HR = 1.01, 95% CI [1; 1.02], p = 0.003), and ANT at discharge (HR = 0.86, 95% CI [0.79; 0.95], p = 0.001), but not ANT before TIPS (HR = 0.95, 95% CI[0.95; 1.01], p = 0.10).
Conclusion: We confirmed that pre-TIPS ANT was not predictive of further OHE in our series of patients treated with elective TIPS. However, ANT at discharge may be useful to early identify patients at higher risk of OHE after TIPS, in whom prophylaxis could be intensified and liver transplantation discussed.

WED-239
Prognostic performance of MELD variants and CLIF-C AD in 958 patients with cirrhosis and ascites

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Background and aims: MELD scores and CLIF-C AD are used to predict mortality in cirrhosis. While MELD scores primarily reflect liver disease severity, CLIF-C AD derived in hospitalized patients also incorporate white blood cells (WBC) as a marker of systemic inflammation. The relative accuracy of these scores in predicting 3-month and 6-month mortality following first hepatic decompensation remains unclear. We aimed to compare the prognostic performance of baseline and longitudinal MELD, MELD-Na, MELD 3.0 and CLIF-C AD in cirrhosis patients with index decompensation by ascites.
Method: We collected data from four centers in Austria, Italy and Denmark between 2003 and 2024. Patients were enrolled if they presented with overt ascites (grade 2 or 3) as their single index decompensation. From baseline through first 6 months, we longitudinally assessed up to 6,896 laboratory data points. Follow-up included data on further decompensation, ACLF, liver transplantation (LT) and death. Predictive performance at 3- and 6-months was assessed using baseline and longitudinal Cox regression models, adjusting for age, sex, ascites grade and etiological cure. Discrimination was evaluated by Harrell's C.
Results: A total of 958 patients (mean age 57 ± 12 years; 66% men; 56% alcohol-related cirrhosis) were included with 47% and 53% presenting with grade 2 and 3 ascites, respectively. Baseline median MELD was 14 (IQR: 11–18), MELD-Na 15 (IQR: 11–20), MELD 3.0 16 (IQR: 12–20) and CLIF-C AD 52 (IQR: 46–57). Mortality and LT rates were 5%/1% at 3 months and 10%/2% at 6 months. Baseline models predicted 3-month mortality ($p < 0.001$), with Harrell's C-statistic of 0.741 (MELD), 0.735 (MELD-Na), 0.760 (MELD 3.0), and 0.765 (CLIF-C AD). Similarly, models reflected 6-month mortality ($p < 0.001$) but with lower discrimination (C-statistic: 0.707–0.735). Considering longitudinal changes of these models improved the discriminative ability for 3-month and 6-month mortality, being highest for CLIF-C AD (3/6 months: 0.834/0.810). In landmark analyses including 3-month laboratory value dynamics, prognostic prediction from landmark to 6-month follow-up improved for MELD scores (C-statistic: 0.736/0.747/0.755 for MELD/MELD-Na/MELD 3.0) but not CLIF-C AD (C-statistic: 0.703). Systemic inflammation marker CRP predicted 3-month mortality (aHR = 1.063, 95% CI: 1.011–1.117, $p = 0.016$), independently of baseline MELD 3.0, age, sex, ascites grade and etiological cure. In contrast, WBC did not ($p = 0.109$). A model combining dynamics of MELD 3.0 and CRP showed the best prediction of 3-month mortality (C-statistic: 0.830).
Conclusion: MELD scores and CLIF-C AD exhibit comparable discrimination of 3-month and 6-month mortality in patients with cirrhosis and an index decompensation of ascites. Longitudinal evaluation of models provides better discrimination, suggesting improved prediction by monitoring model dynamics over time. Incorporation of systemic inflammation markers, such as CRP, into future MELD variants may enhance prediction.

WED-240

External validation of prognostic scores for post-TIPS mortality in a contemporary, australian cohort

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Background and aims: Post-Transjugular Intrahepatic Portosystemic Shunt (TIPS) mortality remains a critical concern, necessitating accurate prognostic tools. Established scoring systems such as MELD and MELD-Na, and newer models such as the Modified TIPS-Score (MOTS) and Freiburg index of post-TIPS survival (FIPS) score have shown potential in refining risk stratification. Given the evolving trends in cirrhosis aetiologies in recent years, these models require ongoing validation in new cohorts. The aim of this study was to externally validate existing tools in predicting 30- and 90-day mortality after TIPS.
Method: This retrospective study conducted at Austin Hospital, Victoria, Australia included 117 patients undergoing TIPS procedures with at least 90-days follow-up. Prognostic scores were calculated using pre-TIPS clinical and laboratory data. Discriminative performance was assessed using Area Under the Receiver Operating Characteristic Curve (AUC). Prognostic accuracy was assessed at established cut-offs for MELD ≥18, MELD-Na ≥20, MOTS >1, FIPS ≥0.92.
Results: Indications for TIPS included ascites and/or hepatic hydrothorax (n = 66, 56.4%), variceal haemorrhage (n = 40, 34.2%), Budd-Chiari syndrome (n = 7, 6.0%) and other (n = 4, 3.4%). A total of 13 (11.1%) and 21 patients (18.0%) had died by 30- and 90- days, respectively. MELD displayed the best discriminative performance for 30-day mortality (AUC = 0.82), followed by MOTS (0.80), FIPS (0.76) and MELD-Na (0.73). MELD was also the best discriminator for 90-day mortality (AUC = 0.77), followed by FIPS (0.76), MOTS (0.75) and MELD-Na (0.69). With respect to prognostic accuracy for 30- and 90-day mortality, FIPS ≥ 0.92 had excellent specificities (94 and 95%, respectively) and negative predictive values (94% and 88%, respectively). These values were slightly better than those for MOTS, and marginally better still for MELD. MELD-Na performed worst. All scoring tools performed moderate-to-poorly with respect to sensitivity and positive predictive value at these thresholds. Kaplan-Meier curves revealed significant survival differences between groups stratified by the established cut-offs for each scoring tool.
Conclusion: Traditional scoring tools such as the MELD, and the newer MOTS and FIPS, demonstrate robust discriminative performance for 30- and 90-day mortality prediction, and consistently outperform MELD-Na. Further research is required to establish the optimal risk thresholds for these tools and support these findings.

WED-241

Changes in spleen stiffness as assessed via vibration-controlled transient elastography at 100 Hz reflect acute hepatic venous pressure gradient response to i.v. propranolol: a european multicenter study

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Background and aims: Acute hepatic venous pressure gradient (HVPG) response to i.v. propranolol is a predictive (potential treatment benefit) and well-established prognostic (direct endpoints) biomarker in patients with cirrhosis and clinically significant portal hypertension (CSPH). While LSM by vibration-controlled transient elastography is incapable of monitoring non-selective beta blocker (NSBB)-induced changes in HVPG, SSM by repurposing the 50 Hz LSM probe has shown promising data. However, this technique was limited by a high technical failure rate, which is overcome by SSM at 100 Hz (SSM-100 Hz). This Baveno Cooperation study aimed at investigating the value of SSM-100 Hz for the non-invasive diagnosis of acute HVPG-responders to i.v. propranolol.
Method: Patients who underwent paired HVPG and SSM-100 Hz measurements pre/post i.v. propranolol application at one of the three contributing expert centers between 2019 and 2024 were included into this cohort study. HVPG-response was defined as ≥10%-decrease in HVPG upon propranolol infusion (0.15 mg/kg body weight).
Results: A total of 94 patients (63.8% males, 36.2% females, mean age: 56.5 ± 12.6 years, BMI: 29.1 ± 22.8) were included. Most patients had ALD/metALD (59.6%) or MASLD (11.7%). Varices were present in 58.5% of patients, and 54.3% had already developed decompensated cirrhosis (ascites present in n = 40 patients). The mean HVPG was 17.4 ± 4.1 mmHg before and 15.7 ± 4.2 mmHg after NSBB administration. There was a mean decrease of 1.7 ± 1.7 mmHg (paired t-test: $p < 0.001$), and 43 (45.7%) patients achieved HVPG-response. Meanwhile, SSM decreased by 10.5 ± 19.2 kPa ($p < 0.001$), which corresponds to a relative decrease of 12.6 ± 25.6%. HVPG-responders showed a mean decrease in SSM of 16.6 ± 16.4 kPa ($p < 0.001$), while in HVPG-nonresponders, no significant change in SSM was noted upon i.v. propranolol (mean decrease: 5.4 ± 20.0 kPa, $p = 0.060$). The between-group difference in relative SSM change attained statistical significance (HVPG-responders: – 22.8 ± 18.7% vs. HVPG-nonresponders: –4.0 ± 27.6%, unpaired t-test: $p < 0.001$). Individual relative changes in SSM and HVPG showed a moderate correlation (Pearson's ρ: 0.345, $p < 0.001$). SSM yielded an area under the receiver operating characteristics curve (AUC) of 0.717 (95% CI: 0.614–0.820, $p < 0.001$) for HVPG-response.
Conclusion: Our multicenter study indicates that dynamics in SSM-100 Hz upon i.v. propranolol administration reflect those of HVPG. Thus, SSM-100 Hz may be used a non-invasive surrogate for the HVPG-lowering effect of medical therapies, which has important implications for clinical drug development.

WED-242
The Impact of lactulose on the gut microbiome and barrier function in patients with decompensated cirrhosis

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Background and aims: Lactulose reverses and prevents HE but its precise mechanism of action remains uncertain. We hypothesize that lactulose increases abundance of beneficial gut bacteria, increases butyrate production, and thus improves gut barrier function. Therefore, we evaluated the impact of lactulose on gut microbiome composition, function, and intestinal permeability in patients at risk of HE.
Method: We enrolled consecutive patients with Childs Pugh Class B or C cirrhosis presenting for outpatient upper endoscopy, excluding patients with recent non-rifaximin antibiotic use or alcohol use. We obtained duodenal tissue biopsies, stool samples, and dietary recalls. Composition of the duodenal mucosal and stool microbiota was determined via 16S rRNA sequencing. Stool butyrate was measured via liquid chromatography. Epithelial permeability was assessed by transepithelial electrical resistance (TEER). Analysis of molecular variance (AMOVA) of Yue and Clayton dissimilarity index compared microbiota community structure between groups. Wilcoxon rank sum tests compared continuous variables between groups.
Results: We enrolled 47 patients, aged 60 (IQR 49, 69) years, 27 (57%) male, 19 (40%) MASLD and 26 (55%) alcohol-related cirrhosis, Child Pugh score 9 (IQR 8,10) and MELD 14 (IQR 11, 16). 24 (51%) had a history of overt HE. 12 patients were on lactulose alone, 18 on lactulose and rifaximin, 2 on rifaximin alone, and 15 on neither. Patients in the 3 largest treatment groups (lactulose alone, lactulose and rifaximin, and neither) had distinct stool microbiomes (3-way AMOVA, $P < 0.001$; each two-way comparison $P < 0.01$), as well as distinct duodenal microbiomes (3-way AMOVA, $P = 0.02$). In LEfSe analysis, 33 stool taxa and 6 duodenal mucosal taxa differed significantly between the 3 treatment groups. Patients on lactulose had higher fecal abundance of *Bifidobacterium* (known butyrate producer).
Stool butyrate concentration was greater in patients on lactulose (± rifaximin) than in patients on no HE medications (11 nmol/mg [IQR 6, 17] vs. 5 [IQR 3, 11], $P = 0.03$). Stool butyrate concentration was numerically greater in the sub-group on lactulose alone than the patients on no HE medications (12 nmol/mg [IQR 11,15] vs. 5 [IQR 3, 11], $P = 0.14$). Duodenal TEER was greater (less permeable) in patients on lactulose alone (21 Ω/cm^2 [IQR 15, 24]) compared to patients on neither HE medication (16 Ω/cm^2 [IQR 12, 20], $P = 0.28$). In logistic regression, total dietary fiber did not account for increased *Bifidobacterium*, stool butyrate, or duodenal TEER in the lactulose group.
Conclusion: In patients with decompensated cirrhosis, lactulose was associated with a distinct mucosal and stool microbiome, separate from rifaximin's influence. Lactulose was associated with greater *Bifidobacteria* abundance, higher stool butyrate and a trend towards less intestinal permeability (higher TEER). This work suggests a possible under-explored mechanism of action of lactulose and warrants further evaluation.

WED-243
Association between body mass index and adverse outcomes in patients with compensated cirrhosis

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Background and aims: The relationship between an elevated BMI in cirrhotic patients and decompensating events remains controversial and requires further investigation. Here, we evaluated the association between BMI levels and the risk of developing esophageal varices, ascites, or variceal bleeding.
Method: We conducted a retrospective cohort analysis, using TriNetX's large administrative dataset including 115,676,318 patients from 66 US healthcare organizations. We examined patients ≥18 years old, with compensated cirrhosis, but without a prior history of esophageal varices or ascites. Based on BMI range, patients were classified into four BMI categories (normal (BMI 18.5–25), overweight (BMI 25–30), grade 1 obesity (BMI 30–35), grade 2–3 obesity (BMI ≥35)). Patients were matched only for age and sex. The development of esophageal varices, ascites, and variceal bleeding was compared across the different groups, using the normal BMI group as a reference. The international Classification of diseases ninth/tenth version (ICD-9/ICD-10) codes were used to identify patients with cirrhosis (ICD-10: K74; K74.6; K70.3) and associated portal hypertensive complications (ICD-10: R18; K76.82; I85.11, I85.01). TriNetX Analytics Platform built-in functions (R, version 4.0) were used for data analysis, including propensity score matching, HR's and 95% CI's.
Results: A total of 423,536 patients with compensated cirrhosis were identified, including 129,804 with normal weight, 169,024 overweight patients, 146,545 with grade 1 obesity, and 111,389 with grade 2–3 obesity. After propensity score matching, the cohorts were comparable in age and gender distribution (mean [SD] age, 59 [13] years old; 41% women). The likelihood of having metabolic syndrome

abnormalities increased in proportion to the severity of increase in BMI. Additionally, the likelihood of developing MASH increased concomitantly with BMI. There were no differences in AST, ALT, total bilirubin, or INR in the different weight groups. The risk of developing a portal hypertension related cirrhosis decompensating event (esophageal varices, ascites, or variceal bleeding) and the risk of all-cause mortality increased in patients with a BMI≥ 25 and those with grade 1 obesity ($P < 0.05$). However, they all decreased slightly in patients with grade 2–3 obesity.
Conclusion: There appears to be a direct relationship between BMI and the risk of developing decompensating events in patients who are overweight and have grade 1 obesity. However, the increase in risk appears to be small (though significant), and peaks at the grade 1 obesity level.

WED-244
Evaluation of the Baveno VII criteria for predicting liver-related events in patients with advanced chronic liver disease – a single centre retrospective study
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Background and aims: Patients with advanced chronic liver disease (ACLD) are at risk of complications of decompensation, primarily related to clinically significant portal hypertension (CSPH). The Baveno VII guidelines proposed criteria using transient elastography (TE) and platelet count (plts) to assist in the diagnosis and prognostication of patients with compensated ACLD (cACLD) at higher risk. The aim of this study was to evaluate the Baveno VII criteria in identifying patients at risk and predicting subsequent liver-related outcomes in a retrospective analysis.
Method: Adult patients undergoing TE in a single tertiary centre for chronic liver disease were retrospectively reviewed. Demographic data, baseline and follow up liver stiffness measurements (LSM), and clinical and laboratory parameters within 3 months of LSMs were collected. Patients were categorised using the Baveno VII 'rule of 5s' as follows: LSM <10 kPa (stage 1 – cACLD excluded), LSM between 10 and 15 kPa with plts $<150 \times 10^9$/L (stage 2 – possible CSPH), LSM between 15 and 20 kPa with plts $<110 \times 10^9$/L (stage 3 – assumed cACLD), LSM between 20 and 25 kPa with plts $<150 \times 10^9$/L (stage 4 – assumed cACLD), and LSM >25 kPa (stage 5 – definitive cACLD). Liver-related events (LREs) including hospital admissions for decompensation with ascites, hepatic encephalopathy or variceal bleeding were recorded. Patients were excluded for suboptimal TE quality (success rate <60%, interquartile range/median ratio >0.3), if incomplete associated clinical/laboratory data or if <18 months of documented follow up.
Results: 1035 patients with chronic liver disease who underwent TE were analysed. The mean age was 49.7 years and 45.1% were female. The most common aetiologies were hepatitis B (53%), hepatitis C (25.1%), metabolic dysfunction-associated steatotic liver disease (21.2%) and alcohol-related liver disease (10.1%). The median LSM at baseline was 5.6 kPa; 75.6% of patients were in stage 1, 10.9% in stage 2, 3.7% in stage 3, 3.0% in stage 4 and 6.9% in stage 5. During follow up, 95 patients developed LREs and the optimal LSM cut-off to predict LREs was 16.4 kPa (AUROC = 0.82). There was a stepwise increase in odds ratio (OR) for developing LREs with each Baveno VII stage progression (comparing to stage 1, stage 2 OR 5.5, stage 3 OR 8.0, stage 4 OR 20.2, stage 5 OR 88.6; $p < 0.001$). The Baveno VII criteria demonstrated utility in both excluding patients at low risk (stage 1 cACLD and those not meeting stage 2 criteria; sensitivity = 90.9%, specificity = 76.3%) and identifying patients at risk of LREs (stages 2–5 cACLD: sensitivity = 81.1%, specificity = 81.3%).
Conclusion: The Baveno VII criteria using non-invasive tools demonstrated excellent utility in risk stratification for patients with cACLD. Further study will aim to validate these findings and determine the application of this model to guide patient management and improve outcomes.

WED-245
Personalized biomarkers scores outperform established scores in the short- and long-term prediction of hepatocellular carcinoma and decompensation
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Background and aims: Predicting the two main complications of compensated advanced chronic liver disease (cACLD) – hepatocellular carcinoma (HCC) and decompensation - is crucial for improving prognosis. We tested various combinations of serum biomarkers to predict HCC and decompensation at 5- and 10-year in a cohort of cACLD patients, of any etiology and compared the results to the established GALAD, aMAP, and EPOD scores.
Method: From 2011 to 2018, we prospectively recruited 545 patients with cACLD. At enrollment, we analyzed 28 serum biomarkers related to inflammation, immunity, metabolism, coagulation, and angiogenesis (Ella ELISA,Bio-Techne). Based on the most effective combinations in the Cox models, we developed personalized biomarker scores (BioMscores) tailored for each condition and specific subgroups categorized by sex and etiology (viral, MAFLD/MASH, alcohol). Additionally, we calculated GALAD, aMAP, and EPOD scores and assessed their predictive capability for HCC and decompensation, versus the BioMscores using Cox proportional hazard regression models and the AUROC method.
Results: Patients were followed for a median of 3.60 and 5.58 years at 5 and 10 years, respectively. We observed 92 incident HCC cases (16.9%). For the entire HCC cohort, a combination of 9 biomarkers linked to inflammation, IGF-1 transport and uptake, and cellular response to hypoxia outperformed GALAD and aMAP (BioMscore HR 4.700, $p < 0.001$; GALAD: HR 1.307, $p < 0.001$; aMAP HR 0.997, p = NS). Notably, BioMscores differed significantly between subgroups, with males and MAFLD/MASH patients showing more inflammation, and females showing more hypoxia-linked biomarkers. GALAD and aMAP did not havepredictive ability in MAFLD/MASH, while BioMscore did (HR1.929, $p < 0.001$). For decompensation, BioMscores revealed inflammation- and angiogenesis-linked biomarkers in all subgroups except females, who lacked inflammatory biomarkers. BioMscore for the entire group had the same predictive ability as EPOD but greatly outperformed it in males, females, and etiology subgroups. EPOD failed to predict decompensation in MAFLD/MASH, while BioMscore did (HR 4.455, p = .002).
Conclusion: HCC and decompensation displayed significantly different risk profiles: HCC was more closely linked to inflammation, while decompensation was associated with coagulation and angiogenesis. Males predominantly exhibited inflammation-associated biomarkers, whereas females were more likely to have markers related to hypoxia and angiogenesis. Notably, personalized scores significantly outperformed traditional ones in predicting both conditions, achieving a higher degree of accuracy across all subgroups.
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WED-246
Long-term outcomes of patients with porto-sinusoidal vascular liver disorder. A single-centre 10 year-follow-up study
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Background and aims: Porto-sinusoidal vascular disorder(PSVD) is a recently described entity with a paucity of data on its natural history. We studied the clinical, histological characteristics and liver related outcomes in patients with PSVD from a single center.
Method: In this single-center, retrospective study(1998–2023), baseline descriptive characteristics and outcomes such as transplant free survival, new onset decompensation such as variceal bleeding, ascites and incidence of portal vein thrombosis (PVT) were evaluated in patients diagnosed with PSVD using VALDIG criteria. Predictors of survival were identified using a machine learning algorithm(Boruta).
Results: A total of 80 patients were included, with a mean age of 44 years and 38% females. At diagnosis, 45% (n = 36) patients had a history of portal hypertension related complications: 24%(n = 24) had variceal bleed and 20% (n = 16) had ascites. Signs of portal hypertension were present in 70% (n = 56) patients. Six (7.8%) patients had PVT at baseline. Median hepatic venous pressure gradient (HVPG) (n = 25) was 11 (5–12) mmHg. Median duration of follow-up was 78 (27–132) months. The cumulative 5-year and 10-year incidence of new onset variceal bleed was 15.4% and 21.8% respectively. New onset/worsening ascites developed in 21.6% and 35% of patients at 5-year and 10-year respectively and cumulative incidence of PVT at 5-years and 10-years was 15.9% and 21% respectively. Nine patients (11.8%) underwent liver transplant and 23 patients (29%) died during follow-up. Sixteen patients (20%) underwent trans jugular intrahepatic portosystemic shunt insertion. Transplant free survival at 5 year and 10 years was 70.5% and 60.7% respectively. A model combining histological variables (incomplete septal fibrosis, nodular regenerative hyperplasia), serum bilirubin and PVT at presentation could predict survival with optimism corrected C-statistics of 0.755.
Conclusion: This natural history study with the longest reported follow-up of PSVD describes the long-term outcomes with 60% transplant free survival at 10 years. Baseline liver dysfunction, presence of PVT and certain histological features could predict the prognosis in the present cohort.

WED-247
Targeted nutrition intervention improves frailty and quality of life in patients with liver cirrhosis

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Background and aims: Inadequate food intake is one of the major contributors to malnutrition in decompensated liver cirrhosis patients, and addressing this issue can significantly enhance their clinical outcomes. Malnutrition is closely linked to frailty and sarcopenia, both modifiable with targeted interventions. This study aimed to evaluate the impact of 16-week nutritional intervention on the liver frailty index (LFI) and health-related quality of life (HRQOL) in patients with cirrhosis.
Method: In this clinical trial, patients with liver cirrhosis attending the portal hypertension clinic at Policlinico Umberto I were enrolled for dietary intervention according to EASL guidelines for nutrition in chronic liver disease, if meeting inclusion (age 18–70 years, CTP ≤ 10, clinically stable) and exclusion criteria (patients already on a diet program or high protein supplements, patients with server co-morbidities, chronic or recurrent hepatic encephalopathy, or patients who refused to participate). Data on clinical parameters, dietary intake, HRQOL, LFI, and anthropometry were recorded at baseline and post-intervention. Dietary intake was analysed to calculate energy intake (kcal/kg body weight/day) and protein intake (g/kg body weight/day). Paired t test was performed using SPSS software (version 28.0.1.1).
Results: Thirty-five patients (age – 56.5 ± 11.2 years; male - 73.3%; etiology : alcohol - 46.6%, MASLD – 26.7%, viral – 26.7%; MELD – 9.2 ± 2.3; MELD-Na – 10.3 ± 2.8; CTP – 5.6 ± 0.7) have been enrolled, with 15 completing the 16-week follow up. Significant improvement was observed in hand grip strength (23.8 ± 12.1 kg vs. 27.1 ± 10.8 kg, p = 0.002) and chair sit-ups (15.6 ± 6.3 secs vs. 12.4 ± 3.8 secs, p = 0.04) after the dietary intervention. LFI also showed significant improvement (4.5 ± 0.7 vs. 3.9 ± 0.5, p < 0.001). Additionally, HRQOL, as measured by the chronic liver disease questionnaire (CLDQ) score, improved significantly (2.5 ± 0.9 vs. 3 ± 0.7, p = 0.025). Energy intake (kcal/kg BW/ day) also increased but did not reach statistical significance (24.2 ± 7.5 vs. 26.2 ± 3.5, p = 0.4). Moreover, protein intake significantly improved from 0.9 ± 0.3 g/kg BW/day to 1.3 ± 0.1 g/kg BW/ day (p < 0.001). Other measures, including body weight, body mass index (BMI), triceps skinfold thickness (TSF), mid-arm muscle circumference (MAMC), and mid-arm muscular area (MAMA), remained comparable between baseline and 16-week follow-up.
Conclusion: The preliminary results indicate that a dietary intervention in cirrhotic patients can significantly improve physical performance, and health-related quality of life. These findings underscore the potential of nutritional strategies to enhance clinical outcomes in this patient group. Future studies should explore long-term adherence and broader applications of such interventions.

WED-248
CT-based clinically significant portal hypertension: predicting complications in HCC hepatectomy

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Background and aims: The role of CT-based clinically significant portal hypertension (CSPH) assessed using deep-learning algorithm in predicting short-term and long-term liver-related complications following hepatic resection has not been evaluated.
Method: This retrospective study included patients with advanced chronic liver disease (ACLD) who underwent partial hepatectomy for hepatocellular carcinoma (HCC) with BCLC stage 0 or A between 2017 and 2018. The presence of CT-based CSPH was evaluated in preoperative contrast-enhanced CT, which included splenomegaly determined by deep learning-based spleen volume measurements with personalized reference thresholds, and the presence of at least one of esophagogastric varix, spontaneous portosystemic shunt, or ascites. We performed multivariable logistic regression and competing risk analysis to evaluate the association of CT-based CSPH with liver-related outcomes. The primary endpoint was severe post-hepatectomy liver failure (PHLF), as defined by International Study Group of Liver Surgery. Secondary endpoints were the occurrence of hepatic decompensation and liver-related death or liver transplantation. Additionally, CT-based CSPH was applied to two well-known PHLF prediction models (Citterio's algorithm and Wang's model), and their performance was compared with that when applying the conventional surrogate CSPH assessment (presence of esophageogastric varix at endoscopy or coexistence of splenomegaly and a platelet count < $100 \times 10^3/\mu L$).
Results: A total of 593 patients (mean age, 57.9 years ± 9.3; 460 male) were included in the study. Severe PHLF occurred in 41 patients (6.9%). The presence of CT-based CSPH was a significant independent predictor for the occurrence of severe PHLF (odds ratio 7.672, 95% confidence interval [CI] 3.209–18.346). The performance of both Citterio's algorithm and Wang's model significantly improved when using the CT-based CSPH criteria compared to the conventional method (AUC 0.724 vs. 0.694, p = 0.036, and AUC 0.854 vs 0.830, p = 0.011, respectively). CT-based CSPH was also a significant predictor for long-term hepatic decompensation (hazard ratio [HR] 4.518, 95%

CI 1.868–10.929) and liver-related death or transplantation (HR 2.756, 95% CI 1.315–5.773).
Conclusion: The presence of CT-based CSPH predicts short-term and long-term liver related outcomes following partial hepatectomy for HCC in ACLD.

WED-253-YI
Endoscopic ultrasound-guided therapies versus standard and modified balloon-occluded retrograde transvenous obliteration for management of fundal varices – a multicentric propensity-matched analysis

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Background and aims: Balloon-occluded retrograde transvenous obliteration (BRTO) or its modifications are viable options for managing fundal varices. Endoscopic ultrasound (EUS) guided glue injection with or without coil is an alternate option. Due to the scarcity of data comparing these two modalities, the present study compared the outcome of EUS-guided therapies and BRTO for managing fundal varices.
Method: We retrospectively analyzed the data of patients with fundal varices undergoing EUS-guided intervention or BRTO from ten tertiary care centers in India, and both groups were compared after propensity matching. The study's primary outcome was the incidence of variceal bleeding within 1 year. The secondary outcomes included procedure-related adverse events (AEs), variceal obliteration, reintervention, and mortality within 1 year.
Results: A total of 167 patients (EUS-guided intervention: 108, BRTO: 59) were included in the analysis, of which 59 patients were included in each group after propensity matching. The incidence of variceal bleeding (15.3% vs. 13.6%, p = 0.793) within 1 year was comparable between the EUS and BRTO groups. Procedure-related AEs, primarily new onset or worsening of ascites, were higher in the BRTO group. The incidence of variceal obliteration at 4 weeks was comparable between groups (83.1% vs. 91.5%, p = 0.167). The need for reintervention within 1 year of the index procedure (30.5% vs. 22.0%, p = 0.296) was comparable between the EUS and BRTO. However, the need for reintervention for GVs was higher in the EUS group (28.8% vs. 5.1%, p = 0.001), and the need for reintervention for esophageal varices (EVs) was higher in the BRTO group (16.9% vs. 1.7%, p = 0.008).
Conclusion: EUS-guided therapy offers a safer alternative with comparable efficacy to BRTO for managing fundal varices. The need for reintervention for GVs was higher in the EUS group, while the incidence of AEs and reintervention for EVs was higher in the BRTO group.

WED-254
Deeplearning allows prediction of portal hypertension from liver biopsies

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Background and aims: Portal hypertension (PH) arises due to profound architectural changes of the liver parenchyma not only limited to fibrosis. Measurement of the hepatic venous pressure gradient (HVPG) represents the diagnostic gold-standard for PH. We employed state of the art deep learning methods to predict HVPG and PH from liver biopsies (LB).
Method: Patients with liver disease were included when both LB and HVPG measurement were performed within ± 3 months. Patients with liver cancer or post liver transplantation were excluded. Hematoxylin-eosin-stained LB specimens were digitized at high resolution (40x, 0.137 mm/px). Whole slide images were downscaled to 1.14 m/px and tessellated into tiles sized 224 × 224px. Feature extraction was performed using two pretrained foundation models: CTransPath (CTrP) and UNI. We performed 4-fold cross validation with attention-based multiple instance learning (attMIL) to train classifiers that predict clinically significant PH (CSPH: HVPG≥10 mmHg) and severe PH (SPH: HVPG≥16 mmHg). Performance was evaluated using AUROC. Further, we trained attMIL regression models with 3-fold cross validation to predict the HVPG value directly, followed by Pearson's r coefficient evaluation.
Results: A total of 160 patients (n = 108, 67.5% showing F4 cirrhosis on LB) were included, the main etiologies were alcohol-related (n = 52, 32.5%) and metabolic dysfunction-associated steatotic liver disease (n = 37, 23.1%). The median HVPG was 15mmHg (IQR = 8mmHg) and 128 (80%) and 77 (48.1%), respectively, had CSPH and SPH. Direct HVPG prediction using CTrP features yielded an average r value of 0.12, with the best performing model reaching an r of 0.29 (p = 0.033). Models trained on UNI features outperformed CTrP models with an average r of 0.40, with the most accurate model reaching an r of 0.51 (p < 0.001). For prediction of CSPH, AUROC analysis revealed an average area under the curve (AUC) of 0.78 ± 0.08 when trained on CTrP features, whereas training on UNI features yielded an AUC of 0.79 ± 0.02. The best performing models using CTrP or UNI features had AUCs of 0.82 and 0.81, respectively. Prediction of SPH had worse overall performance, with an average AUC of 0.68 ± 0.20 with CTrP features and an average AUC of 0.72 ± 0.03 with UNI features. However, the best performing model trained on CTrP features had an AUC of 0.83 for predicting SPH, while the best UNI features-trained model remained with an AUC 0.73. Explainability analysis revealed that both models allocate high attention weights to tiles containing excess fibrosis and immune cell infiltrates.
Conclusion: Deep learning approaches allow prediction of CSPH from LBs to facilitate prognostication in patients with liver disease. Predictive value for SPH was worse, potentially explained by pronounced extrahepatic factors contributing to SPH. The current model for direct estimation of the HVPG value requires further refinement.

WED-255

Three-dimensional computed tomography angiography-based computational fluid dynamics simulation for noninvasive assessment of portal hypertension in patients with cirrhosis

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Background and aims: Portal hypertension (PH) is a severe consequence of chronic liver diseases and is responsible for the main clinical complications of liver cirrhosis. The accurate assessment of portal pressure for cirrhosis patients would aid in risk stratification and improve clinical management. Although measurement of hepatic venous pressure gradient (HVPG) remains the gold standard for diagnosing and evaluating PH, the technical difficulty, invasiveness, and low feasibility of multiple measurements restrict its widespread clinic application. This study aims to demonstrate the feasibility of the combination of three-dimensional computed tomography angiography angiography (3D-CTA) with computational fluid dynamics (CFD) for noninvasive portal pressure assessment in patients with cirrhosis.
Method: A total of 40 cirrhotic patients with PH receiving transjugular intrahepatic portosystemic shunt (TIPS) treatment were retrospectively included. All patients received HVPG and portosystemic pressure gradient (PPG) measurements during the interventional procedure. The preoperative imaging from abdominal contrast-enhanced CT and hemodynamic parameters from color Doppler ultrasound were collected. Patient-specific 3D geometries of the portal venous system and the entire hepatic region were reconstructed. Virtual HVPG (vHVPG) and virtual PPG (vPPG) were noninvasively measured in CFD simulation by considering the liver region as porous media to account for the patient-specific intrahepatic resistance.
Results: A porous media model with porous diameter of 120 μm was considered as the most appropriate model to present the simulation results. vPPG derived from CFD analysis was in great agreement with clinical measured data (17.2 ± 2.3 mmHg vs. 16.3 ± 2.0 mmHg). Validation of the numerical method was performed by post-TIPS PPG measurement (10.1 ± 1.8 mmHg vs. 9.3 ± 1.4 mmHg). vHVPG was significantly correlated with vPPG ($R = 0.7499$, $p < 0.0001$), with an accuracy to distinguish clinically significant portal hypertension (CSPH) as high as 92%. However, PH severity classification was underestimated for 36% patients, especially for patients with hepatic venous collateral formation and presinusoidal portal venous occlusion.
Conclusion: A patient-specific 3D-CTA based CFD simulation for noninvasive portal pressure assessment has been established. This computational model shows favourable performance for evaluating PH in patients with cirrhosis and might guide clinical decisions. HVPG is a relatively reliable diagnostic method for PH when PPG cannot be directly measured. For patients who have clinical symptoms of PH but their HVPG are within a normal range, numerical evaluation of PPG with CFD is an optional method for their diagnosis.

WED-256

Multiparametric ultrasound for the prediction of the outcomes of endoscopic ligation of esophageal varices

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Background and aims: Endoscopic Variceal Band Ligation (EVBL) is a cornerstone in the prophylaxis of esophageal variceal bleeding in cirrhotic patients. However, in most cases, a single EVBL session does not completely eradicate esophageal varices, necessitating a control endoscopy after 2–4 weeks to assess eradication or the need for further ligation. Currently, there are no noninvasive tools available to predict the outcome of EVBL. This study aimed to identify noninvasive predictors of variceal eradication after EVBL using multiparametric ultrasound.
Method: We prospectively enrolled consecutive cirrhotic patients intolerant to or with contraindications to beta-blockers, undergoing EVBL for bleeding prophylaxis. Before the procedure(T0), patients underwent abdominal ultrasound with liver and spleen 2D-ShearWave Elastography and Dynamic Contrast-Enhanced Ultrasound (D-CEUS) with time-intensity curve analysis using VueBox® software, with two regions of interest: liver parenchyma and portal vein. After 1 month(T1), the same exams were repeated before control endoscopy to confirm variceal eradication, defined as either complete absence of varices or residual varices not requiring further ligation. Percentage changes in D-CEUS parameters between T0 and T1 were calculated as $[(T1 - T0)/T0] \times 100$. Logistic regression analyses were performed to evaluate predictors of variceal eradication.
Results: Forty-one patients were included (mean age 63 ± 7.5 years; 75.6% male). After EVBL at T0, 28 patients (68.3%) achieved variceal eradication, while 13(31.7%) required a second ligation at T1. Patients who achieved eradication showed a significant reduction in spleen stiffness (SS) at T1 compared to T0 (39 kPa vs. 52.5 kPa; $p = 0.014$). Logistic regression analyses identified a reduction in spleen stiffness as a predictor of eradication (OR: 1.156, $p = 0.033$). Additionally, changes in D-CEUS parameters between T0 and T1 were predictive of eradication. Regarding the liver parenchyma, the percentage increase in Mean Linear Amplitude Unit (MeanLinAU; OR: 0.92, $p < 0.001$), peak enhancement (PE; OR: 0.905, $p = 0.003$), and area under the curve (AUC; OR: 0.957, $p = 0.009$) were significant predictors. Similarly, for the portal vein, the percentage increase in MeanLinAU (OR: 0.92, $p = 0.009$), PE (OR: 0.947, $p = 0.003$), and AUC (OR: 0.947, $p = 0.006$) also predicted variceal eradication.
Conclusion: Our study demonstrated that reduction in SS and changes in D-CEUS parameters are reliable noninvasive predictors of variceal eradication after EVBL.

WED-257-YI

Long-term albumin treatment improves outcomes in patients with cirrhosis and ascites

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Background and aims: While the ANSWER trial has demonstrated improved survival with long-term albumin treatment in patients with ascites, a benefit was not observed in some other studies. Study design, heterogeneity in study cohorts and albumin dose have been hypothesized to explain these discrepancies. We aimed to assess the

effects of long-term albumin treatment – administered in a real-life outpatient setting – on liver-related mortality in cirrhosis patients with ascites.
Method: 878 cirrhosis patients with ascites as index decompensation between 2003–2024 from four tertiary care centers in Europe were included. 106 patients (11.7%) receiving long-term (i.e., more than > 30 days) i.v. albumin therapy. Patients were characterized from time of albumin treatment initiation or first decompensation. We performed inverse probability of treatment weighting (IPTW) adjusting for age, sex, MELD-Na and etiologic cure to account for differences in disease severity in multivariable cox regression analyses of liver-related mortality.
Results: The main patient characteristics were balanced between patients receiving long-term albumin [ivALB (+)] and those w/o albumin treatment [ivALB(-)]: median age: 60.2 vs 56.9 years (p = 0.008) and MELD-Na 14 vs 15 (p = 0.231). Median ivALB(+) treatment dose was 40 grams per week (mostly 20% 200 mL) and patients were treated for 11.1 (IQR: 5.0–20.3) months. During a median follow-up of 46.5/36.4 months in ivALB(-)/ivALB(+) patients, 44.4%/35.9% died including 39.0%/27.2% liver-related deaths, and 12.3%/17.5% underwent liver transplantation (LT). Incidence of liver-related mortality at 36 months was 38.8% in the ivALB(-) vs. 34.4% in the ivALB(+) patients (log-rank p = 0.100). Cox proportional hazards regression with IPTW for ivALB(+) treatment showed that next to age (aHR per year: 1.04 [95%CI: 1.02–1.06]; p < 0.001), MELD-Na (aHR per point: 1.07 [95%CI: 1.04–1.10]; p < 0.001), female sex (aHR: 0.58 [95%CI: 0.42–0.81]; p = 0.001) and etiologic cure (aHR: 0.56 [95%CI: 0.36–0.88]; p = 0.012) - long-term ivALB(+) therapy was associated with significantly reduced risk of liver-related death (aHR: 0.65 [95%CI: 0.42–0.99]; p = 0.048).
Conclusion: Acknowledging the limitations related to retrospective design and non-standardized treatment schedules, long-term ivALB (+) treatment significantly reduced liver-related mortality in our cohort of cirrhosis patients with ascites.

WED-258
TIPS for portal hypertensive gastropathy bleeding reduces further decompensation and mortality

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Background and aims: Portal hypertensive gastropathy (PHG) is the second leading cause of gastrointestinal bleeding after gastroesophageal varices, affecting 20–80% of patients with liver cirrhosis. Current guidelines recommend non-selective beta-blockers (NSBBs) as the first-line treatment. For PHG patients who are transfusion-dependent and unresponsive to NSBBs or endoscopic therapy, transjugular intrahepatic portosystemic shunt (TIPS) is suggested as an alternative treatment. However, there is a lack of evidence supporting the efficacy of TIPS in improving long-term outcomes, such as further decompensation.
Method: In this retrospective, multicenter study, patients with PHG-related bleeding (32% rebleeding) treated with TIPS were 1:1 propensity score matched (PSM) to patients receiving SOC. Of a total of 110 patients (n = 28 treated with TIPS), 50 patients could be matched: TIPS (n = 25) and SOC (n = 25). Primary outcome was further decompensation. Secondary outcomes included mortality and rebleeding rates. Further decompensation was defined as the new occurrence or worsening of ascites, variceal bleeding, hepatic encephalopathy, jaundice, spontaneous bacterial peritonitis (SBP), or hepatorenal syndrome (HRS). Follow-up was 1 year.
Results: TIPS showed significantly lower rates of further decompensation (TIPS: 15% vs. SOC: 25%, p = 0.027), especially in terms of ascites (HR 0.064, 95% CI: 0.008–0.305, p = 0.002) and hepatic encephalopathy (HR 0.308, 95% CI: 0.122–0.775, p = 0.012), compared to the SOC group. Cox regression analysis indicated a trend towards improved survival in the TIPS group (HR: 0.55, 95% CI: 0.18–1.68, p = 0.3). TIPS group showed a trend for lower rebleeding rates (p = 0.343).
Conclusion: The clinical use of TIPS for PHG-related bleeding significantly reduces further decompensation, is associated with improved survival, and trends toward lower rates of rebleeding within one year.

WED-259
Limited value of liver frailty index to predict symptom control after insertion of a transjugular intrahepatic portosystemic shunt

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Background and aims: Both sarcopenia and frailty are associated with a reduced quality of life and an increased risk for decompensating events in patients with liver cirrhosis. As prevalence of frailty is high among patients with liver cirrhosis eligible for insertion of a transjugular intrahepatic portosystemic shunt (TIPS), the aim of this study was to investigate the impact of frailty pre-TIPS on symptom control post-TIPS.
Method: From 07/2019 to 04/2024, 220 consecutive patients who underwent TIPS insertion at Hannover Medical School were prospectively enrolled. Structured follow-up (FU) was performed one, three, six and 12 months after TIPS insertion, followed by annual visits. Frailty was assessed using the Liver Frailty Index (LFI) categorizing patients into “robust,” “pre-frail” and “frail.” Morbidity post-TIPS was evaluated by applying modified Baveno VII criteria at the respective FU visits with “first decompensation” (FiD) and “further decompensation” (FuD) defined according to the Baveno VII criteria, and modified early (mER) and sustained recompensation (mSR) as absence of decompensating events 3 and 12 months after TIPS, respectively, while maintaining HE prophylaxis and diuretics. Statistical analyses were performed using competing risk analysis (liver transplantation/death as competing events), chi-squared tests and logistic regression.
Results: A total of 87 patients qualified for final analysis after excluding cases with insufficient baseline data on LFI, hepatocellular carcinoma outside Milan, Budd-Chiari syndrome or absence of cirrhosis. Patients were predominantly male (60%) with a median MELD and Freiburg index of post-TIPS survival (FIPS) of 12 (IQR 9–15) and −0.12 (IQR −0.79–0,34), respectively. Before TIPS, 40% (35/87) of patients were classified as “frail,” 54% (47/87) as “pre-frail” and 6% (5/87) as “robust.” Proportions of patients achieving mER and mSR post-TIPS were comparable between frail and robust/pre-frail patients pre-TIPS (mER: p = 0.824; mSR: p = 0.882). In univariable competing risk analysis, frailty status pre-TIPS was neither associated with FiD (HR 0.94, 95%CI 0.53–1.66, p = 0.83) nor FuD (HR 0.97, 95% CI 0.46–2.03, p = 0.93) after TIPS. Additionally, no significant association between

frailty status and any decompensating event after TIPS was detected (HR 1.04, 95% CI 0.59–1.84, p = 0.89). In contrast, a higher FIPS pre-TIPS was associated with a higher incidence of FuD after TIPS (HR 1.50, 95% CI 1.04–2.17, p = 0.031) independent of frailty (aHR 1.52, CI 95% 1.04–2.21, p = 0.031).
Conclusion: Frailty diagnosed by LFI before TIPS was not associated with symptom control stratified according to Baveno VII criteria after TIPS.

Fibrosis – Stellate cell biology

TOP-053
The mechanisms of transcription factor ZEB2 in regulating hepatic stellate cell activation and liver fibrosis
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Background and aims: The pathogenesis of liver fibrosis is highly complex, with the persistent activation of hepatic stellate cells (HSCs) being a critical driver of its initiation and progression. The transcription factor E-box binding zinc finger protein 2 (ZEB2) has been shown to regulate fibrosis in organs such as the kidney and lung. However, its specific regulatory mechanisms in liver fibrosis remain poorly understood. This study aims to elucidate the role of ZEB2 in HSC activation and its mechanisms in liver fibrosis.
Method: Human HSC line LX-2 cells were stimulated with transforming growth factor β (TGF-β), and ZEB2 protein expression was suppressed using Zeb2 siRNA to assess its regulatory effect on liver fibrosis. A mouse liver fibrosis model was established via bile duct ligation (BDL) and a choline-deficient amino acid (CDAA) diet. One week prior to fibrosis induction, mice were tail-vein injected with AAV6-shZeb2 driven by the Postn promoter to achieve HSC-specific knockdown of Zeb2. The impact of Zeb2 knockdown on liver fibrosis progression was evaluated. RNA-seq and ATAC-seq analyses were employed to identify ZEB2 target genes and further elucidate its molecular mechanisms.
Results: In vitro, TGF-β stimulation significantly upregulated both mRNA and protein levels of Zeb2 in LX-2 cells. Zeb2 knockdown markedly suppressed the expression of pro-fibrotic genes such as α-SMA, Postn, and Col1a1. In vivo, compared with control mice injected with AAV6-shControl (shc-BDL and shc-CDAA), HSC-specific Zeb2 knockdown in BDL (shZeb2-BDL) and CDAA (shZeb2-CDAA) mice resulted in significantly lower expression of pro-fibrotic genes and reduced serum levels of liver injury markers ALT and AST. Masson's trichrome and Sirius red staining confirmed decreased extracellular collagen deposition in shZeb2-BDL and shZeb2-CDAA mice. RNA-seq and ATAC-seq analyses revealed that ZEB2 enhances HSC activation by suppressing TGF-β receptor 3 (TGFBR3), thereby amplifying the responsiveness of TGFBR1 and TGFBR2 to TGF-β signaling.
Conclusion: Targeting ZEB2 in HSCs effectively prevents the onset and progression of liver fibrosis and alleviates liver injury in mice. Thus, ZEB2 may serve as a potential therapeutic target for liver fibrosis.

TOP-054
Single cell fixed RNA-seq revealed HSCLMCD1+LIMK2+ is a driver of liver fibrosis by modulating SMAD3-AKT-PRAS40-4EBP1
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Background and aims: Single-Cell Fixed RNA Profiling (FLEX) is an innovative technique that enables the analysis of RNA expression at single-cell resolution from frozen tissues. This study aimed to leverage FLEX technology to investigate human and experimental models of cirrhosis progression and regression, with the goal of identifying novel therapeutic targets for antifibrotic treatments.
Method: Thioacetamide (TAA) was administered intraperitoneally to mice at escalating doses ranging from 50 to 400 mg/kg over a 10-week period to induce liver fibrosis, while control mice received saline. Regression of liver fibrosis was assessed two weeks after TAA cessation. Frozen liver tissues from both mice and human samples were fixed, dissociated into single cells, and analyzed via single-cell RNA sequencing (scRNA-seq). Molecular analyses, including immunoblotting, immunohistochemistry, gene silencing, overexpression studies, and human phosphokinase arrays, were employed to validate findings.
Results: Using FLEX, approximately 40,000 liver cells were analyzed, providing high-resolution transcriptomic data and enabling classification into 10 major cell types. In cirrhotic livers, hepatocyte and LSECs populations were reduced by 30–50%, whereas hepatic stellate cells (HSCs) increased by 150% compared to healthy livers. Transcription factor analysis revealed that regressed HSCs exhibited reduced expression of SMAD3 and FOSL1, alongside increased expression of TP53, ETV4, SP1, SP3, GATA2, and GATA3. Notably, LIM-domain-related genes, including LIMA1, LIMK2, PDLIM2, PDLIM5, PDLIM7, FHL2, FHL3, and LMCD1, were significantly upregulated in cirrhotic HSCs from both mouse and human samples but were downregulated during fibrosis regression. Functional studies demonstrated that silencing LMCD1 or LIMK2 attenuated HSC activation, whereas overexpression of LMCD1 strongly enhanced HSC activation via the SMAD3-AKT-PRAS40-4EBP1 pathway. Specific inhibition using AZD8055 mitigated HSC activation, both spontaneously and under TGF-β stimulation, and significantly reduced the phosphorylation of 16/39 proteins implicated in HSC activation, including CREB, c-JUN, TP53, WNK1, GSK3B, STAT2/3, HSP27/60, and RSK1/2/3. Importantly, LMCD1 was prominently expressed in fibrotic regions of patients with metabolic-associated steatotic liver disease (MASLD) and colocalized with α-SMA and vimentin. Furthermore, LMCD1 expression strongly correlated with fibrosis severity, with an area under the receiver operating characteristic (AUROC) curve of 0.92 (95% CI: 0.76–1; p = 0.006) for predicting advanced fibrosis.
Conclusion: This study highlights previously unrecognized molecular and cellular dynamics of HSCs, identifying LMCD1 and LIMK2 as promising therapeutic targets for antifibrotic interventions.

THURSDAY 08 MAY

THU-035-YI
Bortezomib improves advanced fibrosis by selectively inducing stellate cell apoptosis via downregulation of LGALS2 and CDH3 expression
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Background and aims: Bortezomib (B), a proteasome inhibitor, has been shown to attenuate fibrosis in organs other than the liver. We aimed to evaluate the efficacy of B in ameliorating advanced parenchymal and biliary liver fibrosis in rats and the potential underlying mechanisms.

Method: Advanced liver fibrosis was induced in rats by intraperitoneal injection of thioacetamide (TAA) for 12 weeks or bile duct ligation (BDL) for 3 weeks. Rats were then divided into 3 groups: intravenous injection of B at 0.1 mg/kg in PBS (BL), 0.15 mg/kg in PBS (BH) (defined and calculated from the literature) and PBS alone twice a week for 3 weeks each (fibrotic controls, FC). Age-matched untreated rats served as normal controls (NC). Portal venous pressure (HVPG) was measured before sacrifice. Potential toxicity of B was assessed by hepatic and renal function parameters, hepatic inflammation and fibrosis by HE and Masson's staining, liver collagen content via quantification of hydroxyproline, and fibrosis-related gene and protein expression by RT-qPCR and Western blot. Livers were subjected to NGS analysis and differentially expressed genes (DEGs) were analyzed as fold changes vs controls (greater than 1.5 fold and p-value <0.05). Target genes were enriched from genes that were equally regulated in rats with TAA-induced and BDL-induced fibrosis. Apoptosis was detected in vivo (TUNEL staining) and in vitro (flow cytometry).
Results: After B treatment, HVPG decreased, although p-values did not reach statistical significance in the two fibrosis models. B decreased ALT and AST in both fibrosis models, and serum creatinine and bilirubin levels remained unchanged, indicating a beneficial effect of B on liver function without apparent hepatic or renal toxicity. Liver collagen content and Masson's staining showed a significant reduction in fibrosis. DEG analysis showed that LGALS2 (Galectin-2) and CDH3 (p-Cadherin) were overlapping genes that were prominently upregulated in mice with advanced fibrosis but downregulated after B treatment at two different concentrations. TUNEL assay labeled more apoptotic cells in liver sections from B-treated groups in both models at the doses selected, with prominent signals in hepatic stellate cells, but not hepatocytes.
Conclusion: A narrow dose range of B induces apoptosis of activated HSC in vitro and in vivo through enhanced LGALS2 and CDH3 expression and has a prominent antifibrotic potential in parenchymal and biliary fibrosis.

THU-036-YI

Integrating spatial lipidomics with imaging mass cytometry: a novel approach for metabolic profiling of liver fibrosis

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Background and aims: During steatotic liver disease (SLD), lipid deposition, inflammation, and fibrosis progress heterogeneously across the hepatic tissue, making whole tissue analyses an approximation. It is therefore crucial to employ approaches that retain spatial information to fully characterize the fibrotic niche. The aim of this study is to establish a link between key lipids and different cells within the fibrotic regions, with potential implications for novel therapeutics.
Method: We performed spatial lipidomics using mass spectrometry imaging (MSI) on human SLD-related cirrhotic tissue sections (n = 8). To establish a link between the dysregulated lipid metabolism with different cell types, we performed imaging mass cytometry (IMC) for highly multiplex localisation of 16 protein markers on a subset of adjacent tissue sections (n = 4). Individual IMC channels and MSI single ion images were then co-registered and spatial correlation between lipids and cellular markers was assessed using the Matthews Correlation Coefficient (MCC). MSI was also performed on tissue slices from MASLD patients across various fibrosis stages (F0-F2, n = 9). To test if manipulating lipid metabolism could serve as a potential anti-fibrotic strategy, we targeted sphingolipid metabolic pathways in stimulated LX-2 cells (immortalized hepatic stellate cells cell line; n = 5) and measured alpha-SMA protein expression by western blot.
Results: MSI analysis showed that lipid metabolism is dysregulated spatially, with sphingomyelin (SM)34:1 being one of the top increased lipids in the fibrotic regions. IMC analysis showed that 11 markers were significantly increased in fibrosis, whereas 2 were increased in parenchyma. Next, we co-registered MSI and IMC images and we found that SM(34:1) was highly correlated with alpha-SMA, vimentin and collagen (MCC >0.54). Similar to the cirrhotic samples, SM(34:1) was increased in fibrotic regions in MASLD tissue sections, showing that sphingolipid metabolism is altered in the early stages of LF, when the potential for reversibility is greater. *In vitro*, we inhibited sphingolipid metabolism pathways in activated HSCs, as these cells are key players in driving fibrogenesis. In TGF-beta activated LX-2 cells, inhibition of de novo synthesis of ceramides with myriocin and fumonisin B1 and inhibition of the ceramide salvage pathway with D-PDMP and miglustat, significantly decreased alpha-SMA protein levels.
Conclusion: Overall, this innovative spatial multi-omics approach suggests cell type-specific mechanisms of LF involving sphingolipid metabolic pathways. These results show that sphingolipid metabolic pathways are modifiable targets, which may have potential as an anti-fibrotic therapeutic strategy.

THU-037

Lycorine reduces liver fibrosis by inactivating hepatic stellate cells (HSCs) in mouse models of metabolic dysfunction-associated steatohepatitis (MASH)

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Background and aims: In the context of metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic damage leads to the release of profibrogenic mediators that activate and transdifferentiate hepatic stellate cells (HSCs) into myofibroblasts, the primary source of extracellular matrix. The stage of liver fibrosis is a critical risk factor correlating with disease-associated morbidity and mortality in patients with metabolic dysfunction-associated steatohepatitis (MASH), making it a key target for pharmacological strategies in the treatment of MASH and liver fibrosis. We investigated the efficacy of the compound Lycorine and its derivative, both of which have demonstrated promising preclinical effects in myocardial fibrosis, for the treatment of MASH and liver fibrosis in a murine model.
Objectives: To evaluate the antifibrotic potential of Lycorine and its derivative in the treatment of MASH and liver fibrosis.
Method: The efficacy of Lycorine and its derivative was analyzed in five different models using male C57BL/6J wild-type mice. These included chronic toxic injury induced by CCl4 (6 weeks), advanced liver fibrosis induced by a choline-deficient high-fat diet (CDAHFD; 8 or 10 weeks), and mild liver fibrosis induced by a Western diet (WD; 8 weeks). In the fibrosis models (CCl4 and CDAHFD), short (2 weeks) and long (4 weeks) treatment intervals were evaluated. Additionally, the impact of Lycorine on HSC activation and metabolism was studied in vitro using primary murine cells.
Results: Lycorine inhibited the activation of primary murine HSCs in a dose-dependent manner in vitro. Therapeutic administration of Lycorine reduced inflammatory processes and improved

steatohepatitis and liver fibrosis in independent murine models (CCl4 and CDAHFD). The Lycorine derivative exhibited greater potency in promoting fibrosis regression, with antifibrotic effects of both compounds showing trends correlating with dose and treatment duration. In the model of mild fibrosis (WD), reduced liver damage was observed.
Conclusion: Lycorine directly inhibits the activation of matrix-producing HSCs, representing a novel and promising compound with anti-inflammatory and antifibrotic effects for the treatment of MASH and liver fibrosis.

THU-038
Patients with chronic liver disease present elevated plasma levels of peptidylprolyl isomerase C associated with the degree of fibrosis
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Background and aims: Various members of the cyclophilin family have been associated with the pathogenesis of metabolic dysfunction-associated liver disease (MASLD), but there is scarce information on peptidylprolyl isomerase C (PPIC), whose gene expression has been increased in the liver of animal models and patients with chronic liver disease (CLD). We aimed to characterize the association between PPIC levels and the progression of CLD.
Method: PPIC expression was evaluated by Western Blot in in vitro liver injury models (LX2 cells and human primary hepatic stellate cells treated with 2.5 ng/μL TGF-β, 48 h; Hep3B cells with fatty acid overload, 48 h) and in vivo (livers of C57BL/6J mice treated with CCl_4). Plasma PPIC levels (pg/mL) were determined by ELISA in: 1) a cohort composed of healthy controls (N = 18) and patients with CLD of mixed origin (N = 46) from the Hospital Clínico Universitario of Valencia; 2) a cohort of 149 patients with MASLD from the Hospital Universitario Virgen del Rocío (Seville) and; 3) a cohort with healthy controls (N = 21) and patients with type II diabetes mellitus (N = 38) from the Hospital Dr. Peset-FISABIO (Valencia).
Results: PPIC protein expression was significantly increased in LX2 cells incubated with TGF-β and in liver tissue of CCl_4-treated mice, and showed an increasing trend in the other preclinical models. The determination of PPIC levels in plasma showed: 1) a general increase in patients with CLD of mixed etiology compared to controls (237.5 [202.2–279.2] vs 116.9 [100.7–133], $p \leq 0.0001$); 2) a positive correlation with age ($r = 0.22$, $p \leq 0.01$), indirect [FIB-4 ($r = 0.20$) and VCTE ($r = 0.21$), $p \leq 0.05$] and direct parameters [histological degree of liver fibrosis ($r = 0.22$, $p \leq 0.01$)] and glycemia ($r = 0.21$, $p \leq 0.05$), an inverse association with parameters related to cholesterol levels [total cholesterol ($r = -0.20$), HDL ($r = -19.3$), and LDL ($r = -0.21$), $p \leq 0.05$] and liver function [albumin ($r = -0.24$, $p \leq 0.05$)] in patients with MASLD, and an association with significant fibrosis (F0–F1 149.4 [129.9–168.8] vs F2–F4 196.4 [170.3–222.6], $p \leq 0.01$), which remained significant after correcting for the rest of the variables associated with fibrosis using logistic regression ($p \leq 0.05$); 3) elevated plasma levels of PPIC only in those diabetic patients with high FIB-4 (≥1.45) compared to controls (169.6 [136–203.2] vs 88 [59.6–116.3], $p \leq 0.01$).
Conclusion: PPIC levels in liver and plasma of patients increase in CLD, regardless of its etiology. The increase in plasma PPIC correlates positively with the degree of fibrosis and FIB-4. These results suggest that PPIC could be a therapeutic target for the treatment of liver fibrosis and a marker of the progression of CLD, although more data are needed to clarify the role of this cyclophilin in liver disease.

THU-039
Sex differences in aging rates and superoxide dismutase activity in patients with metabolic dysfunction-associated steatotic liver disease: implications for fibrosis risk
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Background and aims: Gender differences, among other factors, determine the specifics of the course of metabolic dysfunction-associated steatotic liver disease (MASLD), but differences in aging rates (ARs) remain underexplored. Oxidative stress is a key pathogenic mechanism both in aging and steatohepatitis development. Superoxide dismutase (SOD) is the primary antioxidant enzyme, with its activity potentially influenced by gender. This study aimed to evaluate sex-related differences in ARs and SOD activity in patients with MASLD, with a focus on fibrosis risk (FR).
Method: The study included 52 men (53.1 [44.7; 59.5] years) and 48 women (54.5 [47.9; 59.5] years) with MASLD, divided into age-matched subgroups based on FR (FIB-4): low (<1.3) (men 71%, women 58%) and moderate (1.3–2.67). A control group of young adults (n = 24, 25.2 [23.7; 28.5] years) was similarly matched by sex. Phenotypic age (PA) and AR were evaluated using the method by M. Levine et al. (2018), total SOD activity was determined via colorimetric analysis.
Results: Patients with MASLD demonstrated differences in PA, body mass index, WHR, ALT, glycosylated hemoglobin, HOMA-IR, total cholesterol, triglycerides, low-density lipoprotein cholesterol, UA, glomerular filtration rate (GFR), albumin, C-reactive protein, FIB-4, and SOD levels ($p < 0.05$) across both sexes compared to controls. Notable differences ($p < 0.05$) also included in men elevated AST, ALT/ALP, and AST to platelet ratio index (ARPI) ($p = 0.020$); and in women variations in body fat percentage (FAT), muscle percentage (MUS), and ALP. ARs in MASLD patients correlated with visceral fat levels in both men ($p = 0.037$) and women ($p = 0.036$). Within the subgroups categorized by FIB-4, men exhibited lower FAT ($p < 0.001$) but higher ALT/ALP and ARPI levels ($p < 0.05$) compared to women. Men with low FR also showed higher MUS ($p = 0.0001$), GFR ($p = 0.008$), lower HOMA-IR ($p = 0.003$), but higher WHR ($p = 0.0001$), ALT ($p = 0.049$), indirect bilirubin ($p = 0.007$), UA ($p = 0.008$), gamma-glutamyl transferase ($p = 0.003$), and SOD ($p = 0.047$), along with lower HDL-C levels ($p = 0.012$). In the moderate FR subgroup, additional differences were only noted in total protein levels ($p = 0.028$). Importantly, men with moderate FR had significantly higher ARs than women ($p = 0.043$).
Conclusion: Men with MASLD and moderate FR exhibit accelerated aging compared to women, potentially due to cardiometabolic differences that emerge even at low FR. To prevent premature aging and MASLD progression in men, it is essential to address abdominal obesity, HDL-C levels, and liver dysfunction. In women, monitoring for postmenopausal insulin resistance and renal filtration impairment is critical. Increased antioxidant defense via SOD likely acts as a compensatory mechanism in men with low FR.

THU-040

Efficacy of CRV431 and Semaglutide on liver fibrosis in a mouse model of MASH

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a severe form of metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic inflammation and fibrosis that can progress to cirrhosis and liver failure. CRV431, a cyclophilin inhibitor, has demonstrated antifibrotic effects in previous studies, while semaglutide, a GLP-1 receptor agonist, has shown potential therapeutic benefits in metabolic disorders. This study aimed to evaluate the efficacy of CRV431, semaglutide, and their combination on hepatic fibrosis in a MASH mouse model.
Method: Male mice were divided into several treatment groups: healthy controls at baseline (n = 4), MASH model at baseline (n = 4), MASH model treated with vehicle for five weeks (n = 2), MASH model treated with CRV431 for five weeks (n = 2), MASH model treated with semaglutide for five weeks (n = 4), MASH model treated with both CRV431 and semaglutide for five weeks (n = 4), and healthy controls after five weeks (n = 4). Liver fibrosis was quantified by measuring the fibrosis percentage area from histological sections. One-way ANOVA was performed to compare group means, followed by post-hoc tests using the Benjamini, Krieger, and Yekutieli procedure to control the false discovery rate. Statistical significance was set at $P < 0.05$.
Results: A significant difference among group means was observed ($F(6,17) = 2.728$, $P = 0.0482$, $R^2 = 0.4905$). The mean fibrosis percentage areas were: healthy controls at baseline, 12.31% ± 4.49%; MASH model at baseline, 16.00% ± 4.49%; vehicle-treated MASH model after five weeks, 16.00% ± 6.50%; CRV431-treated MASH model after five weeks, 10.83% ± 6.50%; semaglutide-treated MASH model after five weeks, 17.55% ± 4.49%; combination-treated MASH model after five weeks, 18.17% ± 4.49%; and healthy controls after five weeks, 12.31% ± 4.49%. CRV431 treatment resulted in the lowest mean fibrosis area among the treatment groups. Compared to the vehicle-treated group, CRV431-treated mice showed a reduced fibrosis area (mean difference: 5.17%, $t = 1.627$, $P = 0.1221$). Although this difference did not reach statistical significance, CRV431 demonstrated the greatest impact on reducing hepatic fibrosis. Semaglutide did not significantly reduce fibrosis compared to the vehicle-treated group (mean difference: 1.55%, $t = 0.565$, $P = 0.5796$).
Conclusion: CRV431 showed the most substantial reduction in hepatic fibrosis among the treatments tested, aligning with historical observations of its antifibrotic efficacy in liver disease models. The absence of a synergistic effect and the higher fibrosis levels in the combination-treated group suggest possible antagonistic interactions between CRV431 and semaglutide, potentially diminishing the therapeutic benefits of CRV431 when used concurrently with semaglutide.

THU-041

Investigating the role of Fn14 in metabolic associated steatohepatitis: effects on fibrosis, inflammation, and proliferation in a mouse model

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Background and aims: Metabolic associated steatohepatitis (MASH) is a fatty liver disease with inflammation and fibrosis. Improved understanding of the underlying disease mechanisms is needed for development of new treatments. Elevated fibroblast growth factor-inducible 14 (Fn14) levels are seen in advanced fibrosis stages. Fn14, expressed in stellate cells, hepatocytes, and cholangiocytes, is a receptor for TNF-like weak inducer of apoptosis (TWEAK). It is involved in hepatocyte proliferation, regeneration, pro-inflammatory cytokine expression, and fibrosis. Additionally, soluble Fn14, generated via proteolytic cleavage in the blood, plays a role in inflammatory responses. We hypothesized that knockdown of Fn14 in hepatocytes with an investigational Fn14 siRNA would have an improved effect on MASH and fibrosis.
Method: Male wildtype mice were fed either a chow diet (Altromin 1324) or a choline-deficient high-fat diet (CDHFD) (Research Diets, A06071302) for 4 weeks. CDHFD-fed mice then received either a vehicle or GalNAc conjugated siRNA targeting Fn14 (GalXC-Fn14) (weekly at 0.1 mg/kg or 5 mg/kg) for 8 more weeks (n = 16). Body weight was monitored throughout. Terminal plasma (ALT, AST) and liver samples were collected. MASH-related parameters were assessed via histology (HE, CD45, Ki67, αSMA, PSR staining) or bulk liver mRNA sequencing.
Results: GalXC-Fn14 treatment led to a dose-dependent reduction of Fn14 expression in liver and plasma. High dose treatment showed 58% and 72% inhibition after one week, with further reductions over time. Fn14 reduction was hepatocyte-specific, with corresponding decreases in soluble Fn14. ALT and AST levels induced by CDHFD were unaffected. GalXC-Fn14 reduces Pro collagen III in plasma and a trend to a decrease in COL3A mRNA at the low dose, though no effect on hepatic collagen was observed via PSR staining. High dose GalXC-Fn14 induced Growth differentiation factor 15 (GDF15) expression, involved in various biological processes, including inflammation. While high dose GalXC-Fn14 reduced steatosis, it increased inflammation. Bulk liver sequencing revealed limited gene changes with Fn14 GalXC, increasing inflammation (e.g., Trim12c and Timd2) and reducing proliferation (e.g., Ptprt and Usp21).
Conclusion: Fn14 is critically involved in MASH, indicated by elevated Fn14 levels in liver and plasma of MASH patients. However, knockdown of Fn14 in hepatocytes had minimal effect on fibrosis, but reduced steatosis, exacerbated inflammation and reduced proliferation. This could indicate absence of Fn14 disrupts regenerative processes, potentially enhancing inflammation. The mechanism behind the apparent beneficial effect of reduced steatosis in the CDAHFD mouse model is unknown. Balancing the favorable effects on steatosis against adverse impacts on proliferation and inflammation complicates therapeutic use of Fn14 reduction in MASH patients. Further research is essential to fully understand Fn14's role in proliferation and inflammation in MASH.

THU-042

Targeting metabolic dysfunction-associated steatohepatitis with microRNA therapeutics

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a severe form of fatty liver characterized by chronic liver inflammation, hepatocyte injury, and mild to moderate fibrosis. If left untreated, MASH can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). MicroRNAs (miRNAs) have gained attention as promising multitarget therapeutics due to their ability to regulate multiple genes simultaneously, making them ideal candidates for treating complex diseases like MASH. This study aimed to identify miRNAs with therapeutic potential for MASH.
Method: Fibrosis was modeled using the human hepatic stellate cell line LX-2, activated with TGFbeta-1. Proteomic analysis of secretome

and cellular extracts using liquid chromatography-tandem mass spectrometry (LC-MS/MS) identified significantly upregulated "pro-fibrotic" proteins, which were inferred to predict miRNA-target interactions using two tools: the MicroRNA ENrichment TURned NETwork (experimentally validated interactions) and our miRNA Binding Site prediction database (integrating PITA, miRanda, and TargetScan algorithms). To validate these interactions, LX-2 cells were transfected with miRNA mimics, followed by activation with a combination of TGFbeta-1 and L-ascorbic acid, the latter a cofactor of prolyl 4-hydroxylase enzymes. Finally, gene silencing was conducted using small interfering RNA (siRNA) to corroborate the role of specific genes in the fibrotic process. The effects of miRNA mimics and gene silencing on target proteins and fibrosis-related markers were assessed by Western blot.

Results: Among the upregulated proteins found in activated LX-2 cells, the prolyl 4-hydroxylase subunit alpha 2 (*P4HA2*) gene was selected as a key therapeutic target due to its role in collagen fiber stabilization and its dysregulation in fibrotic conditions, such as biliary and pulmonary fibrosis. Target prediction analysis identified miR-9-5p, miR-30a-5p, miR-4640-5p, miR-4726-5p and miR-128-1-5p as potential regulators of *P4HA2*. Among these, only miR-9-5p significantly inhibited P4HA2 protein expression. Additionally, miR-9-5p downregulated TGFbeta-1i protein and maintained LX-2 cells in an inactivated state by preventing the upregulation of fibrosis markers such as COL1A1, FN1, and alpha-SMA, while reducing collagen secretion. Similarly, silencing *P4HA2* mitigated the expression of fibrosis markers, underscoring its role in fibrogenesis.

Conclusion: miR-9-5p mimic therapy shows promise in countering hepatic stellate cell activation in MASH by targeting *P4HA2* and *TGFbeta-1i* genes. Alternatively, silencing the *P4HA2* gene may represent a viable therapeutic approach with a lower risk of off-target effects. Ongoing experiments are focused on optimizing miRNA mimic delivery via nanoparticles for targeted liver therapy.

THU-043

Nuclear factor I-B delays liver fibrosis by inhibiting chemokine ligand 5 transcription

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Background and aims: Liver fibrosis is a vital pathophysiological process in various liver-related diseases, with hepatic stellate cells (HSCs) activation being crucial in its development. Reduced expression of nuclear factor I-B (NFIB) has been observed in patients with cirrhosis and liver fibrosis of mice models. This study aims to investigate whether restoring NFIB expression can alleviate liver fibrosis in mice and elucidate its potential mechanism.

Method: NFIB expression in HSCs was assessed in tissues from cirrhotic patients and liver fibrosis of mice models, by feeding a choline-deficient l-amino acid defined diet (CDAA) and carbon tetrachloride (CCl4) injection. The transcriptome was analyzed using RNA-sequencing. ChIP and luciferase reporter experiments were used to identify the potential target of NFIB during liver fibrosis.

Results: Our study demonstrates that NFIB expression is down-regulated at both the transcriptional and protein levels in human and mouse tissues. Overexpression of NFIB in HSCs inhibited the progression of CDAA and CCl4-induced liver fibrosis. Furthermore, NFIB overexpression in HSCs reduced activation of HSCs, decreased oxidative stress, and attenuated cell inflammation. RNA-seq analysis identified CCL5 as a key target of NFIB-induced changes in HSCs. During liver fibrosis, NFIB bound to the CCL5 promoter and suppressed CCL5 expression. Further analysis showed that the transcriptional inhibitory effect of NFIB on CCL5 was dependent on IRF3.

Conclusion: Our findings elucidate the mechanism of NFIB, and suggest that targeting the NFIB-IRF3-CCL5 axis could be a promising strategy for treating liver fibrosis.

THU-044

CCN5 promotes fibrogenic activation of hepatic stellate cells and serves as a biomarker for liver fibrosis

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Background and aims: Matricellular protein Cellular Communication Network Factor 5 (CCN5) has been implicated in organ fibrosis. This study aimed to investigate the relevance of CCN5 in hepatic stellate cell (HSC) activation crucial for liver fibrogenesis and to evaluate plasma CCN5 as liver fibrosis biomarker.

Method: CCN5 expression in liver and plasma was analyzed bioinformatically from public databases for association with liver fibrosis. Fibroblast-specific *Ccn5* loss- and gain-of-function mice were generated to evaluate the implications of Ccn5 on liver fibrogenesis, and mass spectrometry was conducted to identify CCN5 interacting proteins. Finally, human fibrotic liver and plasma samples were collected to validate CCN5 as the biomarker for liver fibrosis.

Results: CCN5 expression was nearly undetectable in quiescent HSCs but significantly increased in activated HSCs of CCl_4-induced mouse and human fibrotic livers of various etiology. Fibroblast-specific-*Ccn5* deletion mice exhibited reduced myofibroblast formation and ECM production hence inhibited liver fibrogenesis, while fibroblast-*Ccn5* overexpression promoted fibrosis progression. Mechanistically, CCN5 facilitated MOESIN phosphorylation and activated the downstream MRTF-A/SRF pathway, which promoted HSC activation triggering liver fibrosis progression. As a secreted protein, CCN5 plasma level was associated with liver diseases in the UKB population and our cohort demonstrated high diagnosis performance of plasma·CCN5 level for mild liver fibrosis that was superior to the classical tests. Finally, plasma CCN5 level exhibited a strong correlation with the degree of liver fibrosis, and its coefficient value was superior to FIB-4 index, PRO-C3 and MELD score.

Conclusion: CCN5 activates the MOESIN/MRTF-A/SRF pathway in HSCs promoting liver fibrosis progression and plasma CCN5 level is a novel biomarker for early detection and severity assessment of

fibrosis, providing an accurate non-invasive tool to monitor therapeutic outcome.

THU-045

Neo-epitope biomarkers for fibrogenesis and neutrophil activity predict liver-related events in advanced chronic hepatitis C infection

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Background and aims: Patients with untreated chronic hepatitis C (CHC) infection are at increased risk of developing a liver-related event. Despite the availability of simplified direct-acting antiviral therapy, the prevalence of CHC remains unchanged in many industrialized countries. Biomarkers that can predict which chronic liver disease patients with inflammatory injury are at greatest risk of developing a clinical outcome are required. In a well-characterized study population from The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial (HALT-C) (ClinicalTrials.gov #NCT00006164), we investigated the incidence of liver-related outcomes in patients with hepatitis C virus (HCV) who were non-responders to prior interferon-based standard-of-care with either high or low active fibrogenesis, measured by PRO-C3, in combination with high or low neutrophil activity, measured by CPa9-HNE.
Method: In this study population, we measured serum concentrations of the fibrogenesis marker, nordicPRO-C3™ measuring type III collagen formation, and the neutrophil activity marker measuring human neutrophil elastase cleaved calprotectin, nordicCPa9-HNE™. The event-free survival probability over 1511 days was investigated between four groups with combination of high and low PRO-C3 (high >27.8 ng/mL > low) and CPa9-HNE (high >1850.5 ng/mL > low): 1) low PRO-C3 and low CPa9-HNE, 2) low PRO-C3 and high CPa9-HNE, 3) high PRO-C3 and high CPa9-HNE, 4) high PRO-C3 and low CPa9-HNE. The Cox proportional hazards model was used to evaluate differences between the event-free survival curves. Data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases.
Results: Our study population included 339 CHC patients (62% with F3-F4) with a median age of 50 years (47–55), BMI of 29.4 (26.6–32.6), and 65% male. Eighty-nine patients (26%) had a liver-related event (related to decompensation and hepatocellular carcinoma). Patients were divided into four groups based on whether their baseline levels of PRO-C3 and CPa9-HNE were high or low. Among these groups, patients with high PRO-C3 and low CPa9-HNE had the lowest event-free survival rate, with 46.9% (95% CI: 30.4–63.5) remaining event-free after 1511 days. In contrast, patients with low PRO-C3 and high CPa9-HNE had the highest event-free survival rate, with 87.9% (95% CI: 73.5–100) remaining event-free after 1511 days. The difference in survival probability between these two groups was statistically significant ($p = 0.003$).
Conclusion: CHC patients with advanced fibrosis stage, high active fibrogenesis, and low neutrophil activity have a higher risk of developing liver-related events compared to low active fibrogenesis and high neutrophil activity baseline levels. These findings should be validated in other chronic liver diseases with pro-inflammatory activity to identify patients at higher risk of disease progression.

THU-046

Engineering liver fibrosis in a three-dimensional, extracellular matrix-hydrogel, ex-vivo disease model

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Background and aims: The US Food and Drug Administration (FDA) has proposed to reduce reliance on animal models in drug development and promote preclinical models yielding physiologically relevant results. Modeling fibrosis requires replicating the mechano-chemical cues of the extracellular matrix (ECM), including binding sites, three-dimensionality and biomechanics. Here, we present a liver fibrosis model based on native, decellularized ECM with spatial and compositional integrity layered on a hydrogel of polyethylene glycol diacrylate (PEGDA) that provides tunable mechanical properties.
Method: Human liver from consenting donors and porcine liver was sliced at 250 µm thickness, decellularized to retain 3D ECM architecture, and adhered to a PEGDA hydrogel contained in a 48-well plate. PEGDA concentration was modulated to model healthy (~1–5 kPa) or fibrotic (~20–30 kPa) liver stiffness. Primary human hepatic stellate cells (HSCs) repopulated ECM-PEGDA constructs, cultured with medium enriched with transforming growth factor beta 1 (TGF-B1), tumor necrosis factor alpha (TNF-a), chemokine ligand 2 (CCL2), thymic stromal lymphopoietin (TSLP), and interleukin (IL)-1b, IL-4, IL-8, IL-13, and IL-33. In this proof-of-concept study, ECM formation was evaluated with fibrogenesis biomarkers nordicPRO-C1, nordicPRO-C3, and nordicPRO-C6, surrogates of collagens type I, III, and VI synthesis, respectively. The constructs were imaged with two-photon and confocal microscopy.
Results: At 7.5% PEGDA, mimicking healthy tissue, average levels of nordicPRO-C1, nordicPRO-C3, and nordicPRO-C6 on day 8 were measured at 255.87 ± 26.62 ng/mL, 13.73 ± 2.44 ng/mL, and 3.12 ± 0.51 ng/mL, respectively. By comparison, constructs with higher stiffness (15% PEGDA) demonstrated lower average concentrations of these markers on day 8, with values of 187.01 ± 88.29 ng/mL, 9.84 ± 4.64 ng/mL, and 2.65 ± 2.14 ng/mL, respectively. Over a 12-day stimulation period, nordicPRO-C3 levels increased gradually, with average concentrations of 10.55 ± 4.08 ng/mL, 13.73 ± 2.44 ng/mL, and 17.97 ± 4.35 ng/mL measured on days 4, 8, and 12, respectively. HSCs selectively colonize the ECM, with nuclei structure following interstitial matrix anatomy. Fluorescent labelling revealed alpha-smooth muscle actin (aSMA+) cytoskeleton in HSCs, suggesting HSC activation.
Conclusion: HSCs colonize human and porcine ECM and synthesize new ECM. Biochemical signaling induces ECM formation, while biomechanical properties regulate biomarker production, jointly simulating the fibrotic niche. Porcine ECM is anatomically similar to human ECM, readily available, and enables high-throughput modeling with no animals being sacrificed for model fabrication.

THU-047-YI

Inhibition of Adipocyte triglyceride lipase (ATGL) reduces fibrosis and portal hypertension in murine CCl4 liver fibrosis

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Background and aims: Immune cells orchestrate hepatic inflammation and fibrogenesis. Importantly, their intrinsic lipid metabolism is among their key phenotypic determinants in addition to the critical impact of lipotoxicity on hepatocellular injury. We investigated the role of lipolysis in liver fibrosis by studying adipocyte triglyceride lipase (ATGL) that cleaves triacyl glycerides stored in lipid droplets.

Hepatic ATGL deficiency promotes lipid accumulation but in turn, prevents lipotoxicity originating from lipolysis-derived intrahepatic free fatty acids (FFAs). Thus, targeting lipolysis via ATGL may represent a novel therapeutic approach in fibrosis.
Method: Liver fibrosis was induced in male C57BL/6 mice by administration of carbon tetrachloride (CCl_4; 3×/week, 2 ml/kg, oral gavage) for 8 weeks, while healthy control groups received olive oil (OO). Healthy and diseased mice were treated with an ATGL inhibitor (Atglistatin, 2 mmol/kg), via oral gavage (2×/day for 4 weeks; 200 µmol/kg, n = 10), and diet supplementation (2 mmol/kg chow diet for 8 weeks, n = 10), whereas the respective control groups (n = 10 each) received olive oil as vehicle control under pair-fed conditions. Hepatic collagen proportionate area (CPA) was assessed histologically and portal pressure measured invasively, while fibrogenic and inflammatory gene expression were quantified by qPCR and bulk tissue RNA sequencing. Hepatic immune cells were profiled using flow cytometry.
Results: ATGL-inhibition strongly improved features of liver fibrosis (CPA: 5,07 ± 1,16 vs. 3,09 ± 1,28%; p < 0,0002) and portal hypertension (7,94 ± 0,97 vs. 6,87 ± 0,62 mmHg; p = 0,004). This was accompanied by markedly reduced profibrogenic (*Col1a1, Acta2, Tgfb1, Timp1*) gene expression. Intrahepatic lipid accumulation was confirmed by histology supporting sufficient hepatic ATGL inhibition by Atglistatin. Moreover, Atglistatin remarkably increased liver to body weight ratio (4,915 ± 0,48 vs. 5,97 ± 0,49%) and induced a proinflammatory transcriptional signature (*Mcp1)*, suggesting inflammatory hepatic immune cell infiltration. In liver flow cytometry, this was predominantly reflected by a strongly increased abundance of $CD3^+$ T-cells - further identified as $CD8^+$ T-cells (14,32 ± 3,29% vs. 6,76 ± 1,58 of the $CD45^+$ population). The role of hepatic $CD8^+$ T-cells, promoted by Atglistatin treatment, will be functionally dissected *in vitro*.
Conclusion: Our data shows a protective role for Atglistatin in a model of toxic liver fibrosis. The underlying potential mechanism is a profound alteration of the liver immune cell niche and points towards a novel role for ATGL-driven lipolysis in T cell biology during fibrosis. Ongoing transcriptome sequencing and cytokine profiling will allow deciphering of our findings on lipase-mediated immunoregulation in liver fibrosis.

THU-048

Cell-type specific roles of TGF-β2 signaling in cholestatic liver disease progression and therapeutic targeting

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Background and aims: In both healthy and diseased livers, TGF-β2 is predominantly expressed in cholangiocytes and proliferating bile ducts, with its expression upregulated in response to tissue damage and inflammation. However, the role of TGF-β2 and its downstream signaling pathways in the progression of liver disease remains poorly understood. This study investigates the expression dynamics of TGF-β2, identifies target cells, and analyzes signaling outcomes with cell-specific resolution in patients with primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA).
Method: Liver tissues from PSC and CCA patients were analyzed through hematoxylin and eosin (HE) staining and immunohistochemistry (IHC). The localization of TGF-β2 and its receptor, TGFβR3, was determined using RNAscope. In silico analysis of three databases was conducted to identify upstream regulators of TGF-β2 expression, including transcription factors, cytokines, bile acids, and stressors, which were experimentally validated in the human cholangiocyte cell line MMNK1 at both mRNA and protein levels. Pharmacological inhibitors were used to target specific signaling pathways. Bulk RNA sequencing was performed on MMNK1 cells after TGF-β2 treatment at various time points.
Results: In PSC and CCA patients, TGFβR3 was primarily localized in non-parenchymal cells such as activated myofibroblasts and CD31-positive cells within periportal regions, as shown by co-staining analysis. In contrast, TGF-β2 was mainly expressed in cholangiocytes. Bioinformatic analysis of the TGF-β2 promoter revealed several candidate transcription factors, including CREB1, involved in its induction. Bile acids, such as lithocholic acid (LCA), and combinations of ursodeoxycholic acid (UCDA), chenodeoxycholic acid (CDA), and deoxycholic acid (DCA), induced TGF-β2 expression in cholangiocytes. Cellular stressors, such as hydrogen peroxide (H_2O_2), also upregulated TGF-β2 in MMNK1 cells. Inhibition of the farnesoid X receptor (FXR) with GW4064 attenuated TGF-β2 expression induced by LCA or H_2O_2 in MMNK1 cells. Furthermore, TGF-β2 stimulation in MMNK1 cells deregulated extracellular matrix (ECM) components, induced Smad3 phosphorylation, and modulated TGF-β signaling pathways. Spatial transcriptomics in PSC liver tissues further elucidated TGF-β2 signaling activation, providing insights into its role in disease progression.
Conclusion: This study offers a detailed cell type-specific analysis of TGF-β2 and TGFβR3 expression in PSC and CCA tissues. It identifies potential regulatory mechanisms and therapeutic targets to mitigate TGF-β2-driven disease progression, highlighting the inhibition of TGF-β2 expression as a promising strategy for therapeutic intervention.

THU-049-YI

Extracellular vesicle-dependent crosstalk between hepatic stellate cells and Kupffer cells promotes their mutual activation

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Background and aims: Hepatic fibrosis is characterized by activation of hepatic stellate cells (HSCs), resulting in excessive extracellular matrix (ECM) deposition by these cells. Chronic inflammation is the key driver of HSC activation in the liver. Kupffer cells (KCs), the liver-specific macrophages, play an important role in HSC activation. Although KCs can trigger HSC activation, this regulation is not exclusively one-way. Our study aims to explore the reciprocal interaction between HSCs and KCs, focusing on the role of extracellular vesicles (EVs) as mediators of this crosstalk.

Method: Primary HSCs and KCs were isolated from male Wistar rats. HSCs were co-cultured with KCs for 24 hours, and changes in inflammatory markers in KCs and activation markers in HSCs were evaluated. EVs derived from KCs, with or without lipopolysaccharide (LPS) stimulation, were administered to HSCs on day 1. LPS and the Toll-like receptor 4 (TLR4) inhibitor TAK-242 were used to investigate the intercellular communication in detail.
Results: Co-cultured HSCs and KCs exhibited mutual activation, demonstrated by elevated inflammatory markers in KCs and enhanced HSC activation. KCs-derived EVs induced similar activation, with LPS amplifying this bidirectional interaction. Inhibition of TLR4 signaling significantly reduced KC activation and slightly suppressed HSC activation, indicating the involvement of TLR4 signaling in this crosstalk.
Conclusion: HSCs and KCs engage in a positive feedback loop, facilitating mutual activation. This interaction is partly mediated by EVs, with LPS augmenting the effect. TLR4 signaling is partly involved in this reciprocal activation, highlighting its importance in the intercellular communication between liver-resident cells.

THU-050-YI
Dual inhibition of glutaminolysis and de novo amino acid synthesis underpins Pirfenidone's suppression of hepatic stellate cell activation
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Background and aims: Activation of hepatic stellate cells (HSCs) from their quiescent state (qHSC) to activated myofibroblasts (aHSC) is a pivotal event in liver fibrosis, marked by excessive extracellular matrix (ECM) deposition. Metabolic reprogramming, particularly through glutaminolysis and de novo amino acid synthesis, has been identified as a critical driver of HSC activation. Pirfenidone (PFD) is known to inhibit HSC activation and fibrosis in rodent models, though its precise molecular mechanisms remain unclear. This study investigates the role of PFD in suppressing HSC activation by targeting key metabolic pathways.
Method: Primary HSCs were isolated from male Wistar rats and examined at distinct activation stages: qHSC (Day 1), intermediate activating HSC (Day 3), and fully activated aHSC (Day 7). Cells were treated with PFD (10–1000 nM) for 72 hours. LX-2 cells were activated with TGF-β (2.5 ng/mL) and treated with PFD (0.1–1000 μM) for 72 hours. Cellular activation markers and protein levels of key enzymes involved in glutaminolysis (glutaminase 1, GLS1) and de novo proline (pyrroline-5-carboxylate synthase, P5CS) and glycine (serine hydroxymethyltransferase 2, SHMT2) synthesis were analyzed.
Results: PFD exhibited dose-dependent inhibition of HSC and LX-2 cell proliferation and reduced protein expression of activation markers, with limited effect on transcriptional levels. Inhibition of glutaminolysis via glutamine deprivation or GLS1 inhibition (CB-839) was used as a control to confirm PFD's broader effects. PFD reduced GLS1 expression and simultaneously downregulated P5CS (proline biosynthesis) and SHMT2 (mitochondrial one-carbon metabolism) in an ATF4-dependent manner.
Conclusion: PFD effectively suppresses HSC activation by modulating metabolic reprogramming pathways, including glutaminolysis and amino acid metabolism, which are essential for collagen synthesis. These findings highlight PFD's potential as an anti-fibrotic agent and underscore the therapeutic promise of targeting metabolic reprogramming to reverse fibrosis in liver and other organs.

THU-055-YI
Novel natural killer cell immunotherapy through synthesized Neuroligin-4 peptides improved liver fibrosis
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Background and aims: NK cells lose their antifibrotic potential in advanced liver fibrosis, particularly in patients with non-alcoholic fatty liver disease (NAFLD). Neuroligin-4 (NLGN4) receptor was recently found to overexpress NK cells and influence their killing potentials in NAFLD patients with advanced liver fibrosis. NLGN4 and its ligand β-neurexin (β-NRXN) expressed on activated hepatic stellate cells (HSCs) were shown to exert a synergistic inhibitory effect on NK cells. β-NRXN overexpression in activated HSCs indicated its role in fibrogenesis. Herein, we developed newly synthesized NLGN4 peptides to assess their impact on NK cells and HSCs activities in an in vitro and in vivo liver fibrosis model.
Method: Three synthesized peptides were used and incubated for two hours at a concentration of 2,4,8 μg/ml with LX2 cells before co-culturing with NK cells obtained from NAFLD patients with F3/F4 scores for 24 hours. Flow cytometry assessed NK cell activity through CD107a, lysosomal-associated membrane protein-1, and LX2 activations through α-Smooth muscle actin. For the in vivo study, C57/Bl mice were injected with CCl_4-induced liver fibrosis (0.5 μl/g body weight) and synthesized peptides (8 μg/mice) twice a week for 6 weeks. Serum and livers were assessed for pro-inflammatory cytokines and histopathological staining, respectively.
Results: In an in vitro setting, HSCs pre-incubated with NLGN4 peptides reduced their activations (αSMA expressions 1.53 and 1.55-folds in peptide 1 and peptide 2, respectively, $P < 0.001$) with a further prominent reduction in αSMA expressions following incubations with NK cells (2.85 and 2.3-folds in peptide 1 and peptide 2, respectively, $P < 0.001$). Moreover, the studied peptides downregulated expressions of both NLGN4 and β-NRXN in liver extracts isolated from the CCl_4 liver fibrosis mice model. NLGN4 peptides showed delayed progressions of liver fibrosis by improving liver histological findings of inflammatory and fibrotic lesions and reducing liver injury enzymes (ALT). Fibrotic markers (αSMA, Collagen, CREB, and MMP4) were assessed via western blot. RT-PCR was also alleviated following treatment with peptides. These results were associated with elevated NK cell activations assessed by the CD107a and F-actin expressions through flow cytometry and confocal microscopy.
Conclusion: Interruption of NK/myofibroblast cellular synapse by targeting the NLGN4/β-NRXN axis with NLGN4 peptides achieved synergistic antifibrotic effects through (1) cytotoxic NK cells stimulation against myofibroblasts; either directly via NLGN4 inhibition and indirectly by blocking the NK inhibitor β-NRXN, (2) directly inhibit β-NRXN of myofibroblasts and decreased their activation. Thus, immunotherapy targeting the NLGN4/β-NRXN axis represents a novel immune therapeutic strategy in NK cell-mediated diseases.

THU-056
A human-like bile salt pool critically modulates liver fibrosis in bile duct ligation-challenging mice
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Background and aims: Accumulation of hydrophobic bile salts is believed to promote liver fibrosis in human cholestatic liver disease. An important difference between mice and man in regard to liver pathophysiology is their different composition of the bile salt pool with hydrophilic bile salts such as tauro-β-muricholate (TβMC)

predominating in mice, and hydrophobic bile salts such as glycochenodeoxycholate (GCDC) in man. Here, we further explored the capability of various bile salts to activate HSC in vitro and tested the role of a humanized bile salt pool in development of liver fibrosis.
Method: The human HSC line LX2 was stimulated with bile salts in standard culture medium at a slightly acidic pH (7.3) to account for the acidic microenvironment known to be present in the perisinusoidal space. Activation of cells was quantified by Western blotting for αSMA (normalized for GAPDH). C57BL/6 mice were fed a control diet or a diet enriched with GCDC (0.1% w/w) to humanize their bile salt pool and treated with bile duct ligation (BDL). Concentrations of bile acids in serum were measured by LC-MS/MS. Liver fibrosis was quantified by various histological staining and serum biochemistry.
Results: LX2 were stimulated with unconjugated bile salts, including chenodeoxycholate (CDC), cholate, deoxycholate (DC) and βMC at 20 µM, respectively. Among those, only CDC and DC, predominating hydrophobic bile salts in man, led to an increase in αSMA expression by 1.7 ± 0.5- and 1.9 ± 0.6-fold respectively, compared to control ($n = 4$, $p < 0.05$). In vivo, BDL led to development of liver fibrosis, as expected. Supplementation with GCDC increased its plasma level from 0.03% to 22.9% in BDL mice (BDL+ Control vs. BDL+ GCDC, $n = 5$, $p < 0.05$), and additionally aggravated this phenotype, as evidenced by Masson staining (BDL+ GCDC vs. BDL+ Control: 12.1 ± 1.6 vs. 9.8 ± 2.3, $n = 7$, $p < 0.05$), Sirius red staining (13.0% ± 3.3% vs. 9.0% ± 0.7%, $n = 7$, $p < 0.05$) and immunohistochemical staining for αSMA expression (7.2% ± 2.9% vs. 3.3 ± 1.2, $n = 7$, $p < 0.05$). However, GCDC diet did not change the total bile acid concentration in mice. ALT and AST serum levels were unaltered by GCDC feeding in both control and BDL-treated animals, excluding a direct co-toxic effect of GCDC. In control animals without BDL-treatment, bile salt feeding was without pro-fibrotic effects.
Conclusion: Our data add to the growing body of evidence, that human, hydrophobic bile salts can directly activate hepatic stellate cells to promote liver fibrosis. This way of 'humanization' of murine models should thus be further explored when studying liver pathophysiology or exploring novel pharmacological therapies in chronic liver disease.

THU-057
Disease-specific human ECM composition and bioactivity in MASH liver fibrosis

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Background and aims: The extracellular matrix (ECM) is a complex bioactive network of macromolecules. Excessive accumulation of ECM proteins is a hallmark of fibrosis, which can occur in all organs of the body. While normal ECM-cell interactions maintain tissue homeostasis, in fibrotic conditions, the ECM promotes pathogenic responses that contribute to inflammation and fibrosis. The ECM's role in tissue damage and fibrosis progression is not fully understood, presenting an opportunity to identify and evaluate novel therapeutic targets for the treatment liver fibrosis.
Method: We describe a novel approach aimed at studying the contribution of the cirrhotic ECM on cellular functions through the development of a 3D cirrhotic ECM assay.
Results: We developed protocols to generate decellularized ECM from MASH cirrhotic livers ($n = 3$). Tissues were characterized using immunohistochemistry pre- and post-decellularization to confirm maintenance of tissue architecture and decellularization was confirmed by measuring DNA content (≤50 ng/mg of tissue). TMT proteomics was performed to study ECM composition in cirrhotic livers. Matrisome analysis identified MASH livers exhibited an enrichment of pathways related to ECM formation, remodelling, and inflammation. We demonstrated incorporating cirrhotic ECM into a disease-centric 3D assay using primary human hepatic stellate cells (HSCs) supported robust cellular viability (>95%) and led to an altered secretory profile compared with cultures established in healthy ECM. Additionally, these cells maintained their ability to respond to fibrogenic mediators.
Conclusion: The development of fibrosis results from the complex interplay of the extracellular microenvironment and the cells within the liver. This cross talk can lead to the loss of normal tissue architecture and organ function. We describe the development of a novel disease-centric assay to enhance our understanding of the pathogenic mechanisms. This assay focuses on the cross talk between cirrhotic ECM and cells and will support the development of novel anti-fibrotic therapies.

THU-058-YI
Blockage of microfibrillar-associated protein 4 (MFAP4) decreases liver fibrosis in two murine models of steatotic liver disease

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Background and aims: Liver fibrosis, a key feature of chronic liver diseases, represents the progressive accumulation of extracellular matrix proteins that can lead to cirrhosis and subsequent portal hypertension, if left untreated. Microfibrillar-associated protein 4 (MFAP4) is a key protein involved in microfibril formation during fibrillin assembly in elastin formation. MFAP4 levels in the liver increase with ongoing fibrogenesis. Circulating and hepatic MFAP4 showed good predictive ability for liver fibrosis. However, no therapeutic studies were conducted towards this protein. We aimed to investigate the efficacy of a MFAP4 blocking antibody in well-established mouse models of steatotic liver disease.
Method: Hepatic *MFAP4* was determined in human liver transcriptomes (cirrhosis ($n = 22$); non-cirrhotic individuals ($n = 8$)). For the *in vivo* study, two carbon tetrachloride (CCl_4)-based models of experimental liver fibrosis (intraperitoneal injection 2×/week for 7 weeks) were used in male C57Bl/6 mice. A metabolic dysfunction-associated steatotic liver disease (MASLD) model using CCl_4 and Western diet and an alcohol-associated liver disease (ALD) model using CCl_4 + alcohol in the drinking water (stepwise increase to 16%). Mice received either the MFAP4 antibody (20 mg/kg in week 5 and 5 mg/kg in week 6 and 7) or a vehicle intraperitoneally ($n = 8–10$ for each group). Prior to sacrifice, portal pressure (PP) was measured *in vivo*. After sacrifice, hepatic fibrosis was evaluated using Sirius Red staining, hepatic hydroxyproline content and qPCR for *Col1a1* and *Tgfb*. Hepatic elastin and MFAP4 were determined via Western Blotting.
Results: In our human transcriptomic data set, MFAP4 was identified to be highly upregulated during cirrhosis, and was well correlated with established genes involved in fibrogenesis. In the MASLD model mice developed portal hypertension (median PP = 10 mmHg), which trended to improve in the intervention group (median PP = 8 mmHg). Hepatic collagen accumulation (Sirius Red staining) improved significantly in MASLD mice treated with MFAP4-antibody ($p = 0.03$). In ALD mice, this improvement in treated mice was less strong. Hepatic hydroxyproline levels, an important component of collagen synthesis, confirmed the observations from the histological staining in both models (for MASLD: $p = 0.11$). Hepatic collagen (*Col1a1*) and *Tgfb*-expression also trended to decrease in both models, with a stronger effect in MASLD mice. Finally, Western blot deciphered a decrease of hepatic elastin levels in both models after MFAP4 blockage.

Conclusion: Our study showed that blockage of MFAP4 in murine MASLD and ALD models displays antifibrotic effects in the liver and should be therefore further evaluated as antifibrotic treatment for steatotic liver disease.

THU-059

Use of the LiverRisk score for prediction of moderate to advanced liver fibrosis in United States adults

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Background and aims: Resmetirom is the first approved treatment in the United States (US) for noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis [NASH]), conditionally approved for use in adults with moderate to advanced liver fibrosis consistent with stages F2 to F3. Patient selection for treatment with resmetirom may be based on evidence of fibrosis from noninvasive tests (NITs). Liver stiffness measurement (LSM) of 8–20 kPa by vibration-controlled transient elastography (VCTE) (with exclusion of cirrhosis) is considered a potential signal of fibrosis stages F2–F3. The LiverRisk Score (LRS) is a NIT based on blood-based biomarkers and demographics, developed for prediction in the general population of liver fibrosis and future liver-related outcomes. This study evaluated in US adults the performance of the LRS for prediction of LSM ≥8 kPa and ≥20 kPa compared to the Fibrosis-4 (FIB-4) Index.
Method: An observational analysis was conducted of the National Health and Nutrition Examination Survey (NHANES) 2017–2020 cycle, including participants who had complete information to calculate the LRS (i.e., age, sex, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, fasting glucose [imputed from non-fasting when missing], total cholesterol, and platelet count). Performance of the LRS vs. FIB-4 for prediction of LSM ≥8 kPa and ≥20 kPa was evaluated as area under the curve (AUC), estimated by survey-weighted logistic regression of LSM ≥8 kPa/ ≥20 kPa vs. the LRS or FIB-4.
Results: The unweighted study population included N = 7,005 participants. The LRS demonstrated significantly ($p < 0.05$) superior discrimination of LSM ≥8 kPa vs. FIB-4 in all adults, with AUC (95% confidence interval [CI]) of 0.73 (0.71–0.75) for LRS and 0.63 (0.61–0.65) for FIB-4. Discrimination remained numerically superior for LSM ≥20 kPa, with AUC (95% CI) of 0.79 (0.74–0.84) for LRS and 0.73 (0.67–0.79) for FIB-4. Improved accuracy was driven by lower false positive rates (at fixed sensitivity) for LSM ≥8 kPa, and higher true positive rates (at fixed specificity) for LSM ≥20 kPa.
Conclusion: In US adults, the LRS demonstrated superior accuracy vs. FIB-4 for prediction of LSM ≥8 kPa and ≥20 kPa, which could facilitate screening for noncirrhotic MASH with fibrosis stages F2–F3.

THU-060

Insulin-like growth factor binding protein 7 promotes the development of metabolic dysfunction-associated steotic liver disease-related hepatic fibrosis and induces decreased cardiac function

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Background and aims: Individuals with metabolic dysfunction-associated steotic liver disease (MASLD) are at an increasing risk of both liver-related adverse outcomes and cardiovascular diseases. However, the dynamic interplay between liver and cardiac function in the context of MASLD remains poorly understood. This study aimed to uncover the role of insulin-like growth factor binding protein 7 (IGFBP7) in the development of liver fibrosis and its associations with cardiac function.
Method: Circulating IGFBP7 levels and liver tissue expression were analyzed in patients with liver fibrosis. Male C57BL/6J mice (six weeks old) were fed either a control chow or a high-fat, high-fructose diet (HFFD) for 20 weeks to induce MASLD-associated liver fibrosis. Igfbp7-targeting shRNA was placed downstream of the Postn promoter and packaged into AAV6 (AAV-shIgfbp7) to deplete Igfbp7 in mature myofibroblasts. Left ventricle ejection fraction (LVEF) of mice was assessed by echocardiography. Liver histology was evaluated using immunohistochemistry (IHC), hematoxylin-eosin, picrosirius red and Masson's trichrome. Human immortalized hepatic stellate cells (LX-2) were activated with transforming growth factor-beta (TGF-β) for in vitro studies.
Results: Circulating IGFBP7 levels were positively correlated with liver stiffness measurements (LSM) in patients with liver fibrosis and concurrent heart failure. IHC analysis of liver samples confirmed that IGFBP7 expression was proportionally associated with the severity of liver fibrosis. Similar trends were observed in mice subjected to an HFFD. Compared to control mice, MASLD mice exhibited a significant reduction in LVEF, which was attenuated upon Igfbp7 depletion. In primary hepatic stellate cells (HSCs) isolated from wild-type mice, Igfbp7 mRNA levels increased along with myofibroblast markers (*Acta2, Postn, Col1a1*) during spontaneous activation. TGF-β-activated LX-2 cells exhibited increased Igfbp7 expression, along with enhanced migration, proliferation, and contraction abilities. Notably, these effects were mitigated by reducing Igfbp7 expression.
Conclusion: IGFBP7 is a promising biomarker for assessing liver fibrosis severity and cardiac dysfunction in individuals with MASLD. Further studies are warranted to elucidate the underlying mechanisms.

THU-061

The study of pathogenesis of the progression of liver cirrhosis

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Background and aims: In the case of liver cirrhosis (LC) the increased permeability of the intestinal mucosa and portosystemic shunting allows endotoxins and cytokines to penetrate into the system circulation and causes pathogenetic changes. The aim was to evaluate the peculiarities of the LC by studying the main pathogenetic links of the disease, namely endotoxicosis, level of cytokines and the state of the detoxification function of the liver.
Method: 105 patients with LC were examined (14 females and 91 males with age 34–64 years old. The duration of the disease in patients ranged from 2 to 9 years. According to Child-Pugh score, the patients were distributed as follows: 63.8% (67 patients) in class B and 36.2% (38 patients) in class A. The expression of endogenous intoxication was assessed by the levels of bacterial endotoxin. The levels of TIMP-1 and TGF-beta1 were determined by ELISA method (DIACLONE, France). Determination of liver detoxification function was done by the 13C-methacytin breath test (13C-MBT).
Results: The assessment of endogenous intoxication revealed an increase the level of bacterial endotoxin in patients with LC: (81.32 ± 2.1) pg/ml, which was significantly different from healthy individuals (23.6 ± 0.91) pg/ml ($p < 0,05$). Moreover, the level of bacterial endotoxin in patients with class B exceeded this it in the patients with class A by 19.5%. It was established that the levels of the studied indicators increase with progression of the LC and reliably different depending on the severity of the disease. The level of TIMP-1 in

patients with class A was (497.7 ± 5.6) pg/ml, and (538.4 ± 5.9) pg/ml with class B ($p < 0.001$). The level of TGF-beta1 was (453.2 ± 4.7) pg/ml in patients with class A and (496.3 ± 6.1) pg/ml with class B respectively ($p < 0.001$). During assesment of relationships of studied indicators, it was established the direct strong correlation between bacterial endotoxin and TGF-beta1 ($r = 0.75$, $p < 0.05$), bacterial endotoxin and TIMP-1 ($r = 0.72$, $p < 0.05$). Also, a strong inverse relationship was founded between bacterial endotoxin and the indicator of liver detoxification function ($r = –0.85$, $p < 0.05$), and medium power correlation between TGF-beta1 and liver detoxification function ($r = –0.66$, $p < 0.05$).
Conclusion: An increase in the level of indicators of endogenous intoxication leads to an increase of the production of pro-fibrogenic factor TGF-beta1, which stimulate fibrogenesis and decrease the detoxification function of the liver, which causes the progression of the LC.

THU-062-YI
Human umbilical cord mesenchymal stem cells attenuate liver fibrosis in mice and inhibit hepatic stellate cell activation via secreting soluble factors
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Background and aims: Mesenchymal stem cells (MSCs) have emerged as promising candidates to treat clinical liver fibrosis. However, the key factors and mechanisms underlying their anti-fibrotic effects remain largely unclear. Our aims were to assess the therapeutic efficacy of human umbilical cord (UC) MSCs in a murine liver fibrosis model and to dissect the influence of their secretome in vitro.
Method: Liver fibrosis model was induced in mice through 6–10 week CCl_4 administration, combined with weekly intraperitoneal injections of MSCs starting either at week 0 (prevention) or week 6 (therapeutic). Fluorescently-labeled MSCs were used to trace cell distribution post-injection. Liver fibrosis was evaluated using Hematoxylin and Eosin (H&E) staining, Masson's trichrome staining and immunohistochemical (IHC) staining for alpha smooth muscle actin (a-SMA). Human LX-2 (immortalized hepatic stellate) cells were treated with complete UC-MSC-conditioned medium ($CM^{UC\text{-}MSC}$), its soluble factor MSC-CM ($SF^{UC\text{-}MSC}$) or the UC-MSC extracellular vesicles ($EV^{UC\text{-}MSC}$) fraction of the secretome. Expression of fibrosis-related genes was assessed using semi-quantitative PCR, immunofluorescence staining and Western blot analysis.
Results: UC-MSCs preferentially accumulated in the livers of fibrotic mice. Administered UC-MSC reduced histological changes, collagen deposition and a-SMA expression in fibrotic mice which essentially blocked and reversed liver fibrosis. *In vitro*, $CM^{UC\text{-}MSC}$ suppressed LX-2 proliferation and TGF-beta-induced *ACTA2*/a-SMA expression, but not *COL1A1*/collagen I expression. These effects persisted in EV-depleted $SF^{UC\text{-}MSC}$. $EV^{UC\text{-}MSC}$ did not suppress *ACTA2*/a-SMA nor *COL1A1*/collagen I levels in LX-2 cells.
Conclusion: Administered therapeutic UC-MSCs preferentially accumulate in the liver and effectively prevent and reverse liver fibrosis *in vivo*, in rodents while inhibiting hepatic stellate cell activation *in vitro*. The antifibrotic effects *in vivo* are likely primarily mediated by excreted soluble factors rather than extracellular vesicles.

THU-066
Femoral vs hepatic vein plasma levels of collagen biomarkers confirm Pro-C3 as true marker of collagen synthesis in the fibrotic/cirrhotic liver
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Background and aims: There is a direct correlation between the degree of portal hypertension and the extent of fibrosis in advanced liver diseases. A thorough characterization of serum markers of true fibrogenesis vs cross-sectional fibrosis is urgently needed. We therefore investigated the putative collagen formation biomarkers Pro-C3, Pro-C6 and Pro-C5 in a setting that allows their assessment as markers of collagen production and/or removal by the liver or the periphery.
Method: 58 patients with established cirrhosis, mainly due to alcohol abuse, were included (Child-Pugh, CPA-C, n = 20, 20, 18, resp.). Patients with portal hypertension who were abstinent and clinically stable underwent hepatic vein catheterization. Fasting femoral arterial, peripheral (femoral) and hepatic venous plasma samples were collected from patients and healthy controls (n = 13). Biomarkers of collagen formation were determined in EDTA plasma using validated competitive ELISAs.
Results: Pro-C3 levels were increased vs normal controls in all three vessels of CPA, B and- C patients. Pre- and post-hepatic venous biomarker levels showed a significant net production of Pro-C3 in the liver in all CP classes. There was a trend for a progressive increase across CP classes for Pro-C6 pre- and post-liver passage. In CPB and CPC compared to CPA, the values for Pro-C6 were significantly higher in the femoral than in the hepatic vein, indicating prominent production in extrahepatic sites. Pro-C5 was increased in the hepatic vein in all CP classes vs controls, while femoral vein Pro-C5 significantly increased from CPA to CPC. Femoral vein Pro-C5 was significantly lower vs hepatic vein Pro-C5 in both patients and controls, indicating extraction in the extremities. Pro-C3 and Pro-C6 were significantly increased in patients with vs without ascites. Both Pro-C3 and Pro-C6 showed a significant correlation with age, hemoglobin, serum albumin and CP scores.
Conclusion: Pro-C3, Pro-C5 and Pro-C6 were confirmed to be significantly increased in the peripheral blood of patients with cirrhosis. Notably, only Pro-C3 showed an increasing net hepatic production along with the severity of cirrhosis from class CPA to- CPC. Interestingly, levels of Pro-C6 were compatible with a prominent extrahepatic (vascular) source, while (hepatic) Pro-C5 appeared to be extracted or excreted in the periphery.

THU-067
A simple lab based machine learning model (FAET) predicts advanced Liver Fibrosis more accurately in MASLD patients
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Background and aims: Metabolic dysfunction-associated steatosis liver disease (MASLD) is often silent and progressive, affecting nearly one-fourth of the global population. However, liver biopsy remains the only accurate but invasive modality for diagnosis. We aimed to develop a machine learning model to assess liver fibrosis in MASLD patients.
Method: We analysed electronic medical records of biopsy-proven MASLD patients between 2022–23 retrospectively. Demographic, clinical and laboratory parameters were varible incorporated in the

model. Liver biopsy was used as the refrence for fibrosis assesement [NASH CRN score, F3–F4 is considered as advanced fibrosis and others as non-advanced fibrosis(NAF)]. Cleaned data was splitted into a train and test set (90:10). A total of 14 ML models were trained using PyCaret package to confirm the best performer. Extra Tree (ET) classifier, RF, lightgbm, gbc, xgboost,lr,lda, ridge,knn, ada, svm, nb,dt and qda were used. To enhance the usability, a web application "FAET Tool" was developed using Streamlit with the help of a GitHub repository. Fourteen ML models were developed and the best model was compared against the Fibrosis-4 (FIB-4) score, and APRI for detecting AF. The final best model with reduced features and a standard scaler was saved using the pickle library in Python, a web application was created using the Streamlit library. For further online deployment, a GitHub repository was created and this web application provided the remote access for real-time testing.

Results: Total of 452 patients (median age: 41 years; IQR 33–49; 75% male) had biopsy proven MASLD, and 222 (49.1%) had AF on biopsy. The FAET demonstrated the best performance, achieving 84% accuracy, an AUC of 0.82, an F1 score of 0.77, an NPV of 0.81, and a PPV of 0.91 using 13 variables. Compared to FIB-4, FAET improved accuracy by 33%, AUC by 34%, F1 score by 45%, NPV by 15.7%, and PPV by 71%. Similarly, compared to APRI, FAET improved accuracy by 58.4%, AUC by 49%, F1 score by 45.2%, NPV by 20.8%, and PPV by 111%. The higher F1 score reflects a better balance between precision and recall, and the improved NPV demonstrates a more reliable identification of patients who do not have AF. FAET model performed best with 13 features and the the best performance was mantained even with the top 5 features i.e. Age, platelet count, presence of Diabetes, Serum AST, and total Cholesterol. A web-based tool with equivalent accuracy was developed for deployment. The accuracy (79.61%), AUC (0.8725), and F1 score (0.7903) obtained in the FAET tool and was better than other models even in the selected 5 parametrs model.

Conclusion: FAET model offers a superiority over the current Fib-4 and APRI, as a non-invasive assessment tool for advanced fibrosis in MASLD patients. This is simple, easy, cost-effective, web based and has the potential for routine use pending further validation.

THU-068

EmTPx promotes liver fibrosis via enhancing IL-33 secretion from macrophage

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Background and aims: Liver fibrosis is a major characteristic of most chronic liver diseases and results in morbidity and mortality worldwide. *Echinococcus multilocularis* thioredoxin peroxidase (EmTPx) is an antioxidant protein, yet its specific role in liver fibrosis remains poorly understood. This study aims to elucidate the role of EmTPx in carbon tetrachloride (CCl_4)-induced liver fibrosis.

Method: During the CCl_4-induced model establishment, EmTPx was administered intraperitoneally over one month to evaluate its effects on fibrosis severity and macrophage polarization. Additionally, RAW264.7 macrophage cells were treated with EmTPx, and JS-1 hepatic stellate cells were co-cultured with the resultant cell supernatants.

Results: EmTPx administration exacerbated liver fibrosis, enhanced M1 polarization, and increased IL-33 expression in CCl_4-treated mice. In vitro, EmTPx promoted M1 polarization in RAW264.7 cells, and transcriptomic analysis indicated activation of the NF-κB signaling pathway. Selective inhibition of NF-κB using JSH-23 significantly reduced M1 polarization and IL-33 levels. Furthermore, fibrosis severity in JS-1 cells was heightened when co-cultured with the supernatant of RAW264.7 cells, a process mitigated by IL-33 inhibition.

Conclusion: Our findings reveal that EmTPx exacerbates liver fibrosis by enhancing IL-33 secretion through macrophage. EmTPx may represent a potential therapeutic target for managing liver fibrosis associated with *E.m.* infection.

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THU-069

A composite score of PRO-C6 and platelet count is prognostic for liver-related outcomes in patients with chronic hepatitis C

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Background and aims: There is a need for prognostic markers for patients with chronic liver-disease at increased risk of developing a liver-related outcome (LRO). Endotrophin, a potential driving fibroblast activation and promoting fibroinflammatory disease can be assessed using PRO-C6. We previously demonstrated the prognostic value of PRO-C6 in identifying patients with cirrhosis from chronic hepatitis C (CHC) at higher risk of developing a LRO. In this study, the aim was to explore the ability of a composite score of PRO-C6 divided by platelet count (PC) to predict LROs in The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial (HALT-C) (ClinicalTrials.gov #NCT00006164).

Method: nordicPRO-C6™ was measured in serum from baseline, using a fully validated competitive enzyme-linked immunosorbent assay. A composite score was calculated by dividing the baseline value of PRO-C6 with baseline PC. Patients were dichotomized into above and below a PRO-C6/PC of 0.0968, (15/155; 15 ng/mL was the upper quartile value of PRO-C6; 155 was the cohort median of PC × 1000/mm^3. Kaplan-Meier estimates and Cox regression were used to evaluate the prognostic value of PRO-C6/PC to identify patients at higher risk of developing LROs related to decompensation and Hepatocellular carcinoma. The same analysis was performed on a subgroup of all included patients with cirrhosis, n = 151, as previously shown with PRO-C6. Data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases.

Results: 339 patients with CHC infection from the HALT-C cohort, were included in this study. 68% were male, with median (Q1, Q3) age and BMI of 50 (47, 55) years and 29.4 (26.6, 32.6) kg/m^2, respectively. During the study follow-up time of 1400 days, 66 (19%) patients developed a LRO over a median (Q1, Q3) follow-up time of 841 (488, 1132) days. Dichotomizing the 339 patients above and below the PRO-C6/PC score cut-off, no patients in the low group had a LRO for more than a year, and the hazard ratio (HR) for having a LRO was 4.55 (95% CI = [2.66, 7.80], $p < 0.0001$) times higher in the high group compared to the low group. In the subgroup of 151 patients with cirrhosis, there were no LROs in the low group for more than two years, and a HR of 4.81 (95% CI = [2.23, 10.37], $p < 0.0001$) in the high group, with a median (Q1, Q3) follow-up time of 755 (371, 1098).

Conclusion: A composite score using PRO-C6, a biomarker of circulating endotrophin, and platelet count was associated with increased risk of developing a LRO, in patients with CHC. This composite score might provide prognostic value to identify patients with other pro-inflammatory advanced chronic liver disease at higher risk of developing a LRO. Comparison with other extracellular matrix biomarkers, and clinical outcome predictor models is ongoing. Validation of PRO-C6 and PC as prognostic markers following sustained virologic response in CHC, and other chronic liver diseases is still required.

THU-070

Characterizing the differentiation and cellular heterogeneity of hepatic stellate cells derived from induced pluripotent stem cells

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Background and aims: Hepatic stellate cells (HSCs) are the main fibrogenic cell type in chronic liver diseases. Phenotypic heterogeneity and functional diversity of HSCs population have been described using single-cell RNA sequencing (scRNA-seq). We have shown that human induced pluripotent stem cells (iPSCs) derived HSCs (diHSCs) mimic the phenotype and function of primary HSCs. In this study, we characterize the differentiation and activation of diHSCs, with the goal of assessing the dynamics of differentiation and the cellular heterogeneity within the diHSCs population.
Method: diHSCs were generated following a well-established 12-day protocol. Activation was induced by plating diHSCs on plastic or by treating them with 10 ng/ml TGF-b. Bulk RNA sequencing (RNA-seq) was performed at days 0,2,4,6,8,10,12 of the differentiation and in both activation models. diHSCs were analyzed using scRNA-seq and compared to primary HSCs.
Results: Bulk RNA-seq analysis revealed that quiescent HSC markers, (i.e. NCAM1, RELN, DCN, GATA6) started to be upregulated at day 6, while markers associated with activation, such as PDGFRB, COL1A1, ACTA2, and LOX, increased at day 8. Expression of RELN, RSPO3, PCDH7 and PDGFRB was confirmed by immunostaining. Plastic and TGF-b activation induced distinct molecular pathways. Plastic enhanced pathways related to cell contractility, extracellular matrix remodeling, and stress response, whereas TGF-b mediated activation enriched pathways involved in carbohydrate metabolism and glycolysis. Next, we assessed whether iPSCs differentiation could recapitulate the heterogeneity of HSCs. Bulk RNA-seq analysis revealed that markers for HSC populations of the portal and central regions (GPC3, DPT, FBLN1, CCL2) and perisinusoidal regions (DBH, RBP1, CXCL14, HHIP) began to increase at day 6. Additionally, markers associated with regenerative HSCs (HGF), lipid-associated HSCs (ADH4), and antigen-presenting HSCs (PLG) were enriched starting from day 10 of differentiation. scRNA-Seq analysis of diHSCs identified five distinct populations, all of which expressed common HSCs markers but exhibited specific gene signatures related to fibrinolysis, proliferation, contractile-myofibroblastic functions, fibrogenesis, and protein synthesis. The comparison with publicly available human liver single cell data showed that the cellular heterogeneity observed in primary HSCs is present in the diHSCs population.
Conclusion: In this study we outline the dynamics of diHSC differentiation. We also demonstrate that diHSCs constitute a heterogeneous population, recapitulating the expression of markers that define HSCs populations in both health and disease. Overall, our findings highlight that iPSCs are a good tool for studying the acquisition of the phenotype and the cellular heterogeneity of HSCs.

Gut microbiota and liver disease – Liver-organ crosstalk

TOP-051

Veillonella dispar-mediated l-arginine depletion induces leydig cell mitochondrial apoptosis and suppresses testosterone synthesis to drive primary biliary cholangitis

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Background and aims: Gut dysbiosis and testosterone are associated with the pathogenesis of primary biliary cholangitis (PBC). However, whether Veillonella dispar or its metabolites can modulate testosterone levels to rectify immune dysregulation in PBC remains unclear.
Method: We evaluated the in vivo effects of the gut microbiota Veillonella dispar in a mouse model of 2-octynoic acid-bovine serum albumin-induced cholangitis and pseudo germ-free mice, analyzed serum amino acid levels by metabolomics, measured serum testosterone levels by LC-MS/MS, photographed Leydig cell mitochondria by transmission electron scanning microscopy and confocal microscopy, and analyzed the infiltration and function of liver B lymphocytes by single-cell sequencing and flow cytometry. The in vivo effects of heterologous expression of the speA gene were evaluated in normal mice. Circulating testosterone, BAFF, and arginine levels in the PBC cohort were detected by LC-MS/MS and Elisa, respectively.
Results: Our results showed that Veillonella dispar increased serum ALP concentration, total bile acid content, and liver injury in pseudogerm-free mice and aggravated liver injury in the 2OA-BSA-induced PBC model. Compared with the control group of mice with cholangitis, the Veillonella dispar-treated group had lower serum testosterone and L-arginine levels, thereby relieving the feedback inhibition of BAFF secretion, promoting B cell proliferation and focusing in the liver, and damaging bile duct epithelial cells. Testosterone supplementation or BAFF blockade reduced the number and activity of liver B cells. Mechanistically, L-arginine maintained mitochondrial function in Leydig cells by promoting nitric oxide release, reducing mitochondrial permeability pore opening, and limiting ROS release. These effects reduced the release of cytochrome C and mitochondrial apoptosis and enhanced the expression of testosterone synthesis-related proteins (StAR, P450scc, and 3β-HSD). The presence of the speA gene in the genome of Veillonella dispar enables it to efficiently degrade L-arginine. Moreover, heterologous expression of the speA gene eliminated the protective effect of L-arginine. In terms of treatment, L-arginine administration alleviated immune-mediated cholangitis in mice by reducing Leydig cell apoptosis. Similarly, compared with healthy person, PBC patients had lower serum L-arginine and testosterone levels and higher BAFF.
Conclusion: Collectively, our findings identify a key role for L-arginine in regulating testosterone and B cell homeostasis and suggest a potential novel therapeutic strategy for the treatment of PBC.

TOP-052-YI

Baseline oral microbiome composition in liver transplant recipients can help predict graft dysfunction

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Background and aims: Shifting of oral microbiome to gut have been implicated in liver cirrhosis. Impact and profile of baseline oral

microbiota in liver transplant complications remained underexplored. We aimed to study the association between oral microbiome in liver transplant recipients and early post-transplant graft dysfunction (GD).
Method: Saliva and blood samples of cirrhosis recipients (n = 120) of 18–65 years and their donors (n = 120) were collected. V3-V4 Amplicon sequencing done, FastQC were checked for raw read quality, adaptor presence, and other impurities. Sequences were denoised using the DADA2 plugin from QIIME. Naive-Bayes classifier trained on SILVA 16S rRNA gene database was implemented through sklearn to classify representative sequences at 99% similarity. Sequences were rarefied at specific sampling depth prior to diversity calculation. Serum cytokine and metabolome of recipients were done.
Results: At baseline (pre-operative) donors had a higher relative abundance of Bacteroidota ($p < 0.01$), while cirrhotic recipients (n = 120) exhibited Firmicutes. At family level Streptococcaceae and Veillonellaceae were significantly abundant in cirrhotic recipients compared to their donors ($p < 0.05$, $p < 0.01$ respectively). Post-transplant GD was recorded in 44 cases. The principal coordinate analysis based on Bray-Curtis, Jaccard distance, weighted and unweighted unifrac distance followed by PERMANOVA analysis adjusted for age, gender, etiology, baseline MELD Score; showed at baseline; genus Prevotella, was significantly less ($p < 0.001$), and Streptococcaceae and Veillonellaceae were more abundant in those who had developed GD compared to non-GD. Bacteroidota abundance noted in non-GD recipients (n = 63). On follow-up of Firmicutes showed a decreasing trend post-transplantation till 180 days, indicating a shift towards a healthier microbiota. Those had non-anastomotic biliary complication (n = 6) had abundant phyla of Firmicutes (75%), post LT infections (n = 21) also had increased Firmicutes (60%) and Proteobacteria (30%) at baseline. At genus level Rothia (60%) and Streptococcus (50%) were differentially abundant in rejections (n = 17) and non-anastomatic biliary complications. At species level Prevotella salivae (85%) is significantly abundant in those who had infective complications. Indirect cues of dysbiosis were noted on serum cytokine profiling as sTNF-R1, IL-11 and IFN-beta levels were higher in GD (>2 folds). Elevated sTNFR1 levels indicated increase in Proteobacteria (+30%) and Firmicutes (+75%). Bacterial metabolite, DG (18:2(9Z, 12Z)/24:1(15Z)/0:0), PE (20:0/P-18:0) was also found unique to GD.
Conclusion: After adjustment for common confounders, baseline abundance of Firmicutes (75%), Proteobacteria (30%), Rothia (60%) and Streptococcus (50%) in recipients suggesting unhealthy oral microbiota and were associated with GD. Declining of these in non-GD suggesting healthier microbiome shift.

WEDNESDAY 07 MAY

WED-043
Targeting the gut-liver crosstalk: the role of Gardenin A in alleviating alcohol-associated liver disease

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Background and aims: Alcohol-associated liver disease (ALD) remains a major health concern with no FDA (food and drug administration)-approved therapies, highlighting the need for effective treatments. Gardenin A (GarA), a natural compound, has shown promise in metabolic-dysfunction related steatotic liver disease (MASLD), but its impact on the gut-liver axis in the context of ALD has not been explored. This study aims to evaluate the therapeutic potential of GarA in modulating the gut-liver axis in an ALD model using male Wistar rats.
Method: Male Wistar rats were administered a Lieber-DeCarli ethanol diet (5% daily and 31.5% twice during the study) for 28 days to induce ALD. Two treatment groups received GarA at doses of 50 and 100 mg/kg body weight for the final 21 days. Blood was collected for biochemical analysis of liver markers, total cholesterol (TC), and triglycerides (TG). Liver and colon tissues were harvested for RNA extraction and gene expression analysis of inflammatory cytokines, anti-oxidant genes, and gut barrier junction genes. Histological analysis was conducted using hematoxylin and eosin (H&E) staining to assess tissue morphology and damage. All experiments were carried out in replicates (n = 6) and data was expressed as mean with standard deviation. Comparisons between groups were performed using one-way ANOVA followed by Tukey's post hoc test, with a significance level set at $p < 0.05$.
Results: Treatment with GarA led to a consistent decrease in liver markers and biochemical markers of injury. Liver histology showed reduced neutrophil infiltration and necrosis in the 100 mg/kg GarA group. In parallel, colon tissue in this group exhibited improved barrier integrity compared to the ALD control group. Gene expression analysis revealed downregulation of pro-inflammatory cytokines such as Tumour necrosis factor alpha (TNFalpha), Toll-like receptor 4 (TLR4) and Interleukins 1beta, 2 and 6, and upregulation of antioxidant genes – Heme oxygenase 1 (HO1), Nuclear factor erythroid 2-related factor 2 (Nrf2) and Nuclear factor kappa-B (NFkappaB) in the 100 mg/kg GarA treated group. Additionally, genes associated with gut barrier function, including Zonula Occludens-1 (ZO1), Occludin and Claudin-1 (CLDN1), were more strongly expressed, supporting enhanced gut barrier integrity.
Conclusion: These findings suggest that GarA has potential as a therapeutic agent for ALD, by targeting both molecular pathways and organ-level functions critical to gut-liver crosstalk. By reducing key markers of liver damage and promoting gut barrier integrity, GarA may offer a novel approach for managing ALD. Beyond ALD, the observed anti-inflammatory and organ-protective effects of GarA suggest its broader applicability in other liver diseases or systemic inflammatory conditions, highlighting its versatility as a potential therapeutic agent.

WED-044
Microbial changes resulting from vertical sleeve gastrectomy attenuate obesity by modulating bile acid metabolism and the intestinal farnesoid X receptor–fibroblast growth factor 15/19 axis

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Background and aims: Obesity is a global health priority, with more than one billion people suffering from obesity. Bariatric surgery (BS) is the most effective therapy for weight loss and is associated with changes in the gut microbiota; however, the mechanisms by which the gut microbiota contributes to metabolic benefits after BS remain to be further investigated.
Method: A vertical sleeve gastrectomy (VSG) model was constructed in high-fat diet (HFD)-induced obese (DIO) rats. The changes in the gut microbiota after surgery were tested via 16S sequencing analysis, and the bile acid profiles in the serum and ileum were determined by HPLC–MS/MS. The intestinal FXR-FGF15/19 pathway was tested via western blotting, quantitative real-time PCR and immunofluorescence (IF) staining. The serum FGF19 level was examined via ELISA. To evaluate the causal relationship and mechanism of the gut microbiota in the metabolic benefits of bariatric surgery, an antibiotic cocktail was used to eliminate the gut microbiota in obese rats after VSG surgery, and the VSG-shaped gut microbiota was transplanted into obese littermates. An FXR antagonist was used to confirm the roles of intestinal FXR in the metabolic benefits of the VSG microbiome.

Results: VSG significantly improved glucose metabolism and liver lipid accumulation in DIO rats. Depleting the gut microbiota abolished the metabolic benefits of VSG. Fecal microbiota transplantation from the VSG group reversed the metabolic effect of VSG. VSG markedly increased BSH activity and the abundance of BSH-enriched microbes, including Lactococcus and Enterococcus. The abundances of Lactococcus and Enterococcus were negatively correlated with hepatic total triglyceride (TG) levels. Increasing BSH activity in the VSG significantly increased the ratio of unconjugated bile acids in the serum and ileum, which, in turn, activated gut-restricted FXR–FGF19 signaling, including increased mRNA and protein levels of FXR and FGF19 and increased serum levels of FGF19. A similar phenomenon was observed in obese rats that received gut microbiota transfer from the VSG. Inhibiting intestinal FXR with an FXR antagonist eliminated the metabolic benefits of fecal microbiota transplantation derived from VSG.
Conclusion: Our results showed that BSH-enriched microbial changes resulting from vertical sleeve gastrectomy attenuate obesity by modulating bile acid metabolism and the intestinal FXR–FGF15/19 axis. This study suggests that increased intestinal BSH microbes may help consolidate the long-term efficacy of BS and may be a potential obesity therapy.

WED-045

PPAR α is a key molecule mwdiating the diurnal variation of sepsis in mice

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Background and aims: Studies have found that mice exposed to pathogens at ZT0 (the start of the light phase) survive better than those exposed at ZT12 (the end of the light phase). PPARα, a nuclear receptor activated by fatty acids and their derivatives, helps regulate metabolism and inflammation. Its expression changes rhythmically over the 24-hour cycle. This study focuses on understanding how PPARα contributes to the circadian differences in sepsis.
Method: Various techniques were used to study systemic metabolic responses in wild-type (WT) mice after cecal ligation and puncture (CLP) at ZT1 and ZT13, including survival analysis, biochemical assays, ELISA, RNA-seq, and LC/MS. PPAR-α knockout (KO) mice and siRNA-silenced PPAR-α (si-PPAR-α) AML12 cell lines were generated. The respiratory exchange ratio (RER) in PPAR-α KO mice was assessed using animal monitoring system, and rhythmic changes in circadian factors and PPAR-α target genes were evaluated in both PPAR-α KO mice and si-PPAR-α AML12 cells post-serum shock using qPCR. CLP models were created at ZT1 and ZT13 in PPAR-α KO mice and WT mice pre-treated with the ATGL inhibitor Atglistatin. In LPS pre-treated si-PPAR-α AML12 cells, rapamycin and chloroquine were used to investigate changes in autophagic flux through western blot. CLP models were established at ZT1 and ZT13 in Cry1/2 double-knockout (DKO) mice. Statistical analysis was performed using SPSS and R package. Results with p-values <0.05 were considered statistically significant.
Results: In WT mice, CLP at ZT13 had significantly lower levels of blood glucose, survival rates and higher levels of triglyceride compared to at ZT1. RNA-seq and LC/MS analysis of liver tissue after CLP at ZT1 and ZT13 identified the PPAR signaling pathway as the most enriched pathway. PPAR-α showed significant differences between the two time points. In PPAR-α KO mice, the RER was higher compared to WT mice. Although circadian genes retained rhythmic expression in PPAR-α KO mice and si-PPAR-α AML12 cells after serum shock, the rhythmic patterns of PPAR-α target genes were lost. In PPAR-α KO mice and WT mice were treated with the Atglistatin, there were no significant differences in blood glucose, glycerol, or survival rates between ZT1 and ZT13 post-CLP. In AML12 cells, silencing PPAR-α reduced autophagic flux. Adding rapamycin or chloroquine did not reverse these changes. Using the JASPAR database, Cry was identified as potential regulator of PPAR-α. In KO mice, the differences in survival between ZT1 and ZT13 after CLP were eliminated.
Conclusion: The diurnal variation of Cry modulates the diurnal differences in sepsis by regulating the circadian rhythm of PPAR α.

WED-046

The intestinal virome related clinical outcomes, systemic inflammation and immune functions in hospitalized cirrhosis patients – the foremost work in an indian patient cohort

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Background and aims: Association between stool virome in cirrhosis patients and clinical events and outcomes, systemic inflammation and immune functions has only recently come to light. Unlike bacteria, fecal phages are sparsely linked with cirrhosis characteristics and 90-day outcomes while linkages between bacteriophages and cognitive function due to impact on bacteria is known from studies in the US. However, intestinal viral taxa were altered in fecal samples from patients with AH and associated with disease severity and mortality. Studies on virome in hospitalized cirrhosis patients and linked events and outcomes, severity of disease, inflammatory profile and immune functions from Indian patients remain unknown. In this foremost work from the Asian sub-continent, in samples collected at hospital admission, we analyzed stool virome associations with liver disease etiology and severity, long-term clinical events and immune functions and inflammatory profile.
Method: Whole genome sequencing, bioinformatics, and statistical analyses to study intestinal virome associations were performed on stool samples collected at admission from 78 cirrhosis patients who were grouped according to etiology, liver disease severity, quantified pro- and anti-inflammatory cytokines and immune functions (neutrophilic CD64, monocytic HLA-DR, monocytic CD14 expression) and Sepsis Index, a ratio of the expression of the CD64 molecule on neutrophils (NCD64) to the expression of human leukocyte antigen-DR on monocytes.
Results: Viral alpha-diversity was lower in sick MASLD cirrhosis compared to ALD (Shannon, Wilcoxon P = 0.02) while it was higher in those without ascites and hyponatremia (chao1, P = 0.008 and 0.04 respectively). Higher relative abundance (RA) of *Klebisella phage* related *Jiaodavirus* genera and *Siphoviridae* and *Cronobacter phage* spp. were notable in MASLD etiology. Anti-Gram-negative bacterial endolysin producing *Cronobacter phage* was expanded in ACLF patients and those with jaundice, ascites, and encephalopathy while *Klebsiella phage groups* were uniquely abundant in those with infection, variceal bleeding, MELD score ≥25, immune exhaustion (low mHLA-DR expression) at admission and death at 18 months. *Wifcevirus* (*E. coli* phage) was specifically expanded in those with acute kidney injury. Increased RA of *Escherichia virus Goslar* was associated with high Sepsis-Index, pro-inflammatory- and *Cronobacter phage* and *Podoviridae sp.* with anti-inflammatory cytokines.

Conclusion: Specific viral taxa and expansion of bacteriophages that target pathogenic bacterial species were uniquely expanded in sick hospitalized cirrhosis patients, adding to the body of evidence that bacteriophage therapy could be a pertinent tool in the armamentarium against complications in advanced chronic liver failure.

WED-047

A single center experience from India on associations of fungal microbiota (mycobiome) in cirrhosis - orally-predominant fungal dysbiosis in the gut and immune-escaping Candida species drive outcomes in hospitalized patients

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Background and aims: *Candida* play an important role in pathogenesis and progression of various hepatobiliary disorders. Patients with cirrhosis requiring hospital admission have higher relative fecal abundance of *Candida* than outpatients with cirrhosis. Intestinal fungi fuel systemic inflammation in ALD. Candida-related fungal infections are linked with higher rates of ACLF, intensive care, and increased 30-day mortality. Data on fungal microbiota (mycobiome) and association with chronic liver failure and portal hypertension events, long-term survival, systemic inflammation, and immune functions in sick cirrhosis patients is lacking. In this original study on hospitalized sick cirrhosis patients, we analyzed stool mycobiome associations on clinical, inflammatory, and immune events.
Method: Whole genome sequencing and bioinformatics were performed on stool samples collected at admission from 78 cirrhosis patients who were grouped according to liver disease severity, measured pro- and anti-inflammatory cytokines and immune functions (neutrophilic CD64, monocytic HLA-DR, monocytic CD14 expression) and Sepsis Index (ratio of CD64 on neutrophils to mHLA-DR).
Results: Fungal alpha-diversity was significantly higher in patients with overt hepatic encephalopathy (OHE) at admission (chao1, Wilcoxon P = 0.04) and in those with high MCP-1 (protein activated in monocyte and macrophage response to fungal infections) levels (Shannon, P = 0.03). *Candida africana* and *C. albicans* predominated in ALD as well as ACLF, while *C. glabrata, C. tropicalis* and orally predominant *C. dubliniensis* were relatively abundant in MASLD cirrhosis; the latter both, also increased in patients with jaundice. The relative abundance (RA) of Saccharomycetaceae was higher in those with ascites, *C. dubliniensis* in patients with OHE, whereas *C. glabrata* in those without OHE, kidney injury, variceal bleeding, and with hyponatremia. *Kluyveromyces marxianus* and *C. dubliniensis* increased in patients who required intensive care at the outset. Increased RA of *C. glabrata* was consistently associated with lower levels of both pro- and anti-inflammatory cytokines, reduced immune exhaustion and functional monocytic depletion, while that of *C. tropicalis* with higher levels of IL-6 and TNF-alpha. *Candida dubliniensis* was associated with immune exhaustion (lower mHLA-DR expression). A higher RA of both *C. dubliniensis* and *C. glabrata* in stool microbiome was suggestive of probable/proven sepsis as per Sepsis Index variable.
Conclusion: Mycobiome changes at admission in sick cirrhosis patients are associated with specific clinical events and long-term survival. Various species belonging to *Candida* genus were expanded or reduced with respect to systemic inflammation and immune exhaustion demonstrating important role of gut mycobiome in driving cirrhosis-related complications and outcomes.

WED-048

Deep insights on gut bacterial associations with long-term clinical events, host immunology, and inflammatory cytokines in hospitalized Indian cohort of patients with cirrhosis

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Background and aims: Detrimental changes to gut microbiota are closely linked to development of decompensation, prediction of hospitalization, increased risk of extra-hepatic organ failure (mainly hepatic encephalopathy), nosocomial infections and intensive care and death. In this foremost work from the Asian sub-continent, in stool samples from cirrhosis patients collected at hospital admission, we analyzed gut-microbial (GM) associations with disease etiology and severity, long-term clinical events, immune functions and inflammatory profile.
Method: Stool samples were collected at admission from 78 patients. Patients were grouped according to etiology, liver disease severity, immune functions (neutrophilic CD64, monocytic HLA-DR, monocytic CD14 expression and Sepsis Index), and levels of inflammatory cytokines (pro: IL-1α and β, IL-2,6,8, IFN-γ, MCP-1, TNF-α, VEGF/ anti: IL-4,10, EGF). Whole genome sequencing, bioinformatics, and statistical analyses to study microbial associations were performed as per standard protocols.
Results: Males predominated (N = 68, 87.2%) with median age 58 years. MASLD (43, 55.1%) was most common etiology. Around 20% (15) had ACLF and 38.5% (30) required ICU management at the outset. At 18 months, 43.6% (34) patients died. Patients with MELD≥25 had significantly lower alpha-diversity. Relative abundance of *E. coli* and *K. pneumoniae* were remarkably high in MASLD and ALD respectively. Severe and significant reductions in several short-chain-fatty-acid producing probiotic-species were notable in those admitted directly to ICU and ACLF patients. Statistical analysis revealed that *Clostridium spp.* was reduced in Child C class, orally-predominant bacteria *Shaalia odontolytica* expanded in gut of those with variceal bleeding, while *Lactococcus* and *Eubacterium* lessened in patients with higher MELD scores and *Blautia* and *Terrisporobacter* reduced in those dying at 18 months. *Eggerthella spp.* associated with sarcopenia expanded in patients with higher IL-4 levels, the latter, a marker of muscle regeneration. Increased anti-inflammatory responses were associated with *Bifidobacterium*, *Lactococcus* and endogenous steroid-producing *Mycolicibacterium*. Elevated pro-inflammatory cytokines and increased immune exhaustion were associated with significant expansions in *Sutterella*, *Ruminococcus*, and *Roseburia*.
Conclusion: Etiology, higher liver disease severity, decompensation and extrahepatic organ failures in hospitalized cirrhosis patients were associated with specific changes in GM communities. GM

modulation targeting expansion of beneficial bacteria using rational donor fecal transplant or personalized probiotic therapies could be a promising option for further research, in modifying adverse natural history of disease in hospitalized cirrhosis patients.

WED-049
Dietary bacterial D-lactate modulates liver steatosis and ameliorate experimental MASLD

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Background and aims: Probiotic supplementation, particularly with *Lactobacillaceae* strains, has demonstrated notable liver health benefits, including reductions in serum liver enzyme levels, hepatic fat accumulation, and obesity-related complications. Recent studies on *Limosilactobacillus reuteri* DSM17938 highlighted the potential of its D-lactate production in liver protection, particularly through modulation of macrophage activity, which may help mitigate fibrosis. Unlike L-lactate, primarily synthesized by eukaryotic cells, D-lactate is predominantly produced by bacteria and has been shown to possess immunomodulatory properties, influencing macrophage phagocytosis, Kupffer cell function, and tumor suppression in the liver. This study aims to explore the effects of low-dose D-lactate in reducing hepatic lipid accumulation and mitigating MASLD progression, potentially positioning D-lactate-producing probiotics as a groundbreaking therapeutic strategy for managing liver diseases.
Method: We employed two experimental mice models: a methionine choline-deficient (MCD) diet model supplemented with *L. reuteri* DSM17938 and a 20-week High-Fat High-Fructose Diet (HFHFD) model supplemented with either *L. reuteri* DSM17938 *or* 1 mM D-lactate. After sacrifice liver and small intestinal histology and mRNA expression levels related to inflammation, lipid metabolism, and fatty acid transport were assessed. Additionally, D-lactate role was evaluated *in vitro* by examining its effects on palmitic acid accumulation and mRNA expression associated with hepatic lipid transport, synthesis, and storage.
Results: Mice fed an MCD diet with L. reuteri showed reduced hepatocellular vacuolization and inflammation, though serum ALT and AST levels were unchanged. Supplementation lowered liver fibrosis markers and downregulated lipid metabolism and inflammation genes. In vitro, 1 mM D-lactate reduced lipid accumulation and lipid marker expression in PA-exposed hepatocytes. In a 20-week HFHFD model, D-lactate supplementation reduced weight gain, liver-to-body weight ratio, steatosis, serum ALT levels, hepatic inflammation, and fibrosis markers. It also modulated small intestine immunity and gut microbiota, enhancing beneficial bacteria, underscoring its role in the gut-liver axis.
Conclusion: Our findings demonstrate that *L. reuteri* effectively alleviates experimental MASLD, partially through the production of intestinal D-lactate, which modulates hepatic fatty acid metabolism. This study highlights the potential of D-lactate to attenuate MASLD by regulating liver metabolism, reducing inflammation, and reshaping gut microbiota composition. These results position low-dose D-lactate as a promising therapeutic agent, offering an innovative approach for the management and prevention of MASLD.
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WED-050-YI
Fecal microbiota transplant activates hepatic PPAR-alpha resulting in remission of alcohol-related liver disease in murine model

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Background and aims: Fecal microbiota transplantation (FMT) is a promising therapeutic for alcohol-related liver disease (ALD). To combat malnutrition, patients are recommended high protein diet. This study explores how pre-educating donor microbiota with high protein could enhance FMT efficacy and investigates key signaling pathway underlying therapeutic effects of diet optimized FMT in ALD.
Method: ALD was induced in C57BL/6N mice using Lieber-DeCarli ethanol diet with thioacetamide over 8 weeks. FMT was performed from donors on standard or protein enriched diets, with recovery assessed post 7 days. Gut microbiota, stool metabolome and hepatic proteome were analyzed using 16S rRNA sequencing and LC-MS/MS. Based on proteomic findings, role of PPAR-alpha was validated using GW6471 inhibitor in a separate cohort of mice. Liver and intestinal injury was assessed using biochemical, histological and molecular parameters.
Results: Protein FMT (PF) showed superior efficacy over Standard FMT (SF), showing significant reductions in serum ALT (-1.5 fold change [FC], $p = 0.02$), AST (−1.3 FC, $p = 0.04$), hepatic steatosis (−1.8 FC, $p = 0.01$), and fibrosis (−1.4 FC, $p = 0.04$). PF reduced the gene expression of hepatic pro inflammatory markers TNFα (−1.5 FC, $p = 0.03$) and IL6 (−1.6 FC, $p = 0.02$). PF also increased intestinal tight junction protein ZO1 (1.9 FC, $p = 0.05$) with reduction in plasma endotoxin (−1.6 FC, $p = 0.06$), maintaining intestinal barrier integrity. PF significantly enhanced abundance of SCFA producer *Muribaculum* (2.4 FC, $p = 0.002$) and *Lachnospiraceae NK4A136* (2 FC, $p = 0.01$) while reducing opportunistic pathogens *Staphylococcus* (−6.7 FC, $p < 0.001$) with a concomitant increase in stool SCFA levels (butyric and propionic acid, FC > 1.5, $p < 0.05$). Hepatic proteome showed PF mediated upregulation of PPAR signaling, fatty acid degradation and oxidative phosphorylation (FC > 2, $p < 0.05$), with downregulation of necroptosis. In PF, PPAR alpha was most abundant, validated at mRNA level (2.3 FC, $p = 0.04$). A concomitant upregulation of PPAR alpha target genes involved in mitochondrial beta-oxidation (Cpt1, 1.5 FC, $p = 0.008$; Acox1, 1.3 FC, $p = 0.07$; Fabp1, 1.2 FC, $p = 0.001$) was also observed. The mechanistic role of PPAR alpha was validated using inhibitor GW6471. Western blot confirmed −2.3 FC inhibition ($p = 0.01$). PPAR alpha inhibition with FMT abolished therapeutic benefits, causing elevated serum injury markers (AST, 1.7 FC, $p = 0.003$; ALT, 2 FC, $p = 0.002$; Triglycerides, 1.4 FC, $p = 0.06$), increased hepatic lipid accumulation (1.9 FC, $p = 0.03$), and suppressed PPAR alpha target genes ($p < 0.001$; Cpt1 = −5 FC; Acox1 = −4.3 FC; Fabp1 = −4.7 FC).
Conclusion: Diet optimized FMT improves its therapeutic efficacy in ALD through hepatic PPAR alpha activation. Increased SCFA producing bacteria elevate stool SCFAs, which likely act as PPAR alpha ligands, promoting fatty acid beta-oxidation and reducing liver injury. PPAR-alpha inhibition abolished these benefits, highlighting its critical role in FMT mediated disease resolution.

WED-055
Microbiota-derived S-equol ameliolates inflammatory pathway in metabolic dysfunction-associated fatty liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease and increasing worldwide. MASLD progression is associated with gut microbiota and its metabolites. The therapeutic effect of S-equol was highlighted via integrated network pharmacology from our most study. In this study, we aim to evaluate the liver-protective effects of S-equol and identify key microbial species responsible for its metabolism to assess its therapeutic potential in MASLD.

Method: Network pharmacology analysis and 16S rRNA analysis of human stool samples [healthy controls (n = 100) and MASLD patients (n = 100)] were conducted. 5 weeks age male C57BL/6J mice were fed a high-fat Western diet for 12 weeks. S-equol and *Lactobacillus paracasei* were fed 3 times a week orally feeding. Cecal Sample obtained from mice was centrifuged, the supernatant was treated with ACN and MeOH, and analyzed by LC-MS. The progression of MASLD was assessed based on liver histopathology and gene expression levels. Transcriptomic analysis was performed on liver tissue, and changes in microbial composition were examined using 16S-based sequencing of cecal samples.
Results: In human data, *Lactobacillus* levels were decreased (0.2%) in MASLD patients. In the network pharmacology analysis, isoflavone is metabolized to S-equol by L.paracasei JS1 species and S-equol showed inhibitory mechanism in binding to IL-6. In the S-equol-treated group, pathological analysis revealed a reduction in fat layer (steatosis; 2 vs. 1) and inflammation (Stage; 1.5 vs. 0.5) in MASLD mice, along with the regulation of fat synthesis (FAS, PPAR-gamma, SREBP1; $p < 0.01$) and inflammatory genes (MCP-1, TNF-alpha, and TGF-beta; $p < 0.05$) at the mRNA level. In addition, we performed RNA sequencing in liver tissue was confirmed to be a pathway related to inflammation and HSD3B5 the enzyme crucial for steroid hormone biosynthesis significant upregulation ($p < 0.01$) in the s-equol treatment group suggests a potential role in liver injury recovery pathways. Total of 169 substances were searched 68 in positive ion mode, 78 in negative ion mode, and 23 in neutral ion mode. Among them, S-equol obtained results in positive ion mode, and Daidzein obtained results in neutral ion mode. S-equol was higher in Nomarl Control compared to Western group, and it was confirmed that the amount of S-equol significantly increased in the group administered L.paracasei compared to the Western diet group. 16S rRNA sequencing of cecal samples revealed distinct changes in both alpha and beta diversity in the s-equol treatment group, highlighting its impact on microbial community composition.
Conclusion: This study demonstrates the significant liver-protective effects of S-equol in a MASLD model. S-equol is a representative metabolite produced by gut microbiota during the metabolism of daidzein that offering potential for microbiome-targeted therapies for MASLD and related liver disorders.

WED-056

Absence of cholesterol gallstone formation in male C57BL/6 mice by abrogation of hepatic thyroid hormone action

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Background and aims: Thyroid hormone (TH) impacts the hepatobiliary system. Epidemiological studies suggest a link between thyroid dysfunction and cholestatic liver disease. In previous studies we could confirm that a severe systemic TH deficiency promotes cholesterol gallstones. Using the lithogenic mouse model, we investigate whether changes in the systemic TH status or abrogation of hepatic TH action impact cholestatic liver disease.
Method: Male C57BL/6 wildtype (WT) mice received a six weeks lithogenic diet either under iodine sufficient or deficient condition. Male hepatocyte specific TRβ knockout (hepTRβKO) mice received a six weeks lithogenic diet to investigate the role of abrogated hepatic TH action. Biliary cholesterol gallstone and crystal prevalence, liver histology, liver and thyroid functions test, TH- and cholestasis-responsive markers were evaluated.
Results: Cholesterol gallstones were observed in lithogenic diet supplemented WT mice under iodine sufficient condition. In the iodine deficient group, a higher prevalence of cholesterol gallstone formation was observed, and the low iodine regiment reduced both systemic TH concentration and hepatic *deiodinase 1* (*Dio1)* mRNA expression. In hepTRβKO a six-week lithogenic diet treatment could not induce macroscopic visible cholesterol gallstones, whereas a reduced lipid content and elevated gene expression of the cytochrome P450 enzyme *Cyp2c39* were observed.
Conclusion: Systemic TH deficiency increases the pro-lithogenic response of male mice. Abrogation of hepatic TH action in male hepTRβKO mice shows an anti-lithogenic effect with an elevated expression of hepatic *Cyp2c39* encoding for an n-3 fatty acid producing enzyme. The results provide new insights into the regulatory principle of local TH action in the hepatobiliary system.

WED-057

Microbially conjugated bile salts undergo hepatobiliary secretion in humans and mice

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Background and aims: We recently showed that *N*-amidates of (chenodeoxy)cholic acid ([CD]CA) with leucine, phenylalanine or tyrosine, activate bile salt receptors at the cell surface (i.e. TGR5) and inside the cell (i.e. FXR), and are substrates of human bile salt transporters. Despite potential for intestinal absorption, we found levels of these microbial bile salt conjugates (MBSCs) to be negligible in mesenteric and portal blood of patients, while being readily detected in human bile. In this study, we investigated degradation in the intestinal lumen as possible cause of marginal presence of MBSCs in blood, and determined MBSC levels in ductal bile of patients with benign or malignant conditions of the biliary system.
Method: Male C57BL/6J mice were gavaged with a single dose of *D*- or *L*-TyrCA (tyrosocholic acid; 50 mg/kg BW, n = 3 per group), and blood was sampled from the jugular vein at baseline and up to 240 min after gavage. Animals were sacrificed after 4 hours, and portal and hepatic venous blood and bile were collected. TyrCA levels were quantified by LC-MS. Furthermore, MBSCs (i.e. Leu[CD]CA, Phe[CD]CA and Tyr[CD]CA) were determined in ductal bile collected via ERCP from patients with choledocholithiasis (n = 20), benign biliary strictures (n = 7), cholangiocarcinoma (n = 20) or pancreatic ductal adenocarcinoma (n = 20).
Results: In mice, neither TyrCA enantiomer was detected in blood at baseline. Gavage of *L*-TyrCA did not result in quantifiable levels in the systemic circulation (i.e. <2.5 nmol/L), contrasting with readily detection of *D*-TyrCA from the earliest time point after gavage, with median levels reaching 36 nmol/L at sacrifice. Portal TyrCA levels were >200-fold higher in mice gavaged with the *D* enantiomer. Porto-hepatic venous differences indicate that both TyrCA enantiomers underwent marked hepatic extraction. Only the *D* enantiomer was recovered in bile, approaching low millimolar concentration. In patients, MBSCs were detectable in bile with variable incidence among patient groups (from 30% to 86%), with median group levels being similar when considering MBSC-positive samples (from 6.5 to 35.2 nmol per mmol total bile salts; $p = 0.122$). Median levels were

indistinguishable between benign and malignant conditions (17.7 vs. 8.1 ppm; p = 0.146). In CCA, nutritional and immunological status was better in patients having detectable biliary MBSCs.
Conclusion: Following gavage, a plasma response was only observed for *D*-TyrCA. Resistance of the *D* enantiomer to degradation by pancreatic carboxypeptidases and/or bacterial bile salt hydrolases was observed *in vitro*, and this may contribute to the divergent plasma excursions. MBSCs undergo hepatobiliary secretion. MBSCs were detected in bile from patients with different conditions affecting the biliary system. Determinants of their presence in bile and (patho)physiological relevance of biliary MBSCs require further study.

WED-058
An integrative multi-omics and machine learning framework for diagnostic biomarker identification in patients with liver cirrhosis
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Background and aims: Cirrhosis is the final stage of chronic liver disease, presenting significant diagnostic challenges due to its multifactorial nature. Recent advances in integrated multi-omics analyses have shown potential for identifying novel biomarkers and improving diagnostic accuracy. This study aims to leverage shotgun metagenomics data from fecal samples to integrate microbial profiles, functional gene data, and metabolites. The goal is to develop machine learning (ML)-based algorithms for the diagnosis of cirrhosis and to identify potential key biomarkers.
Method: This study enrolled 34 patients with cirrhosis and 49 non-cirrhosis controls for metagenomic and metabolomic analyses. Shotgun metagenomics data were processed to extract microbial species profiles and KEGG Orthology (KO) genes, which were then integrated with metabolite data. The resulting dataset underwent feature selection using the Boruta algorithm, a ML-based feature selection method, to identify significant features for group classification. Four ML algorithms—Support Vector Machine (SVM), Random Forest (RF), 1D Convolutional Neural Network (CNN), and Multi-Layer Perceptron (MLP)—were applied to evaluate the performance of selected features for group classification. Each model's diagnostic performance was assessed using 10-fold cross-validation, with the area under the receiver operating characteristic curve (AUROC) as the evaluation metric.
Results: ML-based feature selection identified 40 microbial species, 64 KO genes, and 24 metabolites as key biomarkers. Among these, *Veillonella parvula* was identified as the most significant microbial species, *K02899* as the most important KO gene, and *deoxycholic acid* as the key metabolite with the highest feature importance. The model's diagnostic performance achieved an average AUROC of 0.91 when using the 40 microbial species, 0.88 with the 64 KO genes, and 0.86 with the 24 metabolites as key biomarkers. Notably, when integrating all 40 microbial species, 64 KO genes, and 24 metabolites, the diagnostic performance reached an AUROC of 0.96. These results demonstrate that multi-omics integration significantly enhances the accuracy of cirrhosis diagnosis and aids in identifying critical biomarkers.
Conclusion: This study highlights the contribution of multi-omics data integration in improving the accuracy of cirrhosis diagnosis and underscores the potential of machine learning-based approaches in identifying key biomarkers associated with cirrhosis. These findings suggest that multi-omics analysis may provide new directions for liver disease diagnosis and personalized treatment strategies, offering promising avenues for future research in liver disease.

WED-059
The role of the gut microbiota in high-fat diet-induced hepatic steatosis in juvenile and adult mice
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Background and aims: A high-fat diet (HFD) disrupts hepatic lipid metabolism and contributes to steatosis, with the gut microbiota playing a key role through bacterial metabolites. As the composition of the gut microbiota changes with age, the timing of HFD introduction could influence hepatic lipid metabolism. Therefore, the aim of this study was to investigate the role of gut microbiota composition in hepatic lipid metabolism disturbances in juvenile and adult mice on HFD.
Method: Male C57BL/6J mice were divided into three groups: a control group on a standard diet (10 kcal% fat, D12450J, Research Diets) and two groups on a HFD (60 kcal% fat, D12492, Research Diets,) starting either in the juvenile (3rd week) or adult phase (9th week). All animals were sacrificed at 17 weeks of age. Liver sections were analyzed histologically and levels of markers of hepatic lipid metabolism were determined by Western blot or qPCR. The composition of the gut microbiota was determined by 16S rRNA sequencing. Metabolites were quantified by HPLC, while their effects on lipid metabolism were assessed by measuring the levels of G-protein-coupled receptor 43 (GPR43) and farnesoid X receptor (FXR) in the liver.
Results: HFD-induced hepatic steatosis occurred in both juvenile and adult mice, although the mechanisms underlying this pathology differed between the two groups. Adult mice showed increased de novo lipogenesis and decreased β-oxidation, whereas juvenile mice showed increased fatty acid uptake and decreased triglyceride secretion. The composition of the gut microbiota and their metabolites differed between groups, resulting in lower total SCFA, acetate, and predicted bile acid production in adults. These results were accompanied by decreased expression of GPR43 and FXR, which could contribute to altered hepatic lipid metabolism in adult mice.
Conclusion: The results show that changes in gut microbiota composition induced by HFD are more detrimental in adult mice, since it is associated with increased de novo lipogenesis and decreased β-oxidation in the liver, as well as reduced production of beneficial microbial metabolites. These results pinpoint that the effect of high-calorie diets on the gut microbiota is age-specific, with more prominent metabolite-driven effects on lipid metabolism in adult mice.

WED-060
Gut microbial antibiotic resistance genes in clinicians taking care of cirrhosis patients shows wide variation according to country income and could be a risk factor for bidirectional transmission
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Background and aims: Antimicrobial resistance (AMR) associates with poor outcomes in cirrhosis, the rates of which vary worldwide. Efforts to reduce transmission of resistant bacteria are critical. Gut microbes of clinicians could be reservoirs. During COVID-19 cirrhosis-related ICU nosocomial infections reduced likely due to lower contact. Aim: Determine presence of antibiotic resistance bacteria in gut microbiota of clinicians taking care of cirrhosis patients.
Method: Clinicians taking care of cirrhosis pts were approached to provide stool and queried regarding demographics, practice region, recent travel, no. of cirrhosis inpatients/outpatients seen & number with resistant infections. Metagenomic analysis including RGI for

AMR carriage were performed and compared between USA vs other regions, foreign travel, & those with infections.
Results: 62 clinicians (51 yrs, 58% men, 91% doctors, rest NPs) were included. 58% were from US, rest from low/middle income countries (LMICs) in Asia (20%), Eastern Europe (11%) & Latin America (11%). 71% were in practice for >10 yrs, most (80%) in public hospitals. Most had recent travel with >65% foreign travel. 53% saw >11 cirr outpts/wk, 35% >11 cirrhosis inpts/wk, & 75% saw ICU pts. Most (80%) saw >1–5 cirr pts with resistant infections/mth. None were on antibiotics. US vs others were statistically similar regarding resistant infections & no. of inpts/outpts seen. Microbiome: *USA vs others*: Short-chain fatty acid (SCFA) producers were higher in US clinicians (*Lachnospiraceae*, *Oscillispiraceae*) while Archaea, Proteobacteria, & sulfur-metabolizers (*Desulfovibrionaceae*) were higher in LMIC clinicians. Anti-tubercular (TB) resistance (Isoniazid, ethionamide & rifampin) genes, high-level fluoroquinolone (gyrB/parc) were ↑ in LMIC while fosfomycin E.coli & eatAv *E. faecium* resistance were↑ in USA. *Foreign travel*: ↑Enterobacteriaceae, Prevotellaceae & Actinomycetes and lower Archaea & SCFA producers were seen with foreign trips. Fluoroquinolone gyrB, S.aureus fusA & rifampin resistance was higher with foreign while E.coli Fosfomycin resistance was higher with domestic travel. *Pts with resistant infections*: Those taking care of resistant infection pts had ↑vancomycin ligase & isoniazid resistance genes with ↑Proteobacteria & Erysipelothricaceae taxa.
Conclusion: We found major variations in gut microbiota & AMR gene profiles among clinicians caring for cirrhosis pts globally. Higher anti-tuberculosis resistance genes in clinicians from low/middle income countries & greater E.coli/E.faecium resistance genes were found in US-based clinicians. Recent foreign travel and caring for patients with resistant infections affected AMR gene content, including anti-TB resistance genes. The higher TB resistance genes in clinicians from LMICs raises the possibility of bi-directional transmission. There is a need to evaluate AMR reserve within clinicians as a source for antibiotic resistance in cirrhosis and vice-versa.

WED-061

Gut metagenomic profiles predict 90-day hospitalizations despite controlling for diet, demographics & cirrhosis details in a multi-country cohort of patients with cirrhosis

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Background and aims: Prediction of outcomes such as hospitalizations is critical in cirrhosis to ensure timely prevention. Microbial composition is altered in cirrhosis but can show wide variation between countries. Aim: define microbial features that associate with 90-day hospitalization in a multi-national cirrhosis cohort.
Method: Cirrhosis outpatients were recruited from 7 countries (USA, Türkiye, Korea, Denmark, Lithuania, Brazil & Mexico). Demographics, cirrhosis severity (MELD, complications, labs, medications), diet history, were recorded, stool collected & pts followed for 90 days for hospitalizations. Shotgun metagenomics for NGS was performed on stool. Regression analysis was performed using Maaslin2 for 90-day hospitalizations prediction. Covariates were chosen after PERMANOVA analysis & microbial species were added. Variables with $p < 0.05$ & $q < 0.05$ were considered significant.
Results: 679 cirrhosis pts (170 US, 90 Brazil, 53 Denmark, 93 each Lithuania & Mexico, 99 Korea & 84 Türkiye) were enrolled. 60% were men, MELD 12 ± 5, albumin3.5 ± 0.70, Na 138 ± 7. Most common etiology was alcohol (35%) then viral (31%) & MASLD (17%). 56% were decompensated (35% on lactulose, 19% on rifaximin, 44% prior ascites, 19% prior variceal bleed, 31% on NS βblockers). Diet varied esp with yogurt & coffee intake. 90-day Hospitalizations: Seen in 169 (25%), most of which 133 (79%) were liver-related. Country-wise rate differed with lowest in Brazil & Türkiye and highest in Lithuania & Korea). PERMANOVA showed that MELD, decomp status, yogurt intake, country of origin & HE-medications were significant covariates. Maaslin2: 15 species associated with hospitalizations after controlling for country, decomp status, MELD score, yogurt, HE medications & alcohol etiology.
Linked with ↓ hospitalizations: All had $p < 0.01$, *Ruthenibacterium lactatiformans* (coeff = 2.9, $q < 0.001$), *Bacteroides uniformis* (−2.3, p & $q < 0.001$), Flavonifactor plautii (−2.2, $q < 0.001$), *Faecalibacterium prausnitzii* (−1.9, $q = 0.02$), *Clostridium fessum* (−1.7, p & $q < 0.001$), Eggerthella lenta (−1.7, $q = 0.01$), *Clostridiales bacterium* (−1.7, $q = 0.01$), *Bifidobacterium pseudocatenulatum* (−1.7, $q = 0.05$), *Anaerobutyricum hallii* (−1.6, $q = 0.02$), *Eubacterium ramulus* (−1.4, $q = 0.02$), *Clostridium leptum* (−1.4, $q = 0.04$), *Intestinimonas butyriciproducens* (−1.3, $q = 0.04$), GGB9614_SGB15049 (−1.2 $q = 0.04$) & GGB2653_SGB3574 (−1.2, $q = 0.03$). These are short-chain fatty acid or lactate producers, or those involved in beneficial immune function. Linked with ↑ hospitalizations: *Enterococcus faecium* (Coeff 2.0, $p < 0.001$, $q = 0.003$), which is a pathobiont.
Conclusion: In a prospective cohort of outpatients with cirrhosis from 7 countries, microbial profiles could predict 90-day hospitalizations despite controlling for diet, cirrhosis details, country of origin, and demographics. Microbial profiling could improve risk prediction in cirrhosis beyond single center studies.

WED-063

Gut fungi in liver cirrhosis: characterizing mycobiota alterations and links to disease stages

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Background and aims: Recent studies have highlighted the significant role of gut microbiota in the pathogenesis of liver diseases. While research on bacterial changes in the gut has grown, the role of gut fungi (mycobiota) in LC has only recently begun to gain attention. However, further studies are essential to fully understand the impact of mycobiota alterations in LC. The aim of this study was to examine changes in the mycobiota profile by comparing stool samples from LC patients to those of a control group, and to explore the relationship between mycobiota alterations and clinical characteristics of the patients.
Method: The study analyzed stool samples from 83 LC patients and 48 control participants. LC group included Child-Turcotte-Pugh (CTP) A – 38%, CTP B – 38%, CTP C – 24%; MELD score ≥15–49%, MELD score <15–51%; Compensated LC – 24%, Decompensated LC – 60%, Recompensated LC – 16%. Additionally, 42% of patients were on lactulose, 29% on proton pump inhibitors, and 32% on carvedilol. Only DNA samples meeting the quality criteria were used for PCR amplification of the fungi-specific ITS2 region. Sequencing was performed using the NanoKit Illumina kit and the MiSeq Illumina platform.

Results: PERMANOVA analysis revealed significant differences in the global fungal profile between the LC group and controls, as well as across groups defined by MELD score, CTP classification, decompensation status, and lactulose prescription. Compared to controls, the LC group showed increased abundance of eight fungi and decreased abundance of twelve. Most significantly abundant fungi were found at multiple taxonomic levels. No significant differences in fungal alpha-diversity were observed. The fungi most associated with poorer health were in the *Saccharomycetales* family, including *Candida* species. Eleven taxa were linked to reduced disease severity in LC patients. Seven fungi were significantly more abundant in patients with decompensated liver function compared to those with compensated or recompensated liver function, while *Basidiomycota* was elevated in the compensated vs. recompensated comparison. Five fungi were associated with the absence of lactulose intake, and three were elevated in patients taking lactulose. Elevated levels of three fungi were also found in patients on non-selective beta-blockers. Our study showed no correlation between bacteria and fungi in terms of abundance or diversity in patient stool samples, with moderate correlations found only in the control group.
Conclusion: The mycobiota profile of LC patients differs from controls and correlates with clinical characteristics, particularly in global profile and specific fungi, but not alpha diversity. *Candida* is enriched in patients with more severe liver function. Minor fungal taxa are associated with reduced disease severity. Lactulose and carvedilol influence mycobiome composition. No strong correlation was found between fungal and bacterial communities in LC patients or controls.

WED-064-YI
Targeting gut-liver axis crosstalk with probiotic Lactobacillus rhamnosus attenuates ductular reaction in Mcpip1-deficient mice
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Background and aims: PBC progression leads to the development of fibrosis, cholestasis, liver cirrhosis. Mcpip1fl/flAlbCre mice, with the Zc3h12a gene (encoding Mcpip1 protein) deleted in liver epithelial cells, exhibit typical PBC symptoms (increased levels of antimitochondrial and antinuclear antibodies, elevated total bile acids, and intrahepatic bile duct hyperplasia, disruption of bile duct epithelium and fibrosis). The primary objective of this project is to elucidate PBC symptoms in these mice following the administration of first- and second-line therapies commonly employed in PBC patients. The study incorporates the use of a probiotic (Lactobacillus rhamnosus) due to emerging evidence suggesting that gut microbiota via gut-liver axis can play a key role in PBC development and progression.
Method: Mcpip1fl/fl and Mcpip1fl/flAlbCre male mice at 6 weeks of age were randomly divided into five groups for drug treatment. Control group received corn oil, other groups received consecutively Lbr (L. rhamnosus, 10^9 CFU per day) suspended in water, ursodeoxycholic acid (UDCA, 15 mg/kg body mass per day) diluted in corn oil, UDCA and Lbr, UDCA and obeticholic acid (OCA, 10 mg/kg body mass per day) both diluted in corn oil. After 6 weeks of treatment, all mice were sacrificed, and the collected material analyzed by, amongst other, detailed serum liver tests, ELISA tests for the presence of anti-PDC-E2 autoantibodies, histological stainings (H&E, PSR) and qPCRs of livers and intestines, next generation sequencing (NGS) of total RNA from livers. Feces were collected for microbiome and shotgun sequencing.
Results: After 6-weeks of treatment significant proliferation of cholangiocytes and fibrosis in livers from Mcpip1 knock-out mice was detected, together with high serum level of total IgM, total bile acids and anti-PDC-E2 autoantibodies. NGS analysis revealed that processes such as humoral immune response and T cell activation are significantly enriched in control knock-out mice. Comparison of Lbr-treated and control knock-out mice revealed significant suppression of these processes. Moreover, in the gut, control knock-out mice exhibit significant increase of intraepithelial lymphocytes infiltration, mucosal and enterocyte height. Pathological phenotype in the gut were ameliorated by Lbr treatment which also provided a positive shift in microbiome composition of knock out mice. Firmicutes to bacteriodetes ratio was increased, as well as abundance of some butyrate-producing strains, such as Lachnospiraceae in mice after Lbr treatment.
Conclusion: This study points out a beneficial effect of probiotic use in complex, chronic, cholestatic liver diseases, such as PBC. The phenotype in Mcpip1fl/flAlbCre mice is significantly ameliorated by targeting gut-liver axis and host microbiome with the use of Lbr, thus the vicious circle can be broken, and the progression of PBC-like disease can be eased.

WED-065
Myricetin alleviates steatotic liver disease through gut microbiota modulation and Wnt-signaling inhibition
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health problem that can lead to the development of severe liver disease. Myricetin, a member of the flavonoid class contained in spinach, berries, tea and red wine, has numerous pharmacological properties such as anti-oxidative, anti-inflammatory, anti-fibrotic, anti-obesity, and anti-diabetic effects. However, it has not been revealed yet whether myricetin is associated with gut microbiota modulation and Wnt-signaling inhibition that regulates lipogenesis. We aimed to evaluate the effect of myricetin on lipid accumulation inhibition in MASLD.
Method: To investigate clinical characteristics of gut microbiota associated with liver disease, network pharmacology analysis and 16S rRNA analysis of human stool samples (30 healthy controls and 40 MASLD patients) were conducted. For animal experiment to prove the efficacy of myricetin, the mice were randomly divided into a normal control (n = 5), normal diet with myricetin treatment (150 mg/kg, n = 7), Western diet (n = 6), Western diet with myricetin treatment (150 mg/kg, n = 5). We used Western diet-induced MASLD, and myricetin was fed to the mice by oral gavage five times a week for 14 weeks. We performed oral glucose tolerance test, mice were fasted for 16 hours before the oral gavage with glucose (2 g/kg). MASLD severity was determined based on liver/body weight, pathological makers. We conducted qPCR analysis for Wnt-signaling pathway target genes.
Results: In human data, *Escherichia* (23.07%) and *Bifidobacterium* (1.34%) levels were increased in MASLD patients. On the contrary, the levels of *Bacteroides* decreased (75.74% → 62.91%). In the network pharmacology analysis, myricitrin is metabolized to myricetin by *Escherichia* species and myricetin showed inhibitory mechanism in binding to GSK3-β of Wnt-signaling pathway. In the MASLD model, myricetin treatment group significantly improved liver/body weight ratio, with lower steatosis grade (1 VS. 2) and NAS score (1 VS. 3) compared to the Western diet group. Myricetin supplementation improved glucose tolerance compared with the control group and

significantly decreased the expression of Acc1 (p = 0.0228) and Scd1 (p = 0.0069) mRNA levels associated with lipogenesis. Additionally, in Wnt-signaling target genes, Lrp5 and Gsk3-beta (p = 0.0045) were down-regulated by normalizing RNA sequencing data. Clustering showed that *Proteobacteria (phylum)* (2.34% → 5.39%), *Escherichia,* and *Bifidobacterium* were enriched in the myricetin group (more than 1%). Additionally, administration of myricetin showed an increase in compared to the control group.
Conclusion: We suggest that myricetin ameliorates lipid accumulation through inhibiting Wnt-signaling pathway and modulating gut microbiota composition. We assess the potential of myricetin to alleviate MASLD.

WED-066
Bacteroides caccae alleviates hepatic fibrosis by suppressing inflammation
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Background and aims: Hepatic fibrosis represent a key pathological change in the progression of chronic liver disease (CLD). Various forms of CLD, including metabolic-associated steatohepatitis (MASH), viral hepatitis, alcohol-related liver disease (ALD), and autoimmune liver disease, can progress to cirrhosis, which serves as a major risk factor for hepatocellular carcinoma (HCC). Recent reports suggest that certain microbiotas may help inhibit or ameliorate the progression of MASH-associated cirrhosis. This study aimed to characterize the role of *Bacteroides caccae (B. caccae)* in the gut microbiome of patients with CLD. Furthermore, using a mouse model of MASH-associated cirrhosis, we evaluated the effects of *B. caccae* on the gut microbiota and investigated the associated molecular mechanisms.
Method: To identify distinctive microbiota in liver cirrhosis, 217 stool samples were divided into healthy control (n = 100), MASH (n = 100), MASH associated cirrhosis (n = 10), and HCC (n = 7) group. To induce a MASH-associated cirrhosis model through dietary intervention, mice were fed a 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine (DDC; 0.1%–0.05%) for three weeks. The diet consisted of 0.1% DDC in the first week, followed by 0.05% DDC for the subsequent two weeks. *B. caccae* was suspended in PBS at a concentration of 8×10^8 CFU/g and administered three times per week. The experimental mice were divided into three groups: a normal diet group (n = 7), a DDC diet group (n = 8), and a strain group (DDC diet supplemented with *B. caccae*, n = 8). CO_2 euthanasia was conducted, and liver tissues were fixed in 4% paraformaldehyde or frozen in liquid nitrogen. The left lobe of the liver was used for mRNA analyses. All experiments were performed in a blinded and randomized fashion.
Results: The relative abundance of *B. caccae* was significantly altered in the gut microbiota of cirrhotic patients compared to healthy individuals (healthy, 1.02%; MASH, 1.41%; MASH associated cirrhosis, 0.0067%; HCC, 1.1235%). In the mouse model, strain group (AST 350.9 ± 239.3, ALT 394.9 ± 230.7, BIL 0.3 ± 0.2) shows significantly improved in serum biochemical markers compared with DDC group (AST; 756.7 ± 103.9, ALT; 1099.6 ± 214.8, BIL; 1.1 ± 0.3). In addition, exhibiting protective pathological effects hepatic inflammation, hepatocellular damage, and fibrosis. The strain group downregulated the expression of inflammation-related markers (TNF-alpha, S100a8, S100a9, Mmp12, and other associated markers) and fibrosis-related markers (Col1a1, alpha-SMA, Acta2, and other related markers) in liver tissues compared with the DDC group, thereby improving liver function and alleviating tissue damage.
Conclusion: Our results suggest that *B. caccae* attenuate MASH-associated cirrhosis in a mouse model by suppressing inflammation and fibrosis.

WED-067
Akkermansia muciniphila inhibits serotonin-induced fibrosis progression in liver injury mouse model
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Background and aims: Serotonin is an important transmitter that mediates various neurological and non-neurological physiological processes. However, paradoxically, while it may promote liver regeneration, it also has the potential to accelerate liver damage. *Akkermansia muciniphila* (*A. muciniphila*) has been reported to improve various metabolic diseases and liver diseases by modulating the gut-liver axis. We identified the exacerbation of liver fibrosis by serotonin treatment in liver injury mouse model and evaluated the inhibitory effect of *A. muciniphila* on serotonin-induced liver damage.
Method: Six-week-old male C57BL/6J mice were divided into 6 groups (n = 5/group; Normal control, normal control + serotonin, 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine diet-fed [DDC, 0.1%], DDC diet + serotonin [100μM], 2 DDC diet-fed + serotonin [100 μM] + *A. muciniphila* [10^9 CFU/200ul for 2 times; live *A. muciniphila*, pasteurized *A. muciniphila*]). Serotonin was injected 100μM once through spleen injection. *A. muciniphila* was administered orally 24 hours and 12 hours before spleen injection. The weight, blood biochemistry, histopathology, and molecular biological analysis were performed.
Results: Directly treatment with serotonin through spleen injection method accelerated the progression of liver fibrosis. However, oral administration of *A. muciniphila* before serotonin treatment inhibited the progression of fibrosis. Supplementation of *A. muciniphila* (live and pasteurized) decreased ALT (Live, p = 0.01; Pasteurized, p = 0.008), AST (Live, p = 0.05; Pasteurized, p = 0.26), liver fibrosis area (Live, p = 0.004; Pasteurized, p = 0.004), and decreased the expression of fibrosis-related genes. In addition, *A. muciniphila* suppresses fibrosis progression by down-regulating 5-hydroxytryptamine receptor (5-HTR) 2A/2B.
Conclusion: Serotonin promote fibrosis progression in a DDC diet-induced liver injury mouse model. *A. muciniphila* is effective in inhibiting serotonin-induced fibrosis progression by down-regulating serotonin receptor 5-HTR 2A/2B.

WED-068
Enterohepatic circulation of microbial bile acid conjugates
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Background and aims: After being secreted to the intestine, bile acids (BAs) are actively re-covered by the ileum, mainly due to the apical sodium-dependent bile salt transport (ASBT). BAs are then released toward portal blood, which returns them to the liver.

Hepatocytes efficiently take up BAs from sinusoidal blood mainly through the Na^+-taurocholate co-transporting polypeptide (NTCP), with a minor contribution of the organic anion-transporting polypeptides (OATPs). Bacteria-mediated conjugation of BAs with non-canonical amino acids has been described to occur during their intestinal transit. Here, we have elucidated whether the most abundant microbial BA conjugates (MBACs) can also enter the enterohepatic circulation and whether they accumulate in patients with hepatobiliary dysfunction.
Method: Three MBACs were chemically synthesized by forming an amide bond between cholic acid (CA) and tyrosine (Tyr-CA), phenylalanine (Phe-CA), and leucine (Leu-CA). MBAC cholephilic behavior was evaluated in cellular and animal models. Transporter interactions were analyzed by molecular docking and dynamics simulations. In patients undergoing surgical or endoscopic bile collection, MBAC levels were determined in the bile by HPLC-MS/MS.
Results: Intravenous injection of MBACs in rats resulted in their efficient secretion into bile, with kinetics similar to glycocholic acid (GCA). Adding MBACs to the microbiota-free *in situ* isolated rat ileum lumen resulted in biliary secretion of intact MBACs. Similar results were obtained with GCA. In cells expressing human BA transporters, MBAC uptake, like that of GCA and taurocholic acid (TCA), was markedly enhanced by NTCP and ASBT. TCA inhibited this transport. In contrast, MBAC uptake was poorly mediated by OATP1B3 and scarcely by OATP1B1. These findings are consistent with results from molecular modeling studies, which provide insights into the interactions between MBACs and BA transporters, ASBT and NTCP. These interactions closely resemble those observed with liver-derived BA conjugates GCA and TCA. The analysis of human bile revealed the presence of MBACs (typically <100/10^6 molecules of total BAs) in samples collected from some (but not all) patients with liver cancer - hepatocellular carcinoma (8/12) and extrahepatic (7/33) and intrahepatic (7/10) cholangiocarcinoma- as well as other malignant - pancreatic ductal adenocarcinoma (27/55) - and non-malignant - benign stenosis (4/10), and choledocholithiasis (8/25) - conditions. An inverse relationship was found with total BA concentrations but not with age or outcomes of cancer patients.
Conclusion: MBACs behave as cholephilic compounds. BA transporters take them up with efficacy in the order of that of major primary conjugated BAs. The appearance of MBACs in the bile of some cancer patients is not related to hepatobiliary dysfunction but probably to changes in the microbiota that favor the proliferation of species able to generate MBACs.

WED-069

Gut microbiota composition of obesity resistant mice protects from high fat diet-induced steatosis

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Background and aims: Obesity, which is characterized by excessive fat accumulation, is a global health and economic burden. While most people on a high-calorie diet develop obesity and related metabolic diseases, some remain obesity resistant (OR). Obesity-induced changes in the gut microbiota increase capacity of the microbiota to harvest energy from the food, leading to fat accumulation and metabolic complications. Therefore, the aim of this study was to investigate the gut microbiota composition that contribute to obesity resistance and protect against the development of hepatic steatosis under a high-fat diet (HFD) regime.
Method: Male C57BL/6J mice were divided into two groups: a control group fed a standard diet containing 10 kcal% fat (D12450J, Research Diets) and a group fed a HFD containing 60 kcal% fat (D12492, Research Diets,). After 14 weeks, the mice on HFD were classified as obese or OR based on a 30% difference in body weight gain compared to the control group. The gut microbiota was analyzed by 16S rRNA sequencing of bacterial DNA isolated from fecal samples. Liver and small intestine sections were examined histologically, while changes in fatty acid uptake in these tissues were assessed by Western blot.
Results: Functional prediction of the gut microbiota activity revealed altered fatty acids metabolism and their biosynthesis in OR mice as compared to the obese group. In addition, a negative correlation between serum triglyceride levels and the relative abundance of Lactobacillus was found, and a positive correlation with the relative abundance of Desulfovibrio and Helicobacter. This change in the gut microbiota composition paralleled the decreased protein levels of free fatty acid transporters in the small intestine and liver of OR mice, which likely protect the liver from ectopic lipid deposition and steatosis characteristic for obese animals.
Conclusion: Increased abundance of Lactobacillus and decreased abundance of Desulfovibrio and Helicobacter is microbiota profile characteristic for obesity resistant animals, which is linked with reduced fatty acid transporters and decreased accumulation of lipids as compared to the obese animals. These results provide possible candidates for the probiotics that could potentially protect against obesity related complications.

WED-070-YI

Fecal microbiota transplantation results in increased caproic acid which alleviates steatosis and reduces ethanol-induced hepatotoxicity (in vivo and in vitro)

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Background and aims: Fecal microbiota transplantation (FMT) shows promise in treating alcohol-related liver disease (ALD). Dietary changes modify donor gut microbiota, which increase short chain fatty acids (SCFA), reduce gut leakiness and dysbiosis. However, how altered microbiota interacts with host remains unclear. We identified the microbial metabolites and explored their efficacy in murine model of ALD.
Method: Donor mice for FMT were fed an egg or soya protein enriched diet for two weeks before stool collection. FMT was performed in ALD mice model withsamples collected at baseline and day7 post-treatment to assess serum liver injury biomarkers, liver histopathology, and RT-PCR for inflammatory and lipid metabolism genes. Gut microbiota (16S rRNA) and metabolomes (fecal, plasma, hepatic) were analyzed using LC-MS/MS. Among the metabolites, caproic acid (CA) efficacy was tested in ethanol-administered Huh7 cells (100 mM ethanol for 3 days, 0.9 mM CA for 24 hours) and ALD mice (2.5% w/w CA). Beta-oxidation was analyzed using the Seahorse Extracellular Flux assay.
Results: Soya-FMT (S-FMT) reduced the liver injury significantly compared to egg-FMT as assessed by reduction in AST (1.2 FC, $p = 0.002$), bilirubin (1.2 FC, $p = 0.03$) and hepatic steatosis (1.7 FC, $p = 0.01$). S-FMT decreased hepatic TNFα (1.5 FC, $p = 0.02$) and IL6 (1.6 FC, $p = 0.02$) and increased the abundance of commensal (SCFA producing) taxa Coriobacteriaceae UCG-002 (1.5 FC, $p = 0.04$) and Acinetobacter (5.2 FC, $p = 2.55E-13$) and reduced abundance of opportunistic taxa Desulfovibrio (2.14 FC, $p = 0.02$) and Staphylococcus (9.6 FC, $p = 2.20E-33$). Metabolomics showed an increase in hepatic glutathione metabolism ($p = 0.04$) and, beta-oxidation of fatty acids ($p = 0.03$) and reduction in linoleic acid ($p = 0.01$) metabolism in S-FMT. It significantly increased stool bile acid and SCFA levels ($p < 0.05$), with increase in stool and plasma caproic acid (3 FC, $p = 0.0065$; 2 FC, $p = 0.01$, respectively). Stool bile acids showed increase in ursodeoxycholic acid (2 FC $p = 0.03$) and decrease in deoxycholic acid (1.8 FC, $p = 0.001$). Caproic acid supplementation reduced AST (2.6 FC, $p = 0.01$), ALT (2.3 FC, $p = 0.1$) and bilirubin (3 FC, $p = 0.06$) compared to untreated with reduction in inflammatory (IL6,

2.3 FC, p = 0.05; TNFa, 1.6 FC, p = 0.001) and lipid metabolites (5 FC, p = 0.03) and an increase in mitochondrial beta-oxidation (CPT1a, 2.5 FC, p = 0.05; Acox1, 3 FC, p = 0.04; PPARa, 4 FC, p = 0.001). After caproic acid administration, Huh7 cells also showed reduction in ethanol injury (IL6, 2.2 FC, p = 0.1; TNFa, 3.6 FC, p = 0.05; NFkb, 2.3 FC, p = 0.05), lipid accumulation (4.3 FC, p = 0.02) and concomitantly found to be dependent on beta-oxidation (3 FC, p = 0.05).
Conclusion: Soya-FMT was more effective in alleviating ALD injury. Caproic acid significantly mitigated steatosis in vitro and in vivo by enhancing beta-oxidation, thereby improving liver function. Caproic acid emerges as a promising therapeutic compound for further studies in alcoholic liver disease.

WED-075-YI
Restoration of gut microbiome-nitrogen metabolism post oral administration of black carrot extracellular vesicles in hepatic encephalopathy
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Background and aims: Dysregulated nitrogen metabolism and gut dysbiosis contributes to hepatic encephalopathy (HE). We aimed to restore mucosal integrity and gut commensals by black carrot extracellular vesicles (BC-EV). Enriched with curative biomolecules, promote gut microbiome rebiosis, may lower ammonia and improve cognition in HE.
Method: BC-EV (52–200 nm, zeta potential-17 ± –2.4 mV)10^9 particles orally administered in thioacetamide (TAA) HE rat model. Fecal metabolomics by LC-MS, 16S rRNA metagenomics, biochemical, histopathological, and cognitive assessments were performed. Baseline CLD-HE patients (n = 10; healthy = 11;no prior treatment) also investigated. The nitrogen-metabolism associated genes profiling by qRT-PCR. The omics was performed to identify BC-EV cargoes. Stability in gastric/ intestinal conditions and effects on *Lactobacillus (LGG*) growth were evaluated.
Results: Fecal metabolomics in CLD-HE patients compared to healthy revealed 156 differentially expressed metabolites (61 upregulated and 95 downregulated). Notably, primary bile acid biosynthesis, fatty acid degradation, pyruvate metabolism, and terpenoid backbone biosynthesis found upregulated, whereas neomycin, kanamycin, and gentamicin, amino acid and amino sugar and butanoate metabolism (acetoacetic acid, p = 0.007) were downregulated. In TAA-HE rats (ammonia: 145.3 ± 43.6 μmol/L, bilirubin: 0.36 ± 0.05 mg/dL, AST: 83.05 ± 4.5 IU/mL, p < 0.001), similar alterations were observed with 53 metabolites downregulated amino acid, nitrogen, and butanoate pathways (butyric acid, p = 0.002) compared to control rats. BC-EV administration reduced ammonia (92.2 ± 23.6 μmol/L; p = 0.004), improved albumin (p = 0.007), hepatic ornithine, arginase levels (p = 0.028), cognitive functions (p = 0.004), than vehicle-HE rats. BC-EV modulated gut microbiota, reducing *Escherichia-Shigella* (p < 0.005) and promoting butyrate-producers *Lachnoclostridium* (p < 0.01), urea cycle/amino acid modulating staphylococcus and corynebacterium inversely corelated with ammonia (r = –0.94; p = 0.017). BC-EV increased occludin (p = 0.01) and anti-inflammation (IL-10, IL-22; p ≤0 .01), validated by PICRUSt analysis. Co-culture with LGG-BC-EV, growth of LGG enhanced (p = 0.004). BC-EV fecal metabolites L-lysine (p = 0.01), D-proline, and butyric acid (p < 0.05) were elevated. However, protein cargoes of BC-EV identified as isocitrate and oxoglutarate dehydrogenases, enzymes of TCA cycle support ammonia-consuming gut microbial metabolism. Gastric digestion *in vitro* reduced particle size with intact zeta potential.
Conclusion: HE patients and TAA-HE rats show impaired butanoate metabolism, restored by BC-EV. Ammonia reduction inversely correlates with Corynebacterium, which consumes ammonia to produce L-lysine, enhancing butyrate production. BC-EV offers a safe, effective therapy to improve gut-liver-brain axis.

WED-076
Association between gut fungal microbiota and subclinical coronary atherosclerosis in patients with MASLD
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is an independent risk factor for cardiovascular disease (CVD). Recent evidence also indicates that gut bacterial microbiota is closely linked to CVD development. However, the role of intestinal fungi in the pathogenesis of CVD, particularly subclinical coronary atherosclerosis (SCA), is still to be determined. This study aimed to investigate the association of gut fungal microbiota with SCA in patients with MASLD.
Method: A cross-sectional study was conducted involving 103 MASLD patients without established CVD. Fibrosis and steatosis were assessed by magnetic resonance elastography (MRE) and proton density fat fraction (PDFF), respectively. SCA was detected based on coronary artery calcification (CAC). The internal transcribed spacer (ITS) sequencing was conducted to examine fecal fungal microbiota composition. Blood samples were analyzed for cytokine levels using LEGENDplex™ Human Cytokine Panel and trimethylamine-N-oxide (TMAO) concentration using liquid chromatography-mass spectrometry (LC-MS/MS).
Results: The mean age of the patients was 60.8 ± 11.2 years, and 53 (51.5%) were men. Thirty-two (31.1%) patients had advanced fibrosis (stage F3–F4). The CAC score positively correlated with MRE measurement (r = 0.459, p < 0.001) and tended to have a weak correlation with TMAO level (r = 0.223, p = 0.098) but was not correlated with PDFF value (r = –0.028, p = 0.837). Patients with F3–F4 had significantly higher CAC scores than those with F0–F2 (548.2 ± 592.7 and 244.1 ± 476.8, p = 0.039, respectively). Regarding fungal microbiota analysis, there was no significant difference in alpha- and beta-diversities between the F0-F2 and F3-F4 groups. A higher abundance of Candida albicans was significantly detected in fecal samples of patients with F3–F4 compared to patients with F0–F2 only in the subgroup with BMI ≥30 kg/m² and/or presence of T2DM (OR = 1.02, 1.01–1.04, p = 0.014). In this subgroup, the relative abundance of Candida albicans was significantly correlated with CAC score (r = 0.407, p = 0.023) and interleukin (IL)-17A level (r = 0.–442, p = 0.013) but not associated with TMAO level (r = 0.082, p = 0.562).
Conclusion: MASLD patients with advanced fibrosis had elevated CAC scores, indicating an increased risk of CVD development. The enrichment of Candida albicans was shown to be associated with subclinical atherosclerosis, particularly among obese patients with or without T2DM.

WED-077
Next-generation beneficial bacteria combined with fructo-oligosaccharides and fecal microbiota transplantation attenuates diet-induced metabolic dysfunction-associated steatohepatitis in mice
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Background and aims: Gut microbiome modulation is gaining attention in the unmet therapeutic need of metabolic dysfunction-associated steatohepatitis (MASH), both with probiotics and fecal microbiota transplantation (FMT). Yet, their combination has never been investigated. Here we investigated next-generation beneficial bacteria (NGBB) *Anaerobutyricum soehngenii*, pasteurized *Akkermansia muciniphila* and *Bifidobacterium animalis subsp. lactis* combined with FMT in a diet-induced MASLD mouse model.
Method: Male C57BL/6J mice received a Western-type high-fat diet and water with 15% fructose (WDF) for 20 weeks to induce MASLD. From week 10, mice received daily gavages with either 1) a combination of A. soehngenii, pasteurized A. muciniphila and B. animalis subsp. lactis (NGBB), 2) FMT of a healthy human donor, 3) NGBB combined with FMT (FMT-NGBB), or 4) placebo. FMT, NGBB and FMT_NGBB treated mice received fructo-oligosaccharides in drinking water. Chow-fed mice were included as control group.
Results: WDF resulted in steatohepatitis. Compared to placebo, only the FMT-NGBB treatment resulted in a lower relative liver weight and a 47% lower hepatic triglyceride concentration (32.4 [95%CI 21.4–43.3] vs. 60.9 [95%CI 42.4–79.5] nmol/mg liver, $p < 0.05$). In line, FMT-NGBB treatment resulted in better histopathological steatosis and lobular inflammation scores. While hepatic lipogenic and oxidative mRNA expressions were not affected by the treatments, FMT-NGBB treated mice had lower *Cd36* expression, which might be indicative for reduced hepatic fatty acid uptake. Expression of *Col1A1* was decreased more than twofold in the FMT and FMT-NGBB group when compared to placebo (p 0.0002 and p 0.0003, respectively). Moreover, a first analysis of RNA sequencing showed a reduction of mRNA expression of genes related to lipid metabolism, inflammation and fibrosis in livers of FMT-NGBB treated mice.
Conclusion: Remarkably and in contrast to the single treatment arms, FMT supplemented with next-generation beneficial bacteria reduced hepatic steatosis in mice by 47%. Histopathological steatosis and inflammation scores improved after FMT_NGBB treatment. RNA sequencing showed a reduction of hepatic mRNA expression of genes involved in inflammation and fibrosis. These findings highlight the potential of combining microbiota modulation strategies for MASH.

WED-078
Sex-specific effects of beta-blockers on the gut microbiome and metabolome in liver cirrhosis

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Background and aims: Beta-blockers (BB) are used in liver cirrhosis to manage portal hypertension and variceal bleeding, with emerging evidence suggesting potential benefits in systemic inflammation. Their effect on the gut microbiome, crucial for cirrhosis progression, remains poorly understood. We aim to investigate the impact of BB on the gut microbiome and metabolome in liver cirrhosis patients, focusing on sex-specific differences.
Method: 121 patients with liver cirrhosis were recruited. MELD scores were available for all, stool samples of 99 patients (metabolome analysis), and 16S rRNA gene sequencing data of 84 (62 men, 65 ± 7 years; 22 women, 58 ± 13 years, $p = 0.012$) patients (microbiome analysis). To explore sex-specific differences, patients were grouped by sex and compared across non-selective beta-blockers (NSBB), selective beta-blockers (SBB), and no intake. Alpha- and beta-diversity, as well as ANCOM and LEfSe, were used to analyze microbiome differences. The metabolome was assessed using NMR and analyzed using orthoPLS-DA in MetaboAnalyst 6.0.
Results: 40 patients took NSBB (11 women) and 22 took SBB (4 women). In men, MELD scores were lower for SBB users compared to NSBB ($p = 0.031$), while no differences were observed in women. Microbiome analysis showed increased alpha diversity in male SBB users compared to NSBB ($p < 0.05$), with no changes in women. Beta diversity was not different between drug groups and sexes. ANCOM and LEfSe identified a higher abundance of short-chain fatty acid (SCFA) producers, Prevotella and Phascolarctobacterium, in both NSBB and SBB users compared to non-users. In contrast, in women, SCFA producers UCG-002 and Subdoligranulum were more abundant in non-BB users, while Ruminococcaceae Incertae Sedis higher in SBB users. In the metabolome, l-valine was associated with no BB intake in men, while the purine derivative hypoxanthine was elevated in BB users, particularly SBB. Hypoxanthine was also linked to BB intake in women, indicating shared metabolomic responses across sexes despite microbiome differences (all VIP ≥2.5).
Conclusion: BB use in liver cirrhosis patients induces distinct microbiome and metabolome changes with notable sex-specific differences. In men, SBB intake was linked to lower MELD scores, increased diversity, and beneficial bacteria, while in women, beneficial bacteria were associated with the absence of BB intake. Metabolome analysis revealed fewer sex-specific differences, with both sexes showing increased hypoxanthine, which has been associated with improved gut permeability and Prevotella abundance. Further research is needed to understand drug-microbiome interactions better.

WED-079-YI
Quantification of genes encoding bacterial sialidases and enzymes of the nan cluster in combination with cutaneous T cell-attracting chemokine (CTACK) in bile for the early detection of cholangiocellular carcinoma in patients with primary sclerosing cholangitis (PSC)

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Background and aims: Primary sclerosing cholangitis (PSC) is a devastating disease of the biliary tract. Affected patients suffer from recurrent bacterial cholangitis due to the destruction of the biliary tract. Many patients develop cholangiocellular carcinoma (CCA) due to recurrent and/or chronic inflammation. However, the detection of CCA in these patients is difficult and in many cases not successful. In a former study we identified the degradation of cholangiocellular glycocalyx by bacterial sialidases as a new pathomechanism in PSC. In

the present study we aimed to analyze the clinical use of detection and quantification of genes encoding bacterial sialidases, N-acetylneuraminate lyases and N-acetylmannosamine kinases in combination with cytokines in bile of patients with PSC for the detection of CCA.

Method: During routine endoscopic retrograde cholangiography (ERC) bile was collected in 112 patients with PSC with and without CCA during 2008–2020. Bile was aliquoted and stored immediately at –80°C. In order to quantify the amount of genes encoding bacterial sialidases, lyases and kinases we developed an in-house qPCR. DNA was isolated after mechanic lysis with the EurX-Kit. In a sub-cohort of 88 patients with 137 samples 29 cytokines were measured.

Results: In the overall cohort, pool 1 (sialidases), pool 4 (lyases) and pool 5 (kinases and lyases) showed significantly higher DNA concentrations in patients with PSC and CCA compared to patients without CCA (pool 1: 2.80×10^4 vs. 7.10×10^5 copies/µl; $p < 0.0001$) (pool 4: 1.31×10^4 vs. 7.22×10^5 copies/µl; $p < 0.0001$) (pool 5: 2.91×10^3 vs. 1.67×10^4 copies/µl; $p < 0.0001$). The area under the curve (AUC) for the pools were 0.831 for pool 1, 0.793 for pool 4 and 0.754 for pool 5. Based on the Youden-Index we identified for each parameter a balanced cut-off with 1.65×10^5 copies/µl for pool 1, 3.16×10^5 copies/µl for pool 4 and 9.83×10^3 copies/µl for pool 5. In the sub-cohort, we identified 4 cytokines differentiating between patients with PSC with and without CCA. Out of these CTACK showed the best performance with a specificity of 0.78, sensitivity of 0.90 and an AUC of 0.872. Based on the Youden-Index we identified a balanced cut-off with 7.6. In a next step we could increase the diagnostic value with a combination of our parameters. Patients with at least 2 out of 4 parameters being positive had a CCA with a specificity of 87.4% and a sensitivity of 84.6%.

Conclusion: Based on our new qPCR for bacterial sialidases, lyases and kinases in combination with CTACK we developed a new diagnostic tool for the early detection of CCA in patients with PSC. Early detection of CCA is crucial for the outcome of affected patients. Therefore, we see a huge diagnostic potential of our approach. However, further prospective studies in independent cohorts is needed to validate our system.

WED-080-YI

Gut multiomics links bacterial-driven increase in Lactate with the development of shock and identifies metabolite panel for prediction of adverse outcomes in ACLF patients

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Background and aims: Acute on chronic liver failure (ACLF) is associated with septic shock (lactate > 2 mM/l) through liver dysfunction and immune dysregulation. Gut microbial and metabolic imbalances worsen inflammation, increasing multi-organ failure and mortality risk. This study screened gut and plasma meta-proteomes and metabolomes to identify indicators linked to adverse outcomes in ACLF patients.

Method: Baseline stool and plasma samples were collected from 50 healthy controls, 50 alcoholic cirrhosis, and 100 alcohol-associated liver failure patients (non-sepsis: 20, sepsis: 30, septic shock: 50). High-resolution mass spectrometry (HRMS) was used to analyze human and bacterial metabolomics and meta-proteomes, which were cross-correlated with clinical parameters and severity indices (MELD, SOFA, CTP, DF). Probability of detection (POD) models for septic shock and early mortality were developed based on bacterial and metabolite markers and validated in 300 patients using HRMS and machine learning (ML).

Results: Stool and plasma metabolome analysis identified over 1,200 metabolites, with more than 300 upregulated (FC > 1.5; $p < 0.05$) in septic shock patients, associated with B-oxidation, TCA cycle, bile acid biosynthesis, fatty acid, and tryptophan metabolism. Notably, septic shock patients showed elevated levels of over 26 carboxylic acid metabolites, including malate, fumarate, oxaloacetate, and lactate, linked to lactate accumulation ($p < 0.05$). Stool and plasma metaproteome analysis identified more than 100 bacterial species of them > 40 bacterial species were upregulated in septic-shock patients ($p < 0.05$). Bacterial diversity was found to be lowest in Septic shock patients ($p < 0.05$) and showed significant increase in Bifidobacterium lactis (FC > 55000, AUC > 0.98), Clostridium botulinum (FC > 20000, AUC > 0.89), Clostridium perfringens (FC > 13, AUC > 0.92) and Clostridium acetobutylicum (FC > 6, AUC > 0.87). Interestingly, septic shock showed increase in Bifidobacterium lactis and Clostridium species; which contribute in acidic metabolites (acetate, butyrate and others) and increased lactate levels. Probability for Diagnosis (POD) of non-survival calculated based on Chenodeoxyglycocholate (FC > 756), Geranyl acetate (FC > 477), Taurochenodeoxycholicacid (FC > 193), Glycocholic acid (FC > 760), Ornithine (FC > 291) correlated with clinical parameters and severity ($R^2 > 0.7$, $p < 0.05$), showing diagnostic efficiency of AUC > 0.95 and HR = 5.2 ($p < 0.05$). Increased Clostridia species and top5 metabolite panel on validation in 300 independent patients demonstrated > 95% sensitivity/specificity for predicting shock and early mortality.

Conclusion: The study identifies Bifidobacterium lactis and Clostridium species as key drivers of lactate increase and septic shock. The metabolite panel offers a reliable biomarker for diagnosing septic shock and predicting mortality in critically ill patients.

WED-081-YI

Role of alcohol-associated gut microbiota in driving liver fibrosis via tgfbr1 kinase alterations in alcohol associated liver disease

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Background and aims: ALD is worsened by gut dysbiosis, affecting inflammation, fibrosis, and metabolism. While gut microbiota influence fibrosis, their role in ALD is unexplored. This study investigates how alcohol-associated gut microbiota (AGM) induces liver kinome alterations, driving inflammation and fibrosis.

Method: ALD rats were developed using a 40% Lieber-DeCarli ethanol diet. AGM-linked kinome changes were studied in humanized rats colonized with stool from SAH patients (SAHs→HR) and compared to ALD rats transplanted with healthy donor stool (HD→ALDR). Stool and liver samples (n = 6/group) underwent metaproteome and phosphoproteome analyses. AGM-associated kinome changes, particularly in fibrosis induction, were identified and validated, with a focus on the roles of *Streptococcus pyogenes* and Lactobacillus in hepatic stellate cell activation (LX2 line).

Results: Stool metaproteome identified significant increase in 10 bacterial genera including *Streptococcus, Staphylococcus, Clostridium,* & others in SAHs→HR similar to ALD ($p < 0.05$). COG functional analysis showed increased post-transcriptional protein modifications (PTM) & reduced lipid transport & metabolism, indicating that AGM contributes to PTM changes & steatosis as seen in ALD ($p < 0.05$). Liver kinome analysis in SAHs→HR rats showed 85 significantly upregulated kinases, with 34 overlapping with ALD rats ($p < 0.05$) associated with inflammation (12: Mapk14, Map3k10, & others), fibrosis (4-Igf1r, Tgfbr1, Col4a1), lipid metabolism (11-Cdk14, Cdk18, Cdk13, & others), & regeneration (3-Bmpr1a, Met, Igf1r). Interestingly, HD→ALDR significantly reversed the levels of *Streptococcus* 10 folds, *Staphylococcus* 3 folds, and *Clostridium* 5 folds & 18 kinases associated

to inflammation (Btk, Camk4, Mapk, Met, Nuak1 & others) & fibrosis (Col4a1, Tgfbr1, Fgfr2 & others, $p < 0.05$). Metaproteome & kinome correlation analysis showed that *Streptococcus* genus directly correlated with inflammation & fibrosis (Btk, Mapk, Tgfbr1) linked kinases ($r2 > 0.9$, $p < 0.05$), suggesting that AGM may promote fibrosis in ALD via modulation of these kinome. A significant reduction in Tgfb (1.5 folds) was also found post FMT in SAH patients validating our observation. Further the linkage of pathogenic strain of *Streptococcus pyogenes* to fibrosis was established by treating LX2 cell line with its secreatome which showed significant induction of TGFβ (5.1 folds) and TGFBR1 (3.8 folds) expression, confirming the role of *Streptococcus pyogenes* in fibrosis induction.

Conclusion: Alcohol-associated gut microbiome alters the liver kinome, driving inflammation, fibrosis, & lipid dysregulation, with *Streptococcus pyogenes* promoting TGFβ/TGFBR1-mediated fibrosis. FMT from healthy reversed these effects, highlighting the therapeutic potential of gut microbiota modulation in ALD & identifying kinases & bacteria as targets for treatment.

WED-082-YI

Gut-oral microbial translocation promotes ammonia metabolism in liver cirrhosis

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Background and aims: Alterations in gut and oral microbiota have been implicated in the pathology of liver cirrhosis (LC). Gut-oral microbial translocation and oralisation of gut microbiota are associated with the progression of LC; yet their contributions to metabolic dysregulation and disease severity remain unclear. This study aims to elucidate the mechanistic link between microbial translocation and metabolic alterations in LC.

Method: Publicly available shotgun metagenomic data of paired saliva and faecal samples from liver cirrhosis patients ($n = 85$) and healthy controls ($n = 61$) were used in this study with different severity, and presence of hepatic encephalopathy. A microbial reactobiome was constructed to profile metabolic gene functions and identify metabolic patterns within oral and gut microbiomes. Unsupervised clustering was performed to explore reactobiome clusters and the association non-parametric test was applied to investigate how the determined reactotypes stratified clinical metadata. The gut-oral reactobiome distance for each individual was determined using Bray-Curtis dissimilarity based on paired data, and their association with disease severity (as measured by MELD scores) was assessed by linear regression. For key species, genome-scale metabolic models and constraint-based modelling were applied to predict the metabolic flux turnovers, including ammonia production, at both the species and community levels. Co-abundance network analysis was integrated with simulation results to identify key microbial contributors within the microbiome.

Results: Distinct metabolic profiles of gut and oral microbiota were identified in LC patients, revealing two oral reactotypes and three gut reactotypes associated with LC severity ($p < 0.05$). The oral-gut reactobiome distance decreased linearly with increasing MELD score ($p < 0.01$). Patients with lower oral-gut reactobiome distances (low-OGD) exhibited co-abundance of sixteen microbial species in both oral and gut niches. Some of these species were predicted to produce significantly higher levels of ammonia compared to healthy gut commensals ($p < 0.05$) via amino acid metabolism pathways. Among these species, predominantly oral-origin species were identified as key contributors to high ammonia production, based on integrated network analysis. Community-level modelling further predicted an increased ammonia level in the low-OGD model when adding the key species, implicating that oral-originating species contribute to exacerbating ammonia toxicity in liver cirrhosis.

Conclusion: This study identifies the gut-oral translocation of specific microbes as a potential driver of increased ammonia production in liver cirrhosis. The convergence of the metabolic profiles of oral and gut microbiota, linked with disease severity, highlights the potential role of oral-originating microbes in exacerbating cirrhosis through enhanced ammonia production in the gut.

Hepatocyte biology

TOP-073

Disruption of mitochondrial dynamics and stasis leads to liver injury, innate immune response and tumorigenesis

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Background and aims: Mitochondrial dysfunction has been implicated in aging and various cancer development. Mitochondria are dynamic organelles that constantly undergo fission via DRP1 (gene name *Dnm1l*) and fusion via MFN1/2 and. However, whether and how dysregulation of mitochondria dynamics would be involved in liver pathogenesis and tumorigenesis is unknown.

Method: *Dnm1l* Flox/Flox ($Dnm1l^{F/F}$), $Mfn1^{F/F}$ and $Mfn2^{F/F}$ mice were crossed with albumin-Cre mice to generate liver-specific *Dnm1l* knockout (L-*Dnm1l* KO), L-*Mfn1* KO, L-*Mfn2* KO, L-*Mfn1, Mfn2* double KO (DKO), and L-*Mfn1, Mfn2, Dnm1l* triple KO (TKO) mice. These mice were housed for various periods up to 18 months, blood and liver tissues were harvested for biochemical and histological analysis. Liver tissues were used for transcriptomic and metabolomic analysis.

Results: L-*Dnm1l* KO mice exhibited elevated serum ALT levels, increased accumulation of hepatic megamitochondria, and fibrosis as early as 2 months of age. By 12 months, a significant 63% of male mice developed spontaneous liver tumors, primarily hepatocellular adenomas, and this incidence rose to 100% by 18 months. Female L-*Dnm1l* KO mice also developed liver tumors, but at a much lower incidence. In contrast, neither L-*Mfn1* KO nor L-*Mfn2* KO mice showed significant liver injury or tumor development. However, a small percentage (29%) of DKO mice did develop tumors between 15 and 18 months of age. In L-*Dnm1l* KO mice, increased DNA damage, cellular senescence, and compensatory proliferation were observed, while these effects were less pronounced in L-*Mfn1* KO, L-*Mfn2* KO, or DKO mice. This suggests that mitochondrial fission plays a crucial role in maintaining hepatocyte homeostasis and preventing liver tumorigenesis. Interestingly, the further deletion of *Mfn1* and *Mfn2* in L-*Dnm1l* KO mice significantly reduced the formation of megamitochondria, liver injury, fibrosis, and tumorigenesis. This indicates that mitochondrial stasis is vital for maintaining hepatocyte function. RNA sequencing analysis revealed substantial activation of the cGAS-STING-interferon and tumor microenvironment pathways in the livers of L-*Dnm1l* KO mice, but these gene expression changes were notably corrected in TKO mice. Additionally, metabolomics and

transcriptomics analyses indicated increased pyrimidine synthesis and decreased expression of genes related to mitochondrial structure and metabolism in the livers of L-*Dnm1l* KO mice, effects that were mitigated in TKO mice.
Conclusion: Mitochondrial dynamics and stasis are essential for maintaining hepatic mitochondrial homeostasis and hepatocyte functions. The loss of hepatic DRP1 promotes liver injury and tumorigenesis; however, these issues can be corrected by the deletion of MFN1 and MFN2, which restores hepatic mitochondrial stasis.

SATURDAY 10 MAY

SAT-042-YI
Rapid multiplex liver gene editing in mice using adeno-associated virus 8 or lipid nanoparticles
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Background and aims: Conventional methods to generate liver-specific knockout mouse models for multiple genes are often time-consuming and inefficient. Here, we present a streamlined, CRISP-Cas9-based approach that enables rapid, efficient and multiplex liver-targeted gene editing using adeno-associated viral 8 (AAV8) or lipid nanoparticles (LNPs). This approach leverages selection pressure from tyrosine metabolism to increase gene editing efficiency: Hepatic fumarylacetoacetate hydrolase (*Fah*) deficiency is lethal in mice, but can be rescued by knocking down upstream enzyme 4-hydroxyphenylpyruvate dioxygenase (*Hpd*). In *Fah* deficient mice, *Hpd* -edited hepatocytes have a survival advantage, thus plasmids targeting *Hpd* and a separate gene of interest (GOI) can therefore be used to rapidly generate mice with multiple liver-specific knockdown and overexpression of nearly any gene product.
Method: In this study, we generated $Fah^{-/-}/spCas9^{Tg}$ mice that constitutively express the spCas9 recombinase. These mice were injected with two AAV8 vectors, each containing two gRNAs targeting an intron of *Hpd* and an exon of a gene of interest (GOI). The successfully-edited hepatocytes with *Hpd* knockdown gain a survival advantage, enabling efficient deletion of two GOIs. Each AAV8 vector also contains a CMV promotor flanked by a multiple cloning site, enabling overexpression of any desired gene as long as it can be packaged in AAV. Additionally, we tested LNP as an alternative non-viral method to deliver individual gRNAs.
Results: Complete *Hpd* knockout in the murine liver was achieved within two months using either AAV8 or LNP delivery systems, with no adverse effect on body weight and liver toxicity enzymes. Using the AAV strategy, we successfully generated humanized sodium taurocholate cotransporting polypeptide (NTCP) mice within 4 weeks by simultaneously deleting endogenous murine NTCP and expressing human NTCP.
Conclusion: This approach provides an efficient and safe strategy for rapid, multiplex gene editing via AAV8 or LNP delivery. The successful generation of humanized NTCP mice demonstrates the potential of this approach for creating advanced humanized mouse models. This system paves way for studying complex polygenetic liver disorders and supports future development of combination therapies.

SAT-043
rhTPO promotes hepatocyte proliferation in rats with acute liver failure through the MAPK and PI3K AKT signaling pathways
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Background and aims: Liver failure is a clinical syndrome with high mortality and poor prognosis. Research showed that TPO analogue treatment could help improve platelets and promote liver function recovery. This study explored the effects and possible mechanisms of Recombinant human thrombopoietin (rhTPO) on liver regeneration in rats with acute liver failure (ALF).
Method: SD rats were randomly divided into control group (n = 24) and TPO group (n = 24). Both groups were given physiological saline or TPO at a dose of 15 ug/Kg/day subcutaneously before modeling for 5 consecutive days. The ALF rat model was induced by D-galactosamine salt (D-GalN) 1500 mg/kg. After modeling, the TPO group and the control group rats were subjected to venous blood collection at 6 hours, 24 hours, and 72 hours, respectively. Eight rats were euthanized in each group to detect peripheral blood platelet count and liver function indicators. The changes in liver function and liver weight were compared. The proliferation of liver cells was analyzed by immunofluorescence staining of liver tissue. Perform transcriptome and proteomic analysis in both TPO group and control group at 72 hours, and compare the differentially expressed genes and proteomic changes in the liver tissues of the two groups.
Results: The PLT count of ALF rats in the TPO group was significantly higher than control group, and the ALT levels in the TPO group were significantly lower than control group at 6 and 24 hours (650.8 U/L vs. 1321.2 U/L, P = 0.044 and 682.0 U/L vs. 1152.7 U/L, P = 0.048). The TBil level in the TPO group at 72 hours was significantly lower than control group (0.3 μ mol/L vs. 7.4 μ mol/L, P = 0.028), and the liver weight after TPO pretreatment was significantly higher than control group (P < 0.01). The Ki67 proliferation index and BrdU positive cell proportion in ALF rat liver tissue were significantly higher than control group (P < 0.05). The mRNA sequencing results showed that compared with the control group, the TPO pretreatment group had 262 upregulated genes and 188 downregulated genes. The proteomics results showed that the TPO pretreatment group had 24 upregulated genes and 12 downregulated proteins. After taking the intersection of differentially expressed genes from transcriptome sequencing and differentially expressed proteins from proteomics, a total of 10 genes were identified as common differentially expressed genes, including IL, Mylk3, Nras, Map2k2, Hgf, Pf4, Map2k1, Mt1, AnxiA8, and Gp1bb. The GO and KEGG showed that the differentially expressed genes were mainly related to the MAPK signaling pathway and PI3K-AKT signaling pathway.
Conclusion: Inducing platelet elevation through rhTPO could promote liver function recovery and increase liver cell proliferation in ALF rats through differentially expressed genes related to the MAPK signaling pathway and PI3K-AKT signaling pathway.

SAT-044-YI
Dynamic hepatocyte adaptations in acute biliary hypertension: role of canalicular remodeling, mechanosensors activation and alternate bile transport
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Background and aims: Cholestasis can cause severe hepatotoxicity and increased biliary pressure leading to biliary hypertension. The role of bile canalicular mechanosensors in response to biliary hypertension is unexplored. We aimed to investigate the canalicular dynamics in response to bile fluid stasis and the mechanisms involved.

Method: Biliary pressure and flow index was monitored in bile obstruction model at B4H (4 hrs) and B24H (24 hrs) hours post-surgery. Primary hepatocyte was isolated, gene and protein expression analysis were done followed by flow cytometry. Biochemical, histological, immunofluorescence imaging, molecular and cellular analysis was carried out on liver tissue.
Results: The biliary pressure was raised (12.2 mmHg) immediately and was stabilized at 4 hr (16 mmHg) and 24 hr (14.2 mmHg) post bile flow obstruction. Bile flow index was increased in B4H (3.3 ul/min/g) and decreased in B24H (2.2 ul/min/g) from baseline (2.8 ul/min/g). Histology revealed increased bile canaliculi diameter, inflammation, macrophage infiltration and ductular reactions in B4H and B24H. Portal fibrosis was observed in both 4 hrs (2×) and 24 hrs (1.5×). However, increased invasive ductular reactions were observed at 24 hr. Interestingly, canalicular marker CD13 was increased at both 4 and 24 hr ($p < 0.01$). Liver enzymes AST, ALT, ALP and GGT were increased, bilirubin was unchanged at both 4 and 24 hr. Mechanistically, hepatocyte junctional proteins, Connexin32, Connexin 26, IntegrinB1 and Claudin markedly reduced at both 4 and 24 hrs ($p < 0.05$). In isolated primary hepatocytes, mechanosensors PIEZO1, YAP, TAZ and it's downstream TEAD1 were upregulated at 4 and 24 hrs ($p < 0.05$). RhoA/ROCK1 dependent cytoskeletal remodelling proteins Cofilin, profilin, calpain were increased at 4 and 24 hr ($p < 0.01$). However, protein expression of RhoA was reduced ($p < 0.05$). Expression of actin was increased in 4 hrs but reduced in 24 hrs ($p < 0.001$). Also, nucleoskeletal genes LaminA/C and Matrin 3 increased in both 4 and 24 hr leading to cell death that was supported with increased expression of HMGB1 and decreased albumin expression in both 4 and 24 hrs ($p < 0.05$). Increased FGFR4, CYP27A1 confirms activation of alternative bile acid metabolism pathway supports hepatocellular damage. Nevertheless, bile transport was increased at 4 and 24 hrs indicating alternative bile efflux mechanism.
Conclusion: This novel study reports that the bile stasis induced pressure on hepatocytes alters bile canaliculi dynamics and activate hepatocellular mechanosensors that further regulates the cytoskeletal and nuclear remodelling. Loss of cytoskeleton and junctional proteins indicates compromised hepatocyte integrity leading to cellular death. Also, in early stages, bile acid synthesis shifts to alternative pathway regulated via FXR signalling leading to decreased bile flow and increased transport of bile. Hence, biliary canaliculi mechanosensors are the key regulators of bile fluid dynamics under bile fluid stasis induced pressure.

SAT-045
10 year analysis and trends in liver biopsy; a single centre experience

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Background and aims: The advent of the widespread use of non-invasive assessment of liver disease has altered practice with regards to liver biopsy. However liver biopsy remains the gold standard diagnosis for certain liver conditions. We have reviewed 10 years of liver biopsy data to assess how our practice has changed over this timeframe. We aimed to assess the impact of improved diagnostic techniques on the biopsy practice in NHS Tayside (NHST).
Method: We conducted a retrospective search for liver biopsies performed in NHST from 2014 to 2023. Biopsy results were linked to demographic data. Statistical analysis was performed using a CHI squared test with a p-value of 0.05.
Results: 1035 liver biopsies were performed on 967 patients with the peak number of biopsies being performed in 2016 (n = 140). 563 (54.4%) were targeted biopsies of liver lesions with the remainder being non-targeted. Over time there has been a reduction in the number of targeted biopsies performed [n = 65 (2013) vs n = 55 (2023)] and a trend to a higher proportion of biopsies positive for malignant disease 78.4% (229/292) in 2014–2018 to 84.9% (230/271) in 2019–2023 ($p < 0.05$). Similarly, there has been a reduction in number of non-targeted biopsies over time [n = 58 (2014) vs n = 43 (2023)]. There has been no significant change in proportion of biopsies diagnostic of autoimmune liver disease over time with 23.2% (n = 71/306) in 2014–2018 and 28.3% (n = 47/166) in 2019–2023 ($p = 0.22$). There have been no recent biopsies for staging viral hepatitis and the indications are almost completely diagnostic uncertainty rather than staging disease. There has been a significant trend to a reduction in liver biopsies showing steatotic liver disease: 43.8% (134/306) in 2014–2018 vs 28.9% (48/166) 2019–2023 [$p < 0.05$]). Additionally, there has also been a trend to a reduction in non-targeted biopsies showing normal histology from 5.6% (17/306) in 2014–2018 to 3.0% (5/166) in 2019–2023 ($p = 0.21$).
Conclusion: There has been a significant increase in the proportion of targeted biopsies yielding malignant pathology, suggesting more judicious use of biopsies possibly related to improved imaging techniques. Additionally, there has is a significant reduction in biopsies demonstrating steatotic liver disease which could be related to the more widespread use of non-invasive techniques for diagnosing steatotic liver disease.

SAT-046
Effects of N-acylethanolamines in an in vitro model of metabolic stress: evidence on autophagy and related pathways in hepatic cells

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Background and aims: Nutrient excess can induce the chronic activation of adaptive cellular stress mechanisms, including autophagy and oxidative stress. Autophagy is a process required for removing damaged molecules and subcellular elements, including proteins, lipids, and organelles to reestablish homeostasis in response to stress. Targeting these stress-related cellular responses can be useful to prevent or treat hepatic dysmetabolism associated with obesity. N-acylethanolamines (NAEs) are endogenous lipid-signaling molecules belonging to noncanonical endocannabinoids, involved in inflammation and energy metabolism. Here, we investigated the role of NAEs in modulating the autophagic process in presence or not of metabolic stress stimulus in hepatocarcinoma cell line (HepG2).
Method: Cells were pre-challenged or not with 100 μM palmitate (PA) for 1 hour; then, they were treated with 3 μM NAEs (palmitoylethanolamide, oleoylethanolamide, linoleylethanolamide, and stearoylethanolamide) for 24 hours, followed by 3-hour treatment with the inhibitor of autophagosome-lysosome fusion bafilomycin (1 μM), used to better evaluate the possible increase of autophagic process. Western blot and Real Time PCR were performed to analyze the expression of proteins and genes involved in autophagic process. SeaHorse XP metabolic analyzer was used to evaluate mitochondrial bioenergetics after PA challenge in presence or not of NAEs.
Results: First, we showed that all NAEs alone induced the activation of autophagy, increasing the expression of LC3-II, a standard marker for autophagosomes, and reducing the proteasomal degradation of ubiquitinated proteins, as shown by decreased p62 protein expression. The stimulation of HepG2 cells with PA mimicked the pathological context linked to lipid overload and following metabolic stress. PA challenge reduced cell viability and induced the compensatory activation of autophagic pathway. Notably, NAEs limited PA-induced cytotoxicity and further increased LC3-II expression

enhancing the degradation and recycling processes involved in the maintenance of hepatic cellular homeostasis. Consistently, NAEs increased the transcription of autophagy-related (ATG)3 and ATG7, which contribute to phagophore elongation. Finally, among all NAEs at 3 μM, solely palmitoylethanolamide improved the mitochondrial bioenergetics compromised by PA restoring basal respiration, inducing proton leak and modulating ATP-linked respiration. This latter finding suggests a different activation and/or potency of all NAEs on mitophagy and related pathways.
Conclusion: This *in vitro* evidence lays the groundwork for identifying new conceivable applications of NAEs in enhancing cellular homeostasis and improving hepatic metabolic alterations by modulating autophagy and/or mitophagy activated by nutritional metabolic stress.

SAT-047
The updated LiverSCA: a widespread and user-friendly cell atlas in human primary liver cancer and steatotic liver disease
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Background and aims: Primary liver cancer (PLC) primarily consists of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), with HCC being the most common, accounting for over 90% of all PLC cases. HCC is characterized by significant cellular and molecular heterogeneity. Metabolic dysfunction-associated steatohepatitis (MASH) is a type of steatotic liver disease (SLD) defined by the presence of hepatic steatosis alongside at least one cardiometabolic risk factor, without any other identifiable cause.
Method: The current version of LiverSCA has greatly improved the comprehensiveness and functionality of the cell atlas. It now includes advanced gene expression analyses using various comparative visualization plots and a more extensive dataset collection that identifies different subtypes and etiological risk factors associated with PLC and SLD.
Results: LiverSCA cell atlas features six phenotypes of liver (normal, HBV-HCC, HCV-HCC, non-viral HCC, ICC, and MASH), encompassing data from 63 patients and over 248,000 cells. We have also integrated comparative visualization methods that enable users to examine and compare gene expression levels between two distinct phenotypes simultaneously. Additionally, the significant differences in tumor microenvironments (TMEs) across PLC subtypes and phenotypes, along with varying immune cell infiltration patterns, underscore the need for more specialized therapeutic strategies that reflect the intrinsic characteristics of PLC.
Conclusion: By utilizing LiverSCA, researchers can visualize single-cell data in an accessible way, promoting collaboration between computational and wet-lab teams and enhancing understanding of PLC. We are dedicated to the ongoing development of LiverSCA and aim to provide a valuable resource for researchers investigating the cellular and molecular landscapes of PLC. For future plan, we will continue to enhance LiverSCA by incorporating more etiologically specific PLC datasets and believe that LiverSCA will be an essential tool for researchers seeking to unravel the complexity and heterogeneity of PLC.

SAT-048
Regulation of thyroid hormone metabolism by HNF4A via modulation of deiodinase activity in hepatocytes
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) comprises a spectrum ranging from hepatosteatosis through steatohepatitis to fibrosis and irreversible cirrhosis. Hepatocyte nuclear factor 4A (HNF4A), a nuclear hormone receptor highly expressed in the liver, plays a central role in regulating hepatic lipid metabolism by modulating fat storage via lipophagy. Previously, we identified type 1 iodothyronine deiodinase (DIO1), a key enzyme in thyroid hormone metabolism, as a crucial metabolic regulator in the progression of MASLD. We hypothesized that HNF4A may regulate DIO1 activity, thereby influencing thyroid hormone regulated gene expression in hepatocytes. To test this hypothesis, we examined the effects of HNF4A on DIO1 activity and T3 responsive genes in a HepG2 cell line with an inducible overexpression of HNF4A or HNF4A knock down.
Method: For HNF4A overexpression, HepG2 cell lines were transfected with a doxycycline-inducible (DOX) myc-tagged HNF4A transgene. For HNF4A knockdown, HepG2 cells were transiently transfected with HNF4A siRNA to reduce HNF4A mRNA expression. DIO1 activity was measured using HPLC with a radioactive rT3 tracer, and *DIO1* and T3 responsive gene expression was quantified by RT-qPCR. Cell experiments were at least performed three times with each experiment having a technical triplicate.
Results: Overexpression of *HNF4A* resulted in a strong increase in *DIO1* mRNA expression and DIO1 activity compared to control cells. This was accompanied with increased expression of *KLF9*, *G6PC1*, *SPOT14*, *CPT1A* and *PCK1* mRNA. In contrast, knockdown of *HNF4A* mRNA in HepG2 cells led to a significant decrease in *DIO1* mRNA expression and DIO1 activity along with reduced expression of most T3 responsive genes, including *G6PC1*, *CPT1A*, and *PCK*1.
Conclusion: In conclusion, this study shows that HNF4A is a potent regulator of DIO1 in hepatocytes. The alterations in DIO1 are associated with contradictory changes in the expression of T3 responsive genes. Further analyses are needed to explain the HNF4A-DIO1 related changes in T3 responsive gene expression but it is clear that HNF4A plays a role in regulating thyroid hormone concentrations via DIO1 in the hepatocyte.

Immune-mediated and cholestatic disease: Experimental and pathophysiology

TOP-363
A novel orally bioavailable small-molecule inhibitor of the sodium taurocholate co-transporting polypeptide (NTCP) prevents HBV infection and ameliorates cholestasis in humanized mice models
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Background and aims: The sodium taurocholate co-transporting polypeptide (NTCP, *SLC10A1*) is the main transporter of conjugated bile acids at the basolateral membrane of hepatocytes and serves as the entry receptor for the hepatitis B virus (HBV) and hepatitis delta

virus (HDV). Daily injection with a synthetic peptide called bulevirtide (previously Myrcludex-B) is approved in the EU for treatment of patients co-infected with HBV and HDV. Pre-clinical studies suggest that pharmacological inhibition of hepatic bile salt uptake using bulevirtide ameliorates cholestatic liver injury. Both treatment of viral hepatitis and cholestatic liver diseases require chronic treatment, thus indicating the necessity of orally available small molecule inhibitors for this liver-specific transporter/receptor.

Method: A comprehensive drug discovery effort was conducted to identify and optimize potent and selective small-molecule inhibitors of NTCP-mediated bile acid uptake and HBV/HDV entry inhibitors with adequate *DMPK* characteristics, suitable for oral dosing. Urokinase-type plasminogen activator-severe combined immunodeficiency (uPA-SCID) mice engrafted with human hepatocytes were used to determine *in vivo* impact on bile acid kinetics and HBV infection. Finally, in vivo effects of the lead candidate were assessed in two distinct DDC-induced cholestasis mouse model transgenic for human NTCP.

Results: We identified a novel chemical series of NTCP inhibitors with multiple compounds with single-digit nM potency for NTCP and high selectivity (>100×) against ASBT and BSEP mediated bile salt transport. Consistently, these compounds dose-dependently reduced intracellular bile acid levels in sandwich-cultured human hepatocytes. *In vitro* infection studies demonstrated low nM HBV and HDV entry inhibition, similar to bulevirtide. We prioritized a lead molecule, CIM212930, with good oral bioavailability and excellent liver distribution. PK/PD experiments with CIM212930 in uPA/SCID mice with humanized livers illustrated dose-dependent and prolonged elevation of serum bile acid levels demonstrating both target engagement and indicative of a once-daily oral dosing regimen. Finally, CIM212930 completely blocked HBV infection in a humanized liver mouse model and largely reduced liver damage in DDC-induced cholestasis models.

Conclusion: We describe novel and specific small-molecule orally bioavailable NTCP inhibitors that have the potential to treat HBV/HDV and cholestatic liver disease.

TOP-364

Lack of CD1d on biliary epithelial cells protects from cholangitis

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Background and aims: Natural killer T (NKT) cell mediated inflammation has been shown to play a role in chronic inflammatory bile duct disorders such as primary sclerosing cholangitis (PSC). These cells are a subset of unconventional T-cells enriched in mouse liver that recognize lipid antigens presented by CD1d. We have previously demonstrated that oxazolone, a NKT cell activating agent, can induce cholangitis in mice. To determine whether biliary epithelial cells (BECs) participate as antigen presenting cells, we challenged mice with a conditional deletion of CD1d on biliary epithelial cells ($Cd1d^{\Delta BEC}$) and WT ($Cd1d^{fl/fl}$) mice with intrabiliary injection of the oxazolone.

Method: $Cd1d^{\Delta BEC}$ mice were generated by crossing *ASBT*cre$^{+/-}$ mice with $Cd1d^{fl/fl}$ mice. 1% oxazolone and 65% DMSO (vehicle) were injected into bile ducts of $Cd1d^{fl/fl}$ and $Cd1d^{\Delta BEC}$ mice. Weight and clinical symptoms were monitored daily. The mice were sacrificed 2 days or 7 days following surgery. Liver tissue was assessed for portal inflammation and inflammatory infiltrates characterized with immunohistochemistry. Serum was analysed for alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and bilirubin.

Results: Intrabiliary injection of oxazolone as compared to vehicle in WT ($Cd1d^{fl/fl}$) mice caused acute cholangitis with severe liver inflammation, significant weight loss (16% *vs.* 6%, * p = 0.03), increased amount of total pain score (1.5 *vs.* 6.5, * p = 0.02), elevated liver enzyme markers of ALT, AST, ALP and bilirubin, and increased histologic grade of cholangitis that peaked at day 2 following surgery. $Cd1d^{\Delta BEC}$ mice were protected against disease with significantly better survival (* p = 0.04), quicker recovery and improved disease parameters compared to WT ($Cd1d^{fl/fl}$) mice, *i.e.* less body weight loss (13.2% *vs.* 18.7%, * p = 0.02), less total pain (2.3 *vs.* 4.4, * p = 0.02) and lower bilirubin serum levels (145 µmol/L *vs.* 340 µmol/L, * p = 0.03). This was parallelled by a milder histopathological phenotype in the liver with decreased periportal infiltration, bile duct hyperplasia and necrosis (2.82 *vs.* 5.11, ** p = 0.007).

Conclusion: In this study we have demonstrated that NKT cells can drive inflammation that is dependent on CD1d on cholangiocytes in the bile ducts when directly exposed to intrabiliary oxazolone. These findings suggest that modulation of NKT driven immune pathways may represent a therapeutic approach in inflammatory cholangiopathies such as PSC.

FRIDAY 09 MAY

FRI-295-YI

Pharmacological modulation of hepatocyte glucocorticoid receptor alpha can toggle enclysis, the deletion of regulatory T cells by hepatocytes

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Background and aims: Glucocorticoids are anti-inflammatories that have been the standard of care for patients with autoimmune hepatitis (AIH) for decades. Most patients respond well; however, up to 20% may fail treatment and require a liver transplant. There are no prediction criteria for response to glucocorticoids; as a result, non-responders are at risk of infection without benefitting from a delay in liver damage. Hepatocytes comprise up to 80% of the liver mass, and we previously showed that they delete regulatory T cells (Treg) by enclysis. Given that Treg cell enclysis was increased in AIH patients who failed treatment compared to those with metabolic dysfunction-associated steatohepatitis (MASH), we were interested in establishing the effect of glucocorticoids on enclysis in human livers.

Method: We used high-content fluorescent imaging-based assays to treat hepatocytes and hepatoma cells with glucocorticoid receptor alpha (GR-α) agonists and antagonists, quantified enclysis by scoring cell-in-cell structures. GR-α expression and cellular localisation were measured by immunofluorescence. Hepatocyte GR-α expression, cellular and spatial localisation were evaluated by immunohistochemistry and digital pathology in formalin-fixed, paraffin-embedded liver sections from non-cirrhotic donors and cirrhotic patients with AIH or MASH (n = 10 each). QuPath software quantified hepatocyte nuclear GR-α in zones 1, 2 and 3. Fresh liver segments from the same conditions were treated with glucocorticoid agonists and antagonists, and the effects on hepatocyte GR-α expression were measured by protein expression and targeted tissue transcriptomic analyses (Nanostring nCounter).
Results: Dexamethasone, prednisolone and budesonide treatment reduced enclysis in vitro, and the GR-α antagonist mifepristone increased enclysis. One hour pre-treatment with glucocorticoids was sufficient to induce hepatocyte nuclear translocation of GR-α in vitro and ex vivo, which correlated with reduced enclysis. In non-cirrhotic livers and MASH, there was no regional difference in hepatocyte nuclear GR-α expression, but AIH livers that failed treatment had reduced nuclear GR-α in peri-fibrous hepatocytes compared to periportal. Glucocorticoid treatment of liver explants ex vivo caused nuclear translocation of hepatocyte GR-α in some patients but not others.
Conclusion: Hepatocyte nuclear GR-α expression correlated with enclysis inhibition, revealing differences in inflammation-proximal hepatocytes in AIH and MASH. Further research is needed to assess any predictive value of hepatocyte nuclear GR-α for response to glucocorticoids in AIH.

FRI-296-YI
Bile and plasma metabolome reveals association of TMA-TMAO pathway metabolites with gallstone disease progression
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Background and aims: India accounts for 10% of the global burden of gallstone disease (GSD) and gallbladder cancer (CaGB). Due to low diagnosis rates, gallbladder cancer has poor prognosis. This study aims to identify plasma and bile metabolites as potential biomarkers for GSD and CaGB and explore their role in gallstone disease progression using a diet-induced mouse model.
Method: Metabolomic profiling was done for plasma and bile samples in the discovery cohort of healthy control, HC (P = 14, B = 14), GSD (P = 30, B = 30), & CaGB (P = 56, B = 26) patients. For validation analysis, HC (P = 22, B = 3), GSD (P = 21, B = 10) & CaGB (P = 22, B = 18) samples were again subjected to untargeted metabolomics. The significantly altered metabolites identified via untargeted metabolomics were then evaluated in human plasma (n = 37) by targeted metabolomics. The key identified metabolite i.e. TMAO, was administered to C57BL/6 mice in supplementation with lithogenic diet to assess its impact on gallstone disease. qPCR was done in human (n = 40) and mice (n = 20) gallbladder tissue samples to study the expression of ATP-Binding Cassette (ABC) transporters involved in bile salts and cholesterol secretion.
Results: Bile & plasma metabolome analysis identified TMA and other metabolites associated with TMA pathway, including TMAO, carnitine, betaine & choline as significantly altered in GSD & CaGB patients. ROC analysis showed that combined TMAO & pipecolic acid yield AUC of 0.99 ($p > 0.05$), indicating strong predictive potential for GSD formation. While, TMAO along with N-acetyl neuraminic acid showed AUC of 0.91 ($p > 0.01$) in CaGB. Further, targeted metabolomics in plasma also showed increased TMAO levels in CaGB (620.82 ± 223.72 µg/ml) compared to GSD (449.12 ± 194.06 µg/ml) ($p = 0.30$) and HC (35.65 ± 19.39 µg/ml) ($p = 0.0001$). C57BL/6 mice fed with lithogenic diet+0.3% TMAO (Gr.1) exhibited an earlier onset and higher frequency of gallstones compared to mice on lithogenic diet alone (Gr.2). At 12 weeks, Gr.1 had 20% (2/10) gallstones formation, while only 10% (1/10) mice showed gallstones in Gr.2. By 20 weeks, 73.68% (14/19) of Gr.1 mice developed gallstones, compared to 62.5% (10/16) of Gr.2. Additionally, the TMAO-administered mice exhibited gallbladder metaplasia, indicating increased cellular proliferation. qPCR analysis of gallbladder tissue in mice showed significantly decreased expression of ABC transporters, ABCC3 and ABCB4 by more than 1.5-fold in Gr.1 compared to Gr.2.
Conclusion: Elevated TMAO levels may drive gallstone disease progression in humans and mice possibly by influencing ABC transporter expression in gallbladder epithelium. Combining TMAO with metabolites like pipecolic acid and N-acetylmuramic acid improves the sensitivity and specificity for predicting gallstones and cancer. The study also highlights the liver-gallbladder axis in gallstone-related diseases, as TMAO is produced in the liver.

FRI-300
Therapeutic application of circular RNA aptamers in a mouse model of primary biliary cholangitis
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Background and aims: Primary biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of intrahepatic bile ducts leading to cholestasis, cirrhosis, and liver failure. The incidence rate of PBC is increasing year by year, but the pathogenesis of PBC has not been clarified. We aimed to evaluate the effect and mechanisms of dsRNA on PBC severity, and explore the possible of therapeutic application of circular RNA aptamers in a mouse model of PBC.
Method: Female C57BL/6J (B6) 5–6-week-old mice (n = 12 per group) were used. Essentially, a 2OA-bovine serum albumin (BSA) conjugate was injected intraperitoneally with complete Freund's adjuvant and was boosted after 2 weeks with 2OA-BSA and incomplete Freund's adjuvant after the first immunization. Poly I:C was injected intraperitoneally at a dose of 5 mg/kg once every 3 days from three days after the initial immunization with 2OA-BSA in CFA (2OA+poly I:C-treated mice). PBC severity and metabolic alterations were evaluated by histology, serum markers and bulk liver RNA sequencing. We detected the expression levels of double stranded RNA in animal models and patient samples using immunofluorescence and dot blot method and explore the mechanism that dsRNA disturbance. Finally, we assessed the therapeutic efficacy of circular RNA aptamers from 8 to 16 weeks of age.
Results: 8-week-old PBC mouse model exhibited a significant increase in CD8 T lymphocytes and pro-inflammatory cytokines such as serum IL-6, IL-12, IFN-γ, TNF-α, leading to liver fibrosis. Liver histological examination shows eosinophil infiltration and bridging like fibrosis changes, which are very similar to the histological findings of human PBC. Furthermore, we found mitochondrial dsRNA into the cytosol in mononuclear phagocyte is a general feature of PBC. Inhibition of the mitochondrial RNA polymerase, the dsRNA sensors RIGI and PKR, or the master inflammatory signaling protein MAVS, all broadly preserving other hallmarks of PBC. Moreover, cells are hypersensitized to mt-dsRNA-driven inflammation due to their reduced levels of PNPT1 and ADAR1, two proteins critical for mitigating the accumulation of mt-dsRNA and the inflammatory potency of dsRNA, Finally we found in our PBC mouse model, treatment with circular RNA aptamers which has been reported to reduce immune overactivation caused by double stranded RNA by regulating PKR activity significantly improved steatohepatitis and ameliorating fibrosis as well.

Conclusion: The level of double stranded RNA is significantly elevated in both PBC patients and mouse models, causing severe immune responses. Blocking the immune pathways related to double stranded RNA can effectively alleviate the symptoms, circular RNA aptamers are effective treatments.

FRI-301

Reactive cholangiocyte-derived orosomucoid-2 (ORM2) drives a pathogenic modulation of the injured biliary niche through macrophage reprogramming

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Background and aims: Injured or reactive biliary epithelial cells participate in most chronic liver injuries in a process referred to as ductular reaction, which involves multicellular interactions with marked local infiltration of macrophages and fibrogenic cell activation. The direct roles of biliary epithelial cells in shaping their cellular niche remain unknown. We aimed at investigating the effects of biliary epithelial cell-derived acute phase response protein orosomucoid 2 (ORM2) in shaping monocyte/macrophage response to liver injury.
Method: Transcriptome datasets from human and mouse livers were used, results were confirmed with multiplex immunofluorescence. A multicellular biliary-niche-on-a-chip derived from primary liver and blood cells (wild-type, Mdr2-/- mice) was established to model ductular reaction. Human blood cells collected from healthy donors and intrahepatic cholangiocyte organoids derived from normal and cirrhotic liver patients were used.
Results: Our transcriptome dataset and multiplex immunofluorescence analyses indicated a previously unrecognized involvement of the acute phase response protein ORM2 in ductular reactions in both human and mouse livers. ORM2 gene expression was increased in biliatresone-, bile acid- and acetaminophen-challenged cholangiocytes. Cholangiocyte-derived ORM2 induced unique transcriptome changes and functional adaptation of liver macrophages. ORM2-activated macrophages exacerbated cholangiocyte cell stress and Orm2 expression, but also promoted fibrogenic hepatic stellate cell activation. Mechanistically, ORM2 effects were mediated by an inositol 1,4,5-trisphosphate receptor type 2 (ITPR2)-dependent calcium pathway.
Conclusion: This study reveals a paracrine communication circuit during ductular reaction, in which reactive cholangiocyte-derived ORM2 reprograms liver macrophages, participating in a pathogenic remodeling of the immune biliary niche.

FRI-302-YI

MUCIN1 positive biliary epithelial cell heterogeneity contributes to cholestatic liver injury and promotes early liver fibrosis

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Background and aims: Biliary epithelial cells (BECs), although quiescent under homeostatic conditions, exhibit significant proliferation and remodelling during injury, termed as the ductular reaction (DR). DR plays a dual role in liver regeneration and disease progression. Specifically, persistent DR is associated with severity of fibrosis. Heterogeneity of BECs and its contribution in disease progression is not known. we aim to investigate the contribution of BEC heterogeneity and its cellular crosstalk in progression of cholestatic liver injury.
Method: Cholestatic injury was induced in mice via bile duct ligation (mBDL) at day-2 (D2), day-4 (D4), and day-7 (D7) and DDC (mDDC) diet at week-2 (W2) and week-4 (W4). In liver tissue histological, immunostaining, and gene expression analysis was done. Sham was taken as control. Primary BECs and HSCs were sorted and acquired. 3D ductal organoids were developed and indirect co-culture with HSCs was performed at D0, D2 and D7 and secretome was analysed.
Results: DDC induced cholestatic model is showing significant increased DR (>3-fold), bile stasis in all newly formed ducts, concentric ductular fibrosis (>2-fold), and necrosis in some regions. Fibrosis was increased with persistent DR as confirmed by immunostaining showing CK19+ (>2-fold, W2), (>3-fold, W4) andαSMA+ (1.5-fold, W2; 2-fold, W4). Similar patterns was observed in the well-established cholestatic BDL-model. Frequency of CK19+ primary BECs was 26% (D2), 62% (D4) and 89.7% (D7) vs. 11% (sham) showing increased population along withα-SMA+ HSCs which also peaked with 13.3% (D2), 33.8% (D4) and 52.7% (D7) vs. 3.7% (sham). 3D-Ductal organoids of D2, D4 and D7 of mBDL were developed and its secretome analysis showed increased concentration of TGF-β1 35 pg/ml (D2) 178 pg/ml (D4) and 699 pg/ml (D7) and Endothelin levels 23 pg/ml (D2), 91 pg/ml (D4), 383 pg/ml (D7) showed strong cross-talk between BECs and HSCs. Gene expression analysis of HSCs showed increased fibrotic markers (α-SMA >2-fold and GFAP 1.5-fold). Next, we checked which BECs population (small or large BECs) was increased, we further acquired epCAM+ BECs with MUC1+(large BECs) and epCAM+ with MUC1- (small BECs). MUC1+ increased with 18% along with MUC1- 67% (D2), 39% MUC1+ and 51% MUC1-(D4) and 75% MUC1+ and 46% MUC1- (D7). Similar results were seen in the IHC of MUC1 and BCL2 (markers for small cholangiocytes) for mBDL timepoints and similar was also seen gene expression of BCL2 (5-fold) and MUC1 (15-fold) indicating increased large cholangiocytes population with increased cholestasis.
Conclusion: This study revealed BEC dynamicity governed by MUC1+ phenotype and is responsible for pathological changes.3D organoid observation MUC1+ BECs promotes HSCs activation in ET1 dependent paracrine manner in cholestatic liver disease. Study also suggest MUC1- phenotype of BEC is closely associated with biliary homeostasis.

FRI-303

Immune profiling in autoimmune hepatitis identifies distinct patterns autoreactivity

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Background and aims: Autoimmune hepatitis (AIH) is a severe disease characterized by elevated immunoglobulin levels. However, the role of autoantibodies in the pathophysiology of AIH remains uncertain.
Method: Phage Immunoprecipitation-Sequencing (PhIP-seq) was employed to identify autoantibodies in the serum of patients with AIH ($n = 115$), compared to patients with other liver diseases

(metabolic associated steatotic liver disease (MASH) *n* = 178, primary biliary cholangitis (PBC), *n* = 26, or healthy controls, *n* = 94).
Results: Logistic regression using PhIP-seq enriched peptides as inputs yielded a classification AUC of 0.81, indicating the presence of a predictive humoral immune signature for AIH. Embedded within this signature were disease relevant targets, including SLA/LP, the target of a well-recognized autoantibody in AIH, disco interacting protein 2 homolog A (DIP2A), and the relaxin family peptide receptor 1 (RXFP1). The autoreactive fragment of DIP2A was a 9-amino acid stretch nearly identical to the U27 protein of human herpes virus 6 (HHV-6). Fine mapping of this epitope suggests the HHV-6 U27 sequence is preferentially enriched relative to the corresponding DIP2A sequence. Antibodies against RXFP1, a receptor involved in anti-fibrotic signaling, were also highly specific to AIH. The enriched peptides are within a motif adjacent to the receptor binding domain, required for signaling and serum from AIH patients positive for anti-RFXP1 antibody was able to significantly inhibit relaxin-2 singling. Depletion of IgG from anti-RXFP1 positive serum abrogated this effect.
Conclusion: These data provide evidence for a novel serological profile in AIH, including a possible functional role for anti-RXFP1, and antibodies that cross react with HHV6 U27 protein.

FRI-304
Bioinformatic analysis of the spatial transcriptomes of inflamed portal tracts in human primary biliary cholangitis
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Background and aims: Though the pathognomonic hallmark of primary biliary cholangitis (PBC) is autoreactive T cell-mediated cell injury against biliary epithelial cells, involvement of B cell and innate immune cells in inflamed portal tracts is also apparent, likely sustaining, modulating, or even establishing the microinflammatory milieu of human PBC. The aim of this study is to analyze the transcriptomes of inflamed portal tracts in PBC, using spatial transcriptome analysis in conjunction with bioinformatics tools.
Method: The liver tissue samples were obtained from four PBC patients (Case 1-3 before UDCA treatment and Case 4 with an insufficient biochemical response after 20 years of UDCA treatment) by USG-guided needle biopsy. Five-micrometer thick sections were cut from formalin-fixed paraffin-embedded (FFPE) block of biopsies and mounted on microscopy slides, followed by spatial transcriptomic analysis using Visium CytAssist Spatial Gene Expression for FFPE Human Transcriptome (10× Genomics, U.S.A.), according to manufacturer instructions (TakaraBio, Japan). Spatial transcriptomic (ST) data in each sample were analyzed by Space Ranger 2.0.0 (10× Genomics) to obtain unbiased clustering of spots. With the aid of paired HE-staining and the relative enrichment of zone 3 genes (i.e., CYP2E1) compared to entire dataset, distinct ST clusters were aligned to the inflamed portal tracts (PT) and the putative zone 3 in each sample. Firstly, in order to perform bioinformatic pathway analysis, differentially expressed genes (DEGs) in PT in comparison to that in zone 3 were uploaded into IPA software (version 12.2, Qiagen Bioinformatics, USA). Secondary, to evaluate significant similarities, PT-DEGs were compared among samples and to those in public domain dataset ($n > 215000$) by IPA Analysis Match. An absolute value Z-scores greater than 2 was considered as significant threshold for either activation/inhibition of pathway or similarities of transcriptomes.
Results: ST spots in each PBC liver sample segregated into 4 to 5 distinct clusters. While canonical pathways of PT-DEGs with the highest Z score were neutrophil degranulation (Case 1, 2, 3; 14.765, 4.583, and 6.481, respectively) and RHO GTPase cycle (Case 4; 13.304), those with the lowest were RHO GTI signaling (Case 1, 3; −6.155 and −2.673, respectively), mitochondrial dysfunction (Case 2; −3.051), and PTEN Signaling (Case 4; −5.217). Even after long-term UDCA treatment, PT-DEGs in Case 4 with insufficient biochemical response revealed the significantly most similar biological signature with that in untreated Case 1 (Z score = 89.38).
Conclusion: Transcriptomes of PT in human PBC are enriched in the activities of genes for innate immune cells, cell migration and cell adhesion, highlighting potential therapeutic targets; UDCA treatment without sufficient biochemical response might not alter transcriptomes of PT.

FRI-305
Protectin DX as a novel anti-inflammatory and anti-fibrotic therapeutic candidate for the treatment of autoimmune cholangitis
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Background and aims: Primary biliary and sclerosing cholangitis (PBC; PSC) are rare liver diseases causing an accumulation of toxic bile acids (BAs) in hepatocytes. Such event promotes the development of inflammation, fibrosis, cirrhosis, and ultimately liver failure. *Reducing hepatic BA levels is an important pharmacological target for PBC and PSC treatments.* Currently, Ursodiol® (UDCA) and Ocaliva® (OCA), two BA lowering drugs, are approved for the treatment of PBC, while no drugs are available for PSC. However, since a significant proportion of PBC patients either do not respond to or are intolerant to UDCA and/or OCA, *there is an urgent need for new therapeutic options*. Our lab has shown that adding the omega-3 DHA to OCA and UDCA reduce the required doses to achieve optimal BA reduction. However, most of the effects of DHA are known to be mediated by its specialized pro-resolving mediators' derivatives, notably protectin DX (PDX), a derivative with strong anti-inflammatory properties. Thus, this study will test the hypothesis that PDX can protect liver cells against BA accumulation, BA-induced inflammation, ER stress and fibrosis.
Method: HepG2 cells and murine hepatocytes were treated with vehicle, 5 μM PDX or 50 μM DHA (positive control) for 24H. To induce ER stress and fibrosis, HepG2 cells received the same treatments, with an additional 400 μM BA mixture for 24H and 2 ng/mLTGF-β for 72H, respectively. For inflammation, THP-1 cells were treated with 100 ng/mL LPS, in addition to the previous treatments for 24H. Transcriptomic (qRT-PCR), proteomic (Western blot, ELISA), or metabolomic targeted (LC-MS/MS) approaches were then employed to assess the effects of PDX.
Results: Similarly to DHA, PDX exposure significantly reduced BA synthesis in liver cells by inhibiting *CYP27A1* gene expression ($p < 0.05$) and lowering CDCA secretion ($p < 0.05$) in HepG2 cells as well as total, primary and (un)conjugated BA ($p < 0.01$) in murine hepatocytes. PDX also promoted BA detoxification through increased mRNA expression of the transporters OSTα/β and the conjugating enzyme SULT2A1 ($p < 0.001$). Moreover, PDX displayed notable anti-inflammatory effects by significantly inhibiting the expression of the pro-inflammatory cytokines TNFα ($p < 0.001$), MCP-1 ($p < 0.001$), IL-6 ($p < 0.001$), and IL-1β ($p < 0.01$) in THP-1 macrophages, both at the transcriptomic and proteomic levels. Additionally, PDX reduced the expression of the BA-induced ER stress markers BIP ($p < 0.01$) and CHOP ($p = 0.101$), as well as of the TGF-β-induced fibrosis gene COL1A1 ($p < 0.001$) in HepG2 cells.
Conclusion: These findings suggest that PDX reduces BA hepatic levels while also mitigating inflammation, ER stress, and fibrosis in liver cells and macrophages. Given the role of BAs in the development of PBC and PSC, PDX may provide a pharmacological option for these

diseases. Further *in vivo* analyses are, however, required to validate this hypothesis.

FRI-306

Protectin DX improves the efficiency of low dose obeticholic acid to reduce hepatic bile acids and mitigate inflammation, ER stress and fibrosis in liver cells

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Background and aims: Primary biliary and sclerosing cholangitis (PBC; PSC) are rare and progressive autoimmune liver diseases, characterized by an accumulation of toxic bile acids (BA) in liver cells. *The reduction of these toxins is an important pharmacological target for the treatment of these pathologies.* Currently, obeticholic acid (OCA), an inhibitor of BA synthesis, is one of the few drugs approved for the treatment of these diseases. Despite being efficient in normalizing liver enzymes, OCA is associated with dose-related side effects that led the EMA to publish novel contraindications for the treatment of decompensated PBC patients. Hence, a potential strategy involves reducing the optimal required dose of OCA to enhance its safety profile, while mitigating development-associated burdens. Thus, this study investigates whether protectin DX (PDX), an omega-3 derivative with hepatic anti-inflammatory properties, can improve the response to low OCA dose in terms of BA reduction, BA-induced inflammation, ER stress and fibrosis.
Method: HepG2 cells and murine hepatocytes were treated with vehicle and low dose OCA (0.5–1 μM), in the presence or absence of 5 μM PDX or 50 μM DHA (positive control) for 24H. To induce ER stress and fibrosis, HepG2 cells received the same treatments, with an additional 400 μM BA mixture for 24H and 2 ng/mL TGF-β for 72H, respectively. For inflammation, THP-1 cells were treated with 100 ng/mL LPS, in addition to the previous treatments for 24H. Transcriptomic (qRT-PCR), proteomic (Western blot, ELISA), or metabolomic targeted (LC-MS/MS) approaches were employed to assess the effects of PDX on low dose OCA.
Results: In the presence of PDX, liver cells exhibited a stronger response to 1 μM OCA when compared to the drug alone. Indeed, OCA 1 μM caused a 54.3% reduction of CYP7A1 levels, while in the presence of PDX, the same amount led to a stronger ($p < 0.05$) reduction of this transcript to 64.7%. The combination of OCA and PDX also led to a stronger reduction of CDCA ($p < 0.05$) secretion in human liver cells medias as well as a significant decrease in total, primary conjugated ($p < 0.001$) and unconjugated ($p < 0.01$) BA in murine cells. Moreover, the addition of PDX significantly increased the mRNA expression of essential BA export transporters such as OSTα-β and MRP2 ($p < 0.001$). Additionally, PDX improved the response of OCA on inflammation by reducing the expression of the pro-inflammatory cytokines, TNFα, MCP-1, IL-6 ($p < 0.001$), and IL-1β ($p < 0.01$) in THP-1 macrophage. The PDX + OCA combination was also found to decrease the expression of ER stress marker BIP ($p < 0.01$) as well as the fibrosis gene COL1A1 ($p < 0.001$).
Conclusion: These experiments demonstrate that PDX improves the ability of a low OCA dose to inhibit BA synthesis and export as well as to mitigate inflammation, ER stress and fibrosis development in liver cells. Further analyses are, however, required to validate this hypothesis.

FRI-307-YI

IL-27 drives activation of tissue-destructive CD8+ T cells and is functionally indispensable in immune checkpoint inhibitor-induced hepatitis

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Background and aims: Checkpoint inhibitor-induced hepatitis (CPI-hepatitis) is a key immune-related adverse event of cancer immunotherapy, likely mediated by monocyte-mediated $CD8^+$ T cell recruitment and activation. Here, we assess the role of IL-27 in mediating this pathogenic immune crosstalk.
Method: Serum levels of IL-27 in healthy controls (HC, n = 35) and patients with CPI-hepatitis (n = 22) were measured using U-PLEX assays. $CD8^+$ T cell activation was assessed in HC peripheral blood mononuclear cells (PBMCs) conditioned in HC (n = 3), CPI-hepatitis (n = 6) or IL-27-neutralised CPI-hepatitis (n = 6) serum for 48 hours. Experimental CPI-hepatitis was established in wild-type (C57BL/6J) 8–12 weeks old male mice through dosing with toll-like receptor 9 agonist (TLR9-L) for priming of hepatic inflammation, in combination with anti-CTLA-4/PD-1 (200 ug each; CPI) or PBS (vehicle) for up to 7 days (n = 4–8/group). To assess the role of IL-27, mice were treated with neutralizing anti-IL-27 on day 5, two days before peak liver injury. Multi-colour flow cytometry, histology/immunofluorescence and mRNA sequencing were used to characterise liver myeloid/lymphoid subsets and inflammation. Hepatocyte damage was assessed by plasma cytokeratin 18 measurement.
Results: Patients with CPI-hepatitis showed increased IL-27 serum levels, compared to HC (median concentration: CPI-hepatitis = 288.4 pg/ml, HC = 123.3 pg/ml; $p = 0.0003$). Serum IL-27 concentrations correlated positively with CD8 cytotoxicity (granzyme B: $r = 0.493$, $p = 0.03$) and activation (ICOS: $r = 0.539$, $p = 0.02$). The frequency of activated $ICOS^+CD8^+$ T cells, induced by CPI-hepatitis serum conditioned medium, was significantly reduced by antibody-mediated IL-27 neutralization ($p = 0.03$). In mice, the frequency of IL-27 producing cells was increased within the $CD11b^+$ myeloid cell compartment of CPI-treated animals, specifically liver infiltrating monocytes, compared to vehicle group ($p = 0.02$). In vivo neutralisation of IL-27 using anti-IL-27 mAb, significantly reduced $CD8^+$ T cell liver infiltration, clustering, and activation (granzyme B, perforin, IFNg), and prevented disease (normalisation of liver histology and plasma cytokeratin 18 levels).
Conclusion: Our data indicate that IL-27 is important for the recruitment and activation of tissue damaging $CD8^+$ T cells, and is functionally indispensable for liver injury in CPI-hepatitis, identifying IL-27 as a key therapeutic target in CPI-hepatitis. Future work will further characterise the mechanisms of IL-27-mediated immune regulation in tissue, including in cancer settings, to fully assess the applicability of IL-27 blockade as a viable therapeutic strategy in CPI-hepatitis.

FRI-308

Active transport via bile salt export pump (Bsep/Abcb11) is not required for cholehepatic shunting and choleretic actions of Norucholic acid (NCA/norUDCA) in mice

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Background and aims: Choleretic properties of conjugation-resistant Norucholic acid (NCA, previously known as norUDCA) are associated with it's capability to undergo cholehepatic shunting inducing a bicarbonate (HCO_3^-)-rich choleresis. Previously it has been demonstrated that the apical sodium-dependent bile acid (BA) transporter (Asbt), organic solute transporter-α (Ostα), and organic anion transporting polypeptide 1a/1b (OATP1a/1b) transporters are not required for NCA-induced bile flow and biliary HCO_3^- secretion. However, the role of the canalicular bile salt export pump (Bsep) as key and rate-limiting step in biliary BA excretion was not investigated. Therefore, the goal of this study was to identify the role of Bsep for the choleretic actions of NCA.
Method: Eight weeks old male FVB/N wild type (*wt*) and *Bsep*$^{-/-}$ mice were fed with a 0,5%NCA containing diet over 4 weeks. Bile flow, BA profiling from bile, liver biochemistry and (immuno)histology, as well as RNA sequencing from bulk liver tissue and mRNA profiling by RT-PCR were performed.
Results: NCA feeding in *wt* mice increased bile flow from 1 µL/min/gLiver to 3 µL/min/gLiver. Accordingly, HCO_3^- ouput was increased 3-fold (45 nmol/min/gL in *wt* mice vs 150 nmol/min/gL in NCA-fed *wt* mice). While *Bsep*$^{-/-}$ mice had no measureable bile flow at baseline, in NCA-fed *Bsep*$^{-/-}$ mice bile flow reached 0.5 µL/min/gLiver with a HCO_3^- ouput of 14 nmol/min/gL. After NCA feeding biliary concentrations of unconjugated NCA were10-fold higher in *wt* compared to *Bsep*$^{-/-}$ mice (760 µM in *wt* versus 70 µM in *Bsep*$^{-/-}$), while the amount of taurine-conjugated NCA was100-fold higher in *wt* compared to *Bsep*$^{-/-}$ mice (5220 µM in *wt* versus 50 µM in *Bsep*$^{-/-}$). RNAseq revealed *Sult2a1, Sult2a2, Sult2a4, Sult2a5* as well as *Abcc3* and *Abcc4* among the most up-regulated genes in *Bsep*$^{-/-}$ mice fed with NCA, indicating increased BA sulfation/hydroxylation and alternative BA efflux into the blood. Of note, although serum ALT and AST levels were increased in *Bsep*$^{-/-}$ mice after NCA feeding, (immuno)histological stainings and genexpression profiling did not reveal any signs of liver inflammation and/or fibrosis.
Conclusion: Our data indicate that transport via Bsep/Abcb11 is not essential for choleretic effects of unconjugated NCA. In contrast, transport of taurine-conjugated NCA into bile requires Bsep/Abcb11.

FRI-309

Single-cell profiles of intrahepatic and peripheral immune cells reveal AIH-specific CD8+ T cells promote disease progression through cytotoxicity and macrophage interactions

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Background and aims: The pathogenesis of autoimmune hepatitis (AIH) remains poorly understood, hindering accurate diagnosis and novel therapeutic target identification. In this study, we used single-cell RNA sequencing (scRNA-seq) and immune repertoire analysis to explore the immune characteristics and mechanisms in both blood and liver tissues of AIH patients.
Method: Single cells were isolated from liver biopsy and paired peripheral blood samples of 9 AIH and 3 primary biliary cholangitis (PBC) patients for 10× Genomics scRNA-seq and immune repertoire profiling. Public data from healthy individuals served as controls. Clinical analyses, scRNA-seq data from external animal models, and multiplex immunohistochemistry (mIHC) of liver biopsy sections were used for validation. Serum cytokines and chemokines were measured using liquid phase chip technology.
Results: A total of 159,411 high-quality cells were identified, categorized into CD8+ T, CD4+ T, γδT, NK/NKT-like, myeloid, B, plasma B, parenchymal, and proliferating cells. Cell distribution analysis revealed significant changes in the proportion and transcriptomic profiles of CD8+ T cells within the liver microenvironment of AIH patients. Further subcluster analysis identified a CD8+ T cell cluster in AIH patients that was positive for GZMB and VCAM1, showing high expression of TNFRSF9 and IFNG, indicating cytotoxic activity. Single-cell immune repertoire analysis confirmed active proliferation and transcriptional transition of these cells. Similar findings were validated in liver tissue from dnTgfbr2 Aire -/- mice. Co-occurrence analysis revealed six multi-cellular modules (CMs), with CM3 containing CD8+ T cells, TREM2+ macrophages (Mph), and CD5L+ Mph. The proportion of these macrophage populations was significantly elevated in AIH livers. CellphoneDB analysis showed significant interactions between CD8+ T cells and macrophages in CM3, leading to CD8+ T cell recruitment and sustained liver injury in AIH patients, compared to HC and PBC groups. Cytokine-chemokine analysis confirmed elevated serum chemokine levels in the AIH group. Preliminary validation via mIHC confirmed these findings.
Conclusion: In conclusion, we present a comprehensive single-cell immune atlas of AIH, identifying an AIH-specific cytotoxic CD8+ T cell cluster. Our findings suggest that macrophage-derived chemokines drive liver damage through interactions with CD8+ T cells, offering new insights into AIH pathogenesis and potential therapeutic targets.

FRI-310

Quantitative MRI metrics in the liver and pancreas for disease assessment in IgG4-related sclerosing cholangitis with autoimmune pancreatitis

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Background and aims: This study used standardised parenchymal and ductal MRI metrics in the liver and pancreas to develop a novel quantitative description of IgG4-related sclerosing cholangitis and autoimmune pancreatitis (IgG4-SC and IgG4-AIP). The metrics were evaluated for their potential to monitor disease activity and distinguish between IgG4-SC and primary sclerosing cholangitis (PSC).
Method: Ten participants with IgG4-SC/AIP underwent multiparametric MRI including iron-corrected T1 (cT1) and scanner-referenced T1 mapping (srT1) to measure inflammation in liver and pancreas parenchyma respectively. Quantitative MRCP analysis of the biliary tree, common bile duct (CBD) and pancreatic duct (PD) was performed using MRCP+.
Results: cT1 and srT1 values were compared with age, sex, and BMI-matched healthy controls (n = 100) and controls with type 2 diabetes (n = 100) from UK Biobank. Metrics of the biliary tree (tree volume, number of ducts, number of strictures), PD (duct diameter, visible duct length) and CBD (duct diameter) were compared with age-matched healthy volunteers (n = 10) and participants with PSC (n = 10). Of the ten IgG4-SC/AIP participants, 7 had active pancreatic involvement ('active IgG4-SC/AIP') determined by PET-CT imaging. In the liver parenchyma, cT1 was elevated in IgG4-SC/AIP compared to matched controls (median 747 ms vs 696 ms healthy, 718 ms with type 2 diabetes; $p = 0.001$). In the pancreas, srT1 was significantly elevated in active IgG4-SC/AIP compared to matched controls (1371 ms in active disease, 744 ms healthy, 757 ms with type 2 diabetes; $p < 0.001$) but was not elevated compared to controls in

inactive disease (795 ms inactive, n.s.).Whole biliary tree volume, number of ducts and number of ducts with strictures were all significantly elevated in IgG4-SC/AIP compared to healthy controls but not PSC. Median CBD diameter was elevated in IgG4-SC/AIP compared to healthy controls and PSC (6.1 mm, vs 5.0 mm healthy 4.7 mm PSC; $p < 0.05$), regardless of IgG4 disease activity. Alongside elevated srT1, active IgG4-SC/PSC showed characteristic PD changes with either compression (reduced diameter and visible length) or focal dilation, but PD diameter did not distinguish between healthy control or PSC groups.

Conclusion: Standardised T1 mapping of increased inflammation in pancreas parenchyma distinguishes active IgG4-SC/AIP from healthy controls and should be investigated for its potential to distinguish IgG4-SC/AIP from PSC. Quantitative MRI metrics of the whole biliary tree distinguish IgG4-SC/AIP from healthy controls, while extrahepatic metrics such as CBD diameter may aid differentiation between IgG4-SC/AIP and PSC.

FRI-311

Restoring gene function in cholangiocyte organoids through lentiviral transduction

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Background and aims: Cholangiocyte organoids derived from primary tissue are useful tools for studying biliary diseases and could potentially be used for cell-based therapy in bile duct disorders. Such approaches would also allow correction of genetic mutations affecting the bile ducts for instance as seen in cystic fibrosis. This study aimed to establish a system for functional gene restoration in cholangiocyte organoids using lentiviral transduction. We sought to demonstrate that this approach could restore function of a knocked-out gene, validate the recovery through GFP tagging and utilize co-culture experiments to demonstrate a functional effect. We used a mouse model lacking an antigen-presenting molecule (CD1d) that is functional on cholangiocytes, allowing functionally relevant co-culture assay to be used.

Method: Cholangiocyte organoids were derived from *Cd1d*$^{-/-}$ knock-out mice. Organoids were transduced with a lentiviral vector (VB220423-1199tqn) encoding the knocked-out *Cd1d* gene and a GFP reporter tag. Transduction efficiency was visualized via fluorescence microscopy and confirmed by flow cytometry with a anti-CD1d antibody. Functional restoration was evaluated using a co-culture system with natural killer T (NKT) cells and the glycolipid antigen alpha-galactosylceramide (alpha-GalCer). Cytokine production of interleukin-2 (IL-2) by alpha-GalCer activated NKT cells was measured using ELISA.

Results: Cholangiocyte organoids (n = 3 lines) were successfully transduced as evidenced by fluorescence microscopy showing clear GFP expression. The transduction efficacy was evaluated by flow-cytometry demonstrating that the transduced organoids were positive with CD1d expression. In co-culture experiments, *Cd1d* transduced organoids bound and presented alpha-GalCer to NKT cells, eliciting IL-2 release as an indication of activation. These responses were comparable to those observed with wild-type organoids and absent in KO organoids, confirming successful restoration of gene functionality after lentiviral transduction.

Conclusion: This study demonstrates that it is feasible to restore gene function in cholangiocyte organoids using lentiviral transduction. The ability to achieve both efficient transduction and functional restoration enables studies using this as a platform for studying gene-specific roles, their impact on immune interactions as shown herein, and ultimately translation into clinical medicine. These findings also lay the groundwork for refining and extending the approach to more complex systems, such as organ-on-a-chip platforms or *in vivo* studies.

FRI-312

A cfChIP-seq liquid biopsy for the diagnosis of autoimmune hepatitis

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Background and aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease associated with morbidity and mortality. Diagnosis often requires a liver biopsy to confirm the condition and affirm subsequent remission. While advances in liquid biopsy techniques have shown promise in cancer diagnosis, their application in liver diseases has yet to be extensively investigated. Cell-free DNA (cfDNA) in human plasma, a noninvasive liquid biopsy, offers molecular insights into the pathological processes of the organs of origin. These fragments reflect transcriptional activity within the dying cells. This study aims to evaluate the ability of chromatin immunoprecipitation and sequencing (cfChIP-seq), which informs on gene transcription in dying cells, to differentiate AIH from other chronic liver diseases.

Method: We applied cfChIP-seq to analyze plasma samples from 95 patients with AIH, either at diagnosis or during biochemical remission, and a control group comprising 18 healthy individuals and 79 patients with various liver diseases including fatty liver, primary sclerosing cholangitis, viral hepatitis and metabolic disease.

Results: Comparative analysis of plasma samples identified immune-related transcriptional processes uniquely active in the hepatocytes of AIH patients. Several significantly elevated genes were identified, including those linked to hepatic inflammation (CXCL9/10/11, GBP1, GBP5, UBD, TRIM31, HLA-DOB, and HULC) and immune mediated liver pathology (FOXP3, IL32). These genes constituted an 'AIH score' that achieved an area under the curve (AUC) of 0.9 in a validation set,

effectively distinguishing AIH from all other chronic liver diseases. RNA-seq analysis of liver biopsies from the same patient cohort further confirmed, the AIH cfChip-seq signature, of the differential expression of these genes.
Conclusion: Plasma cfChIP-seq demonstrates potential as a non-invasive diagnostic tool for AIH, offering an alternative to liver biopsy. This approach not only enhances diagnostic accuracy but also provides deeper insights into AIH pathogenesis, potentially transforming clinical management of the disease.

FRI-313

Epstein-Barr virus is targeted by converging T and B cell responses in primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is an autoimmune liver disease characterized by progressive inflammation and fibrosis of the bile ducts. The cause of PSC is unknown, yet multiple studies have implicated different human leukocyte antigen (HLA) genetic variants in disease development, e.g. HLA-B*08:01 and HLA-DRB1*13:01. Other studies have shown alterations in T cell responses of people with PSC. Nonetheless, the antigens driving these adaptive immune responses have not yet been identified.
Method: We aimed for an integrated analyses of adaptive immune responses in PSC; by the comprehensive profiling of the blood T cell repertoire of 504 individuals with PSC and 904 healthy controls using T cell repertoire sequencing, along with profiling of the functional antibody repertoire of 120 individuals with PSC and 202 matching healthy controls using phage-immunoprecipitation sequencing (PhIP-Seq). In follow up to the molecular data, we queried the health care records of 116 individuals in the TriNetX database for relevant disease associations.
Results: Using a hypothesis-free statistical analysis framework, we identified 1,008 T cell clonotypes that were associated with PSC. These clonotypes were mostly restricted to PSC-risk HLA variants such as the HLA-B*08:01-HLA-DRB1*03:01 haplotype as well as HLA-DRB1*13:01 and were shown to target different Epstein-Barr virus (EBV) epitopes, particularly, lytic-phase antigens such as BZLF1. Furthermore, for the PhIP-Seq data we detected elevated antibody responses toward different EBV lytic-phase antigens, predominantly the BMRF1 protein. In the TriNetX database, we detected a robust association between infectious mononucleosis, which is mainly caused by EBV, and PSC (odds ratio [OR] = 8.46; 95% CI: 4.53–15.80).
Conclusion: We report for the first time that in PSC there are expanded T and B cell responses against EBV. Furthermore, these responses were predominantly detected for lytic-phase antigens which may indicate that EBV-reactivation is a central theme in the pathogenesis of PSC. Whilst similar findings have been reported for multiple sclerosis, the OR for the association between PSC and infectious mononucleosis was more than 4-fold higher than that found for multiple sclerosis in the TriNetX database.

FRI-314-YI

Mitochondrial dynamics and auto(mito)phagy are altered in experimental models of primary biliary cholangitis, contributing to disease pathogenesis

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Background and aims: Primary biliary cholangitis (PBC) is a chronic immune-mediated cholestatic liver disease of unknown origin. We have previously reported that the expression of microRNA-506 (miR-506) is increased in PBC cholangiocytes, targeting the $Cl^-/HCO3^-$ exchanger AE2 and leading to intracellular pH (pHi) disturbances and PBC-like features, such as PDC-E2 overexpression and immune activation. Mitophagy, an essential anti-inflammatory and quality-control mechanism that eliminates dysfunctional mitochondria, is highly dependent on pHi for its activation, though its role in PBC has not been explored. Our aim was to characterize the mitochondrial dynamics and auto(mito)phagy processes in PBC and evaluate their contribution to disease pathogenesis.
Method: miR-506-overexpressing cholangiocytes (H69 miR-506), an experimental in vitro PBC model [Banales JM, et al. Hepatology 2012; Erice O, et al. Hepatology 2018], and control cells (H69 miR- and H69)], were characterized by mass spectrometry proteomics. Mitochondrial dynamics, integrity and activity, autophagy/mitophagy, and cell viability were assessed in baseline conditions and in

the presence of different anti-cholestatic drugs or autophagy activators.
Results: High-throughput proteomics revealed that several proteins involved in mitochondrial dynamics and auto(mito)phagy are altered in H69 miR-506 cholangiocytes, compared to controls. Importantly, gene-set enrichment analysis (GSEA) revealed that processes related to antigen presentation, inflammation and mitochondrial organization/translation are increased in H69 miR-506 cells. Flow cytometry indicated a decrease in mitochondrial functionality (Mitotracker Red) in H69 miR-506 cholangiocytes compared to controls, suggesting the accumulation of dysfunctional mitochondria and impaired mitophagy. In line, the exposure of cholangiocytes to auto(mito)phagy inhibitors (3-MA and bafilomycin) induced cell death, particularly in miR-506 cells, while the activation of autophagy with Dactolisib (BEZ235) significantly reduced the toxic bile acid-induced apoptosis. Importantly, the treatment of H69 miR-506 cholangiocytes with the anti-cholestatic drugs ursodeoxycholic acid (UDCA), bezafibrate (BZF) or obeticholic acid (OCA), improved mitochondrial functionality and energy metabolism, reducing PDC-E2 overexpression.
Conclusion: Our data suggest that PBC cholangiocytes are characterized by disturbances in mitochondrial integrity and auto(mito)phagy, leading to the accumulation of dysfunctional mitochondria and aberrant presentation of mitochondrial antigens. Of note, different anti-cholestatic drugs modulate these mitochondrial disturbances, providing insights into their mechanism of therapeutic action. Besides, targeting mitochondrial dynamics and mitophagy presents a promising novel approach for PBC treatment.

FRI-315
ATP8B1 deficiency causes steatosis and PDE4-mediated glucagon resistance in liver
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Background and aims: Deficiency of the phospholipid flippase ATP8B1 causes infantile-onset progressive familial intrahepatic cholestasis type I (PFIC1). The *Atp8b1*$^{G308V/G308V}$ mouse, an established model for human PFIC1, carries the orthologous mutation of the Amish index kindred. Upon cholate challenge, the *Atp8b1*$^{G308V/G308V}$ mice develop cholestatic liver injury. Unexpectedly, *Atp8b1*$^{G308V/G308V}$ mice developed hepatic steatosis on normal chow, which was not present when challenged with cholate to model cholestatic injury. In the present study, we investigate how ATP8B1 deficiency affects lipid and glucose metabolism in the liver.
Method: Age-matched male *Atp8b1*$^{G308V/G308V}$ and wild-type C57BL6/J littermates on normal chow were examined. Hepatic lipid and glycogen was evaluated by histology and enzymatic quantification. Metabolic syndrome was evaluated by body weight (BW), oral glucose tolerance test (OGTT), fasting plasma glucose and lipid levels. Expression of glucagon target genes and cAMP-degrading phosphodiesterases (PDEs) were measured by real-time quantitative PCR (RT-qPCR) in primary mouse hepatocytes (PMH), human hepatoma cells HepG2 overexpressing glucagon receptor (HepG2-GCCR), and liver biopsies from control and PFIC1 patients. cAMP levels were measured by ELISA. Lentivirus-mediated shRNA expression was used to knockdown ATP8B1 in HepG2-GCCR cells.
Results: Compared to wild-type mice, *Atp8b1*$^{G308V/G308V}$ mice had increased liver/BW ratio and liver triglyceride content. Liver histology showed microvesicular steatosis; OGTT showed no evidence of insulin resistance. Remarkably, fasting levels of plasma glucose, triglyceride, and cholesterol were significantly reduced in *Atp8b1*$^{G308V/G308V}$ mice, indicating reduced hepatic glucose production and lipid secretion. Consistently, *Atp8b1*$^{G308V/G308V}$ PMH had dramatically reduced glucagon-dependent *G6pc1* expression. The cAMP levels both at the basal state and after glucagon stimulation were significantly lower in *Atp8b1*$^{G308V/G308V}$ PMH, indicating increased cAMP degradation by PDEs. RT-qPCR confirmed increased *Pde4b* and *Pde4d* expression in *Atp8b1*$^{G308V/G308V}$ PMH. Treating *Atp8b1*$^{G308V/G308V}$ PMH with glucagon and the PDE4-selective inhibitor rolipram rescued *G6pc1* expression. Similarly, ATP8B1 knockdown in HepG2-GCGR cells resulted in increased *PDE4D* expression and impaired *G6PC1* induction by glucagon. Native livers of PFIC1 patients also have increased PDE4D at mRNA and protein levels and showed extremely low glycogen content.
Conclusion: ATP8B1 deficiency leads to upregulation of cAMP-degrading PDE4D, which causes glucagon resistance, impaired gluconeogenesis, and compensatory glycogenolysis. As glucagon signaling promotes lipolysis and fatty acid oxidation, PDE4-mediated glucagon resistance likely also contributes to hepatic steatosis in *Atp8b1*$^{G308V/G308V}$ mice.

FRI-316
Urinary proteomics: a new diagnostic approach for primary biliary cholangitis
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Background and aims: Early manifestations of primary biliary cholangitis (PBC) are often atypical. Urinary proteomics offers a non-invasive, accessible approach to identify potential biomarkers. This study aimed to use urinary proteomics to identify non-invasive biomarkers for PBC diagnosis.
Method: Clinical data and urine samples from 30 PBC patients and 20 healthy controls were collected. High-performance liquid chromatography (HPLC) was used to separate the peptide segments, which were then analyzed by Electrospray Ionization Ion Trap Mass Spectrometry (ESI-IT/MS) for peptide identification. Protein identification and quantification were performed using the Spectronaut 14.8 database. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were conducted to identify immune-related differential proteins. The correlation between differential proteins and clinical indicators was assessed using Pearson's correlation test. Finally, Enzyme-Linked Immunosorbent Assay (ELISA) was used to validate the expression of selected proteins in PBC patients and healthy controls.
Results: No significant differences between the two groups were observed in terms of gender, age, bile acids, albumin, and serum creatinine ($p > 0.05$). However, there were significant differences in ALP, GGT, bilirubin, and immunoglobulin IgM ($p < 0.001$). Further, the urinary proteomics analysis revealed that a total of 109 proteins were upregulated, and 85 proteins were downregulated in PBC patients. GO analysis and KEGG pathway enrichment of the top 50 upregulated proteins were performed. And then, 10 differential proteins were found to be associated with immune regulation and inflammatory

responses (OPN, RAMP3, CD44, ACVRIB, CXCL12, CD74, CCN4, S100A8, LAMP3, PIK3Cd). Correlation analysis of the 10 differential proteins with clinical biochemical markers revealed that OPN, RAMP3, and S100A8 were significantly correlated with AST, ALT, ALP, and GGT. ELISA validation further confirmed that the expression trends of these proteins in the urine of PBC patients and healthy controls were consistent with the mass spectrometry results.
Conclusion: The urinary levels of OPN, RAMP3, and S100A8 were significantly elevated in PBC patients compared to healthy controls, highlighting their potential as diagnostic biomarkers for PBC.

FRI-317
Pharmacokinetics, safety, and tolerability of seladelpar in people with renal impairment
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Background and aims: Seladelpar is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in people unable to tolerate UDCA. Seladelpar is primarily eliminated in urine as metabolites, which are not expected to have clinically relevant pharmacological activities. In a mass balance study in humans, a single 10 mg oral dose of radiolabelled seladelpar was recovered in urine (73.4%) and faeces (19.5%). Here, we report on the effect of different degrees of renal impairment (RI) on the pharmacokinetics (PK), safety, and tolerability of a single 10 mg dose of seladelpar.
Method: In a Phase 1, open-label, parallel-group study (CB8025-11942), participants with normal (≥90 mL/min/1.73 m^2), mild (≥60 to <90 mL/min/1.73 m^2), moderate (≥30 to <60 mL/min/1.73 m^2), or severe (<30 mL/min/1.73 m^2) RI, defined by estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease equation, were evaluated. Participants receiving haemodialysis were excluded. Participants with normal renal function were demographically matched by age, sex, and body mass index to participants with mild, moderate, or severe RI. A regression analysis was used to evaluate the relationship between eGFR and seladelpar PK in plasma and urine. Safety and tolerability were reported.
Results: Of 36 participants who completed the study, 12 had normal renal function and 8 each had mild, moderate, or severe RI. Seladelpar maximum plasma concentration (C_{max}) and area under the plasma concentration curve extrapolated to infinity (AUC_{0-inf}) were not meaningfully changed in participants with different degrees of RI when matched to participants with normal renal function. The geometric least-squares mean (GLSM) ratios for seladelpar C_{max} were 1.17 for mild, 0.99 for moderate, and 1.01 for severe RI. The GLSM ratios for seladelpar AUC_{0-inf} were 1.10 for mild, 1.52 for moderate, and 1.01 for severe RI. GLSM ratios for seladelpar C_{max} and AUC_{0-inf} were calculated after regrouping participants based on absolute eGFR in mL/min and were consistent with those based on body surface area–indexed eGFR in mL/min/1.73 m^2. Regressions of eGFR and seladelpar plasma or urine PK parameters had R^2 <0.04, indicating a lack of correlation between RI and seladelpar plasma exposure or urine excretion. In this study, seladelpar treatment was well tolerated, with only mild adverse events reported (Grade 1, unrelated to seladelpar).
Conclusion: Exposure to seladelpar was not meaningfully increased with different degrees of RI and appeared safe and well tolerated regardless of RI status following a single 10 mg dose. The data support that dose adjustment is not necessary for people with mild, moderate, or severe RI receiving seladelpar treatment.

FRI-318
Evaluation of the potential impact of seladelpar on the pharmacokinetics of midazolam, tolbutamide, simvastatin, rosuvastatin, and atorvastatin
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Background and aims: Seladelpar is a first-in-class oral delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. Seladelpar is mainly metabolised by cytochrome P450 (CYP) CYP2C9, and to a lesser extent by CYP2C8 and CYP3A4. Here, we summarise the perpetrator effects of seladelpar on CYP3A4, CYP2C9, organic anion-transporting polypeptide (OATP), and breast cancer resistance protein (BCRP), using midazolam (CYP3A4), tolbutamide (CYP2C9), simvastatin (CYP3A4 and OATP), rosuvastatin (OATP and BCRP), and atorvastatin (CYP3A4 and OATP) as probe substrates across clinical drug-drug interaction studies.
Method: To test the effect of seladelpar on CYP3A4, CYP2C9, OATP, and BCRP, healthy participants received a single dose of midazolam (15 mg), tolbutamide (500 mg), simvastatin (80 mg), or rosuvastatin (20 mg) with or without seladelpar coadministration (single or multiple doses) in crossover studies. The effect of seladelpar on CYP3A4 and OATP was also assessed in moderately obese hyperlipidemia patients in a parallel group design comparing atorvastatin (20 mg) with or without seladelpar. Pharmacokinetic (PK) parameters included maximum plasma concentration (C_{max}) and area under the plasma concentration curve (AUC).
Results: Midazolam levels were not affected by seladelpar; geometric mean ratio (GMR) (90% CI) of midazolam C_{max}, and AUC_{0-inf} with vs without seladelpar (200 mg once daily [QD]) were 0.94 (0.84, 1.06) and 0.98 (0.91, 1.06), respectively. Tolbutamide levels were not affected by seladelpar; GMR (90% CI) of tolbutamide C_{max} and AUC_{0-inf} with or without seladelpar (200 mg, 2 doses, at least 7 days apart with washout) were 1.03 (0.97, 1.09) and 1.00 (0.98, 1.03), respectively. Simvastatin levels were not altered with seladelpar (200 mg single dose); GMR (90% CI) for simvastatin C_{max} and AUC_{0-inf} were 0.95 (0.78, 1.14) and 1.17 (0.97, 1.41), respectively. Seladelpar did not significantly increase rosuvastatin levels; GMR (90% CI) for rosuvastatin C_{max} and AUC_{0-inf} with or without seladelpar (10 mg single dose) were 1.17 (0.93, 1.45) and 1.15 (0.93, 1.43), respectively. Atorvastatin levels were similar with or without seladelpar (50 mg QD); GMR (90% CI) for atorvastatin C_{max}, and AUC_{all} with or without seladelpar were 0.88 (0.54, 1.43), and 0.85 (0.57, 1.27), respectively.
Conclusion: Seladelpar did not significantly impact the PK of sensitive probe substrates including midazolam (CYP3A4), tolbutamide (CYP2C9), simvastatin (CYP3A4 and OATP), rosuvastatin (OATP and BCRP), and atorvastatin (CYP3A4 and OATP). Based on these data, it is unlikely that seladelpar would have a clinically significant impact on drugs that are substrates of CYP3A4, CYP2C9, OATP, or BCRP.

FRI-319
Dnmt1 deletion impairs liver regeneration and stem cell activation during cholestatic liver disease
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Background and aims: Epigenetic mechanisms, particularly DNA methylation, play an essential role in regulating gene expression during development and maintaining tissue as well as stem cell homeostasis in response to acute and chronic damage. Central to this regulation is DNA methyltransferase 1 (DNMT1), which is essential for maintaining postmitotic DNA methylation patterns. While its role during development is well explored, its relevance for activation of stem/progenitor cells during regeneration is less well explored. This project aims to explore the impact of hepatocyte-specific DNMT1 loss on liver progenitor cell-induced regeneration.
Method: We used the 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) injury model, in which mice were fed a diet containing this porphyrinogenic hepatotoxin that induces cholestatic liver damage. Liver-specific Dnmt1 knockout mice (Dnmt1-KO) and control animals (WT), aged 8 weeks, were fed a diet with 0.1% DDC for up to 4 weeks. At 1, 2, and 4 weeks post-treatment, 5 animals from each group were sacrificed and the organs harvested for further analysis. Liver injury was assessed by histopathology and the spatial distribution of CK19, a marker of biliary/progenitor cell, was evaluated. Global transcriptomic changes were examined by RNA sequencing.
Results: Macroscopically, livers from both groups exhibited a pronounced dark discoloration due to cholestatic liver damage. No significant differences in macroscopic number of nodules were observed. Histological examination of liver sections demonstrated significantly more pronounced liver injury, progressive structural abnormalities, and a higher degree of infiltrating immune cells in Dnmt1-KO animals in comparison to WT. Additionally, Dnmt1-KO animals exhibited a reduced liver/body weight ratio compared to WT animals, reflective of the impaired regenerative capacity in Dnmt1-KO animals. Supporting this, expansion of CK19-positive cells was significantly reduced in Dnmt1-KO animals indicating impaired stem/progenitor activation and expansion compared to WT animals. The distinct clustering of genes, combined with enrichment analysis, highlights that Dnmt1 deletion significantly impacts gene expression in pathways associated with liver homeostasis and regeneration. Specifically, pathways such as cell cycle progression, DNA replication and repair, cell cycle checkpoint regulation, and apoptosis were significantly enriched.
Conclusion: Our findings establish a critical role of DNMT1 in maintaining liver homeostasis and stem/progenitor cell activation during excessive liver damage. Loss of postmitotic methylation patterns by inhibition of DNMT1, thus, interferes with key processes involved in liver repair and cellular organization during cholestatic liver disease.

FRI-320-YI

Single-cell profiling reveals increased IGHG2+ memory and activated IGHA1+ intrahepatic B cells in primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is an immune-mediated liver disease featuring a high prevalence of undetermined antibody reactivities and strong association with the gut-liver axis. We previously showed that clonal B cells overlap the gut and liver in PSC patients but little is known about the complete repertoire of intrahepatic B cells. To deeply characterize B cells in PSC livers, we performed single-cell RNA sequencing (scRNA-seq) and compared the phenotype and clonal overlap of B cells infiltrating PSC and disease control explants.
Method: B cells from 12 PSC and 12 disease control explants (9 PBC, primary biliary cholangitis; 3 ALD, alcohol-related liver disease) were enriched by negative selection from liver mononuclear cells, sorted for viability and analyzed by scRNA-seq for total gene and B cell receptor (BCR) expression (10× Genomics). B cell clustering was computed using Seurat v.5 and B cell clonotypes were defined by BCR expression using Loupe VDJ. Mean abundance of B cell isotypes represent the number of isotype+ B cells divided by total B cells per cluster for each disease indication. Clonal overlap among B cell clusters was calculated by Immunarch. P-values between PSC and disease controls were determined using Mann-Whitney and between PSC, PBC and ALD using Kruskal-Wallis followed by Dunn's multiple comparison testing.
Results: ScRNA-seq of 44,954 B cells from PSC, PBC and ALD explants revealed 13 distinct clusters and assigned as naïve (*IGHD*, *TCL1A*), activated (*CD80*, *CD86*), plasma (*CD38*, *SDC1*) and memory (*CD27*) B cells by differential gene expression. *IGHG2*+ B cells that largely recognize bacterial polysaccharides were enriched in memory B cells of PSC livers compared to disease controls (PSC: 8.6%, disease controls: 2.4%; $P = 0.003$) and mucosal-associated *IGHA1*+ B cells constituted a greater proportion of activated B cells in PSC compared to PBC (PSC: 17.2%, PBC: 2.9%; $P = 0.004$) but not ALD (17.4%; $P > 0.05$). Conversely, PBC livers were enriched for proinflammatory *IGHG3*+ plasma cells versus PSC and ALD (PBC: 29.4%, PSC: 4.2%, ALD: 0.0%; $P < 0.05$) and ALD explants were increased for *IGHA2*+ activated B cells compared to PSC and PBC (ALD: 17.9%, PSC: 2.3%, PBC: 1.9%; $P < 0.05$). Overlap of B cell clonotypes in PSC was strongest between activated and unswitched memory B cells, and atypical *FCRL5*+ B cells and activated B cells, whereas the greatest clonal overlap in PBC was among activated B cells and plasma cells.
Conclusion: We detected an enrichment of *IGHG2*+ memory B cells in PSC livers versus non-PSC disease controls and greater proportions of *IGHA1*+ activated B cells in PSC compared to PBC. Collectively these findings imply that intrahepatic B cells in PSC may recognize unique antigens compared to disease controls, which may originate from the inflamed gut-liver axis.

FRI-321

Identifying transporters of the solute carrier (SLC) group involved in cholangiocyte defense against toxic bile acids

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Background and aims: Human cholangiocytes, consistently exposed to high millimolar levels of hydrophobic bile salts, form 5% of the liver cell population and are responsible for ~30% of bile fluid production, primarily composed of bicarbonate and water. The 'biliary bicarbonate umbrella' hypothesis proposed a protective role of bicarbonate maintaining an alkaline pH above the apical membrane and thereby preventing membrane permeation of protonated apolar glycine-conjugated bile acids, which may trigger apoptosis and subsequently

immune attack. Defects of the 'biliary bicarbonate umbrella' have been described in primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and IgG4-related cholangitis (IRC) more recently. In PBC, SLC4A2, the main apical biliary chloride-bicarbonate exchanger, is downregulated. The present study aims to identify additional 'umbrella genes' (SLC transporters) that may be involved in maintaining pH homeostasis and protecting against damage by hydrophobic bile acids, potentially affected in fibrosing cholangiopathies.

Method: This study utilized immortalized human H69 cholangiocytes with short hairpin RNA (shRNA) knockdown of 8 SLC genes involved in pH regulation (SLC4A4, SLC4A7, SLC9A1, SLC26A2, SLC26A4, SLC26A6, SLC26A9, SLC26A11). Fluorometric measurement of intracellular pH, radiochemical determination of 3H-glycochenodeoxycholic acid uptake, and quantification of apoptosis by caspase-3/7 assays were performed. Publicly available RNA sequencing data were analyzed using R2 Platform (https://r2.amc.nl, (GSE206364, GSE159676)).

Results: Knockdown of the SLC transporters SLC9A1 and SLC26A2 resulted in decreased cholangiocellular intracellular pH; knockdown of SLC9A1, SLC26A2 and SLC26A6 enhanced uptake of GCDC, and increased GCDC-induced apoptosis in H69 cells. Analysis of published data revealed that mRNA of SLC9A1, SLC26A2, and SLC26A6 were differentially expressed in the blood transcriptome of PBC or PSC patients compared to healthy individuals. Additionally, mRNA of SLC9A1 was upregulated in liver tissue of PBC and PSC patients relative to healthy individuals.

Conclusion: The SLC transporters SLC9A1, SLC26A2, and SLC26A6 may be involved in human cholangiocyte defense against toxic bile acids and deserve further studies as potential therapeutic targets in fibrosing cholangiopathies.

FRI-322-YI

A combined immunotherapy that maintains the balance and stability of intrahepatic regulatory T cells to enhance biliary regeneration

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Background and aims: Dysfunction of Tregs and the imbalance of Tregs to T effector ratios have been reported in cholangiopathies. Tregs-expansion immunotherapies are introduced clinically to increase Tregs numbers. However, how the injured microenvironment affects the balance between Tregs and effector T cells that regulate liver inflammation and repair remains unclear. This study investigates the dynamic of Tregs during liver injury and the impact of Treg numbers and stability on bile duct repair.

Method: Intrahepatic Tregs of the Foxp3GFPDTR transgenic mice were reduced during DDC diet-induced biliary injury through Diphtheria Toxin injection. For intrahepatic Tregs fate mapping and dynamic studies, the Foxp3CreERTAi14 mice were used. The Tregs will express red fluorescence protein (RFP) after tamoxifen to trace Tregs fate. Interleukin-2 complex (IL-2c) and Ox40L blocking antibodies were used to expand and stabilise Tregs. The extent of liver injury, liver fibrosis and ductular reaction were investigated with transcriptomics, immunohistochemistry and biochemical analysis.

Results: The number of intrahepatic Tregs in PSC livers did not increase compared to healthy livers, showing limited Treg infiltration. Limiting Tregs infiltration in the Foxp3GFPDTR mice suppressed ductular reaction and enhanced liver fibrosis in mice. Transcriptome analysis of bile ducts also showed downregulation in genesets involved in ductular reaction. We previously demonstrated that IL-2c injection suppressed the ductular reaction, increased liver fibrosis, and raised the serum bilirubin level. IL-2c also expanded an "ExTreg" population, characterised by the Tregs losing Foxp3 expression and acquiring a pro-inflammatory phenotype. We found the expression Ox40L co-stimulatory molecule positively correlates with the extent of liver fibrosis in PSC patients. Blocking Ox40L after IL2-c injection promoted Tregs expansion and significantly reduced the proinflammatory ExTreg population by half compared to IL-2c treatment alone. The increase in intrahepatic Tregs and stability promotes ductular reaction and reduces scarring and cholangiocyte senescence in murine cholangitis model.

Conclusion: This study shows the importance of maintaining Treg stability and sustaining a pro-regenerative intrahepatic Treg to Teff ratio during biliary injury. When Tregs are reduced or dysfunctional, biliary regeneration is impaired, and liver injury worsens. Although the IL-2c treatment successfully doubled the intrahepatic Tregs during biliary injury, it is insufficient to promote biliary regeneration due to the instability of Tregs during biliary injury. We overcame the limitation by blocking the OX40 signalling pathway to stabilise and restore Treg functions. This increased intrahepatic Tregs versus Teff ratio, restored biliary regeneration and reduced liver fibrosis. Overall, we propose a combinational approach to improve the efficiency of Treg-mediated immunotherapies for enhancing bile-duct repair.

FRI-326

Spatial transcriptomic analysis of archived primary sclerosing cholangitis livers reveals distinct molecular signatures

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Background and aims: Primary sclerosing cholangitis (PSC) is characterized by progressive fibrosis and inflammation of medium and large bile ducts. There is no effective treatment for PSC due to poorly understood pathogenesis. Detailed spatial transcriptomics of PSC bile ducts remains unexplored. This study aimed to assess the feasibility of spatial transcriptomics using archived formalin-fixed paraffin-embedded (FPE) liver tissue and to compare the transcriptomic profiles of PSC and control bile ducts.

Method: FPE liver slides from 6 PSC patients (3 males, 3 females; Caucasian and African American) and 6 control patients (3 with cirrhosis of other etiologies, 3 with histologically normal liver adjacent to metastatic cancer) were analyzed. Samples were collected 2–12 years ago after liver transplant or resection. NanoString GeoMx® Digital Spatial Profiler with the Human Whole Transcriptome Atlas probe set was employed, targeting bile ducts (EpCAM), immune cells (CD45), and myofibroblasts (αSMA). EpCAM-positive bile ducts <100 μM were classified as small ducts, while those 100–300 μM were defined as septal ducts. After normalization and batch correction, regions of interest (ROI) with disproportionate library size relative to surface area were excluded, resulting in comparable exclusions in EpCAM-positive regions. CD45-positive regions had insufficient samples for analysis. Differentially expressed genes (DEGs) were analyzed using Ingenuity Pathway Analysis (IPA) to uncover disrupted biological pathways and upstream regulators.

Results: The highest DEG count was observed in PSC regions of small bile ducts compared to fibrotic controls (EpCAM: 261, αSMA: 585; FDR <0.05). Small PSC ducts exhibited reduced expression of hepatic fibrosis and ribosomal translation pathways compared to control fibrotic small ducts. IPA revealed deactivation of fibrosis-related upstream regulators, including TGFB1. When compared to non-fibrotic counterparts, PSC small ducts showed similar

downregulation of hepatic fibrosis pathways but not ribosomal genes. Conversely, PSC septal bile ducts showed upregulated ribosomal gene expression compared to both control septal ducts and PSC small ducts. PSC septal ducts also showed suppressed hepatic fibrosis pathways compared to fibrotic counterparts, with IPA highlighting MYC oncogene activation and upregulation of cancer-associated processes. In αSMA-positive regions, PSC samples showed reduced expression of hepatic fibrosis pathways, including genes encoding matrix proteases critical for collagen degradation.
Conclusion: This proof-of-concept study demonstrates the feasibility of spatial transcriptomics in FPE liver tissue and reveals transcriptomic alterations unique to PSC. Findings include "exhausted" fibrogenesis and fibrosis remodeling, divergent ribosomal gene expression—decreased in small bile ducts but increased in septal ducts—and MYC activation in PSC septal ducts, suggesting links to cholangiocarcinogenesis.

FRI-327-YI
Genetic ablation of interleukin 17A augments fibrosis in a mouse model of cholestatic liver injury
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Background and aims: Interleukin-17A (IL-17A) has been implicated in cholestatic liver diseases like primary sclerosing cholangitis, but its precise role remains unclear. This study aimed to examine the effect of IL-17A genetic ablation in a mouse model of cholestatic liver injury.
Method: Wild type (WT) and *Il-17a*$^{-/-}$ C57BL/6 mice were fed an intermittent 0.1% 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet for 21 days to induce cholestatic liver injury. Liver injury and fibrosis were assessed by serum biochemistry, histology, and immunostaining. Intrahepatic leukocyte (IHL) populations were analyzed by mass cytometry. Gene expression in IHLs was profiled using NanoString analysis. Flow cytometry identified immune cell subsets expressing the profibrogenic cytokine LIGHT.
Results: *Il-17a*$^{-/-}$ mice displayed more abundant Desmin-positive myofibroblasts and increased fibrosis following the DDC diet despite similar levels of liver injury and ductular reaction compared to WT littermates. Serum biochemical parameters of cholestasis were comparable between genotypes. Mass cytometry revealed similar increases in myeloid cells in both genotypes after the DDC diet, with a shift from lymphocyte-dominant to myeloid-dominant immune landscape in cholestatic livers. NanoString analysis of IHLs identified upregulation of seven genes in DDC-fed *Il-17a*$^{-/-}$ mice, including *Tnfsf14* (encoding LIGHT). Flow cytometry showed LIGHT expression was restricted to CD4+ T cells, particularly Th1-polarized cells, which were more abundant in *Il-17a*$^{-/-}$ mice. Hepatic stellate cells expressed LIGHT receptors, but direct stimulation with recombinant LIGHT did not increase profibrotic gene expression in vitro.
Conclusion: Genetic deletion of *Il-17a* augments hepatic fibrosis in cholestatic liver injury, likely through increased expression of LIGHT by Th1-polarized CD4+ T cells. These findings provide new insights into the role of IL-17A and CD4+ T cell subsets in cholestatic liver fibrosis, with implications for therapeutic strategies in human cholestatic liver diseases.

FRI-328
CCL24 blockade alters the proteomic profile of patients with primary sclerosing cholangitis and down-regulates central disease processes
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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic progressive disease, characterized by inflammation and strictures of the biliary tree within and around the liver. In the phase 2 SPRING Study evaluating the safety and tolerability of CM-101 (a CCL24 blocking monoclonal antibody) in patients with PSC, there was clinical evidence of anti-inflammatory, anti-fibrotic and anti-cholestatic activities over 15 weeks of treatment. We present the findings of a proteomic analysis exploring alterations in the circulating proteins of CM-101-treated patients compared to placebo, to further highlight the drug's mechanism of action.
Method: The Olink proximity extension assay (PEA) quantified approximately 3,000 proteins in the sera of patients with PSC treated with CM-101 at doses of 10 mg/kg (n = 21), 20 mg/kg (n = 27), and placebo treatment (n = 18). A linear mixed model was used to find differentially expressed proteins (FDR < 0.05, LogFC > 0.5) between CM-101 treated patients and those receiving placebo. Protein levels affected by treatment were used for gene set enrichment analysis (GSEA). Protein-protein interaction (PPI) networks were built to further define functional relationships between proteins.
Results: CM-101 treated patients exhibited significant changes in multiple proteins, including ones that play a role in chemotaxis, immune cell recruitment and inflammation. GSEA showed that CM-101 treatment led to down-regulation of biological processes such as cell-cell adhesion and extracellular matrix (ECM) organization, and molecular functions including binding of growth factors and integrins. PPI analysis linked treatment with CM-101 to down-regulation of gene onthology (GO) terms and pathways for leukocyte migration, cytokine and chemokine activity, and collagen binding.
Conclusion: A comprehensive proteomics analysis provided new insights into PSC disease-related pathways and additional biological evidence of the clinical activity of CM-101, specifically its impact on chemotaxis, immune cell recruitment, and fibrosis in patients with PSC. These results highlight the therapeutic potential of CM-101 and the pivotal role CCL24 plays in PSC pathology.

Immune-mediated and cholestatic disease – Clinical aspects

TOP-346
Statins are associated with decreased risk of disease progression and death in non-cirrhotic patients with primary biliary cholangitis
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Background and aims: Statins seem to have pleotropic actions in patients with chronic liver diseases, including the improvement in

events related to portal hypertension. Our aim was to evaluate whether statins in non-cirrhotic patients with primary biliary cholangitis (PBC) might have an effect on disease progression, as attested by development of cirrhosis, all-cause mortality, including liver-related death (LRD) and non-liver-related death (NLRD), as such data is missing.

Method: We retrospectively analyzed prospectively collected data in 466 non-cirrhotic PBC patients (411 females, age: 54.6 ± 13 years, follow-up: 71.5 (88) months) from 2 tertiary referral centers that were either treated with statins for > 12 months due to increased cardiovascular risk (n = 227) or had a follow-up >12 months without statin treatment (n = 239).

Results: These were no significant differences between the two groups in baseline demographic, clinical and laboratory characteristics except for higher LDL levels in statin users. No differences in treatment response to UDCA (GLOBE score, Paris II) were noted between the groups. Statin users had lower rate of cirrhosis development (3.5% vs 9%, p = 0.037), lower all-cause mortality (4% vs 16.7%, p < 0.001), lower LRD (0.5% vs 6.3%, p < 0.001) and NLRD rates (3.5% vs 10.4%, p = 0.004) compared to non-statin users. Cox regression analysis revealed lower risk of progression to cirrhosis (HR = 0.486; 95% CI 0.226–1.044), significantly lower risk of all-cause mortality (HR = 0.282; 95% CI 0.137–0.583), LRDs (HR = 0.091; 95% CI 0.12–0.692) and NLDRs (HR = 0.345; 95% CI 0.155–0.766) in statin users compared to non-users.

Conclusion: Statins are associated with lower risk of cirrhosis development, of all-cause mortality, including LRDs and NLRDs in non-cirrhotic PBC patients.

TOP-347-YI

Low vitamin B6 status associates with cholangiocarcinoma in primary sclerosing cholangitis

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Background and aims: Cholangiocarcinoma (CCA) in primary sclerosing cholangitis (PSC) is difficult to diagnose and treat. There is a large unmet need for biomarkers for risk prediction and early diagnosis. We recently showed that low levels of pyridoxal 5′-phosphate (PLP, the active form of vitamin B6) in blood are associated with an increased risk for liver transplantation or death in PSC. Since mortality in these analyses were driven by CCAs, we aimed to determine the role of PLP as a biomarker for CCA in PSC.

Method: We included a Norwegian PSC cohort (n = 317; 77% male; median age 43; 79% with IBD) and a Swedish PSC cohort (Swehep, n = 98). Serum PLP was quantified using liquid chromatography-tandem mass spectrometry. We categorized patients as either (i) PSC with CCA at time of sampling (PSC-CCA), (ii) PSC with CCA within two years after sampling (PSC-to-CCA), or (iii) PSC with no development of CCA within two years after sampling (PSC-no-CCA). Differences in PLP levels were compared by Wilcoxon tests, and logistic regression was used to estimate the probability of CCA. Statistical analyses were performed in Stata (18.0).

Results: The Norwegian cohort included 25 PSC-CCA, 21 PSC-to-CCA and 271 PSC-no-CCA. Circulating PLP concentrations were lowest in the PSC-CCA (median 11 nmol/L, IQR 8–14) and PSC-to-CCA (median 11 nmol/L, IQR 10–27) groups, compared with PSC-no-CCA (median 22 nmol/L, IQR 15–32). Despite similar median levels, there was a trend towards lower PLP in PSC-CCA compared to PSC-to-CCA (p = 0.09), while there was strong association of lowered PLP in PSC-CCA and PLP-to-CCA compared to PSC-no-CCA (p < 0.001 and p < 0.05, respectively). In the Swedish cohort, PLP concentrations were generally higher than in the Norwegian PSC cohort, but again, the PLP concentration in combined PSC-CCA and PSC-to-CCA (n = 18) was lower compared to the PSC-no-CCA group (n = 80; median 25 nmol/L (IQR 16–37) vs median 34 nmol/L (IQR 24–52), p = 0.03). Since it would be of importance to differentiate the known association between PLP and advanced PSC from the presence or future risk of CCA in the Norwegian PSC cohort we further separated PSC-no-CCA into “early disease” (as defined by and Amsterdam-Oxford score <2; n = 153), who had median PLP 26 nmol/L (IQR 19–38), and “advanced disease” (Amsterdam-Oxford score≥2; n = 118), who had median PLP 17 nmol/L (IQR 12–25). Notably, in early disease PSC, PLP was lower in both PSC-CCA and PSC-to-CCA compared to PSC-no-CCA (p < 0.001), while the PLP distribution in the PSC-to-CCA subgroup was not statistically significantly different from that of PSC-no-CCA with advanced disease. In a logistic regression analysis, a doubling of PLP was associated with a reduced risk of developing CCA within two years (OR = 0.51, 95% CI [0.31, 0.86]). In a multivariable analysis, the Amsterdam-Oxford score did not explain additional variation in this outcome compared to PLP alone (LR χ^2 p = 0.99).

Conclusion: Vitamin B6 in blood may identify a PSC subgroup with increased risk of CCA, particularly in the early stages of PSC.

TOP-348-YI

The association between metabolic comorbidities and clinical outcome in patients with primary biliary cholangitis

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Background and aims: Metabolic comorbidities are increasingly present in patients with primary biliary cholangitis (PBC). While Diabetes Mellitus (DM) has been associated with unfavorable outcomes, this is not known for other metabolic comorbidities. The aim of this analysis was to assess the association between these comorbidities and the liver transplantation (LT)-free survival in a nationwide PBC population.
Method: The Dutch PBC Cohort Study (DPCS) is a retrospective study which includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019-2023) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. Survival analyses were used in all patients on ursodeoxycholic acid (UDCA) for whom baseline data were available on DM, arterial hypertension, dyslipidemia and Body Mass Index (BMI). Laboratory values at 1 year were imputed using joint model multiple imputation.
Results: In total 2365 patients were included; 2094 (88.5%) were female, median age was 56.2 (IQR 47.8-66.0) years and 177 (7.5%) patients had cirrhosis. At baseline, 238 (10.1%) had DM, 441(18.6%) had arterial hypertension, 404 (17.1%) had dyslipidemia, and 1317 (55.7%) had a BMI >25 kg/m2. The median follow-up duration was 6.9 (IQR 3.1-12.3) years. In a multivariate analysis adjusted for calendar year, age, sex, cirrhosis, and liver enzymes after 1 year of UDCA, only DM was associated with the risk of LT or all-cause mortality (aHR 1.52, 95%CI 1.02-2.29, p = 0.04), while dyslipidemia (aHR 1.15, 95%CI 0.82-1.63, p = 0.41), arterial hypertension (aHR 1.17, 95%CI 0.83-1.66, p = 0.36) and a BMI>25 kg/m2 (aHR 0.83, 95%CI 0.63-1.10, p = 0.20) were not. Findings were consistent among patients without DM; neither having 1 (aHR 0.91, 95%CI 0.65-1.26, p = 0.57) or ≥2 (aHR 1.06, 95%CI 0.71-1.58, p = 0.79) metabolic comorbidities were associated with the LT-survival. In patients with DM, no statistically significantly differences in 10-years cumulative LT-free survival between patients with or without additional metabolic comorbidities were observed (63.9% vs. 68.3%, p = 0.42).
Conclusion: Presence of DM was independently associated with an unfavorable survival free of LT among patients with PBC. In contrast, arterial hypertension, dyslipidemia or being overweight were not related to the risk of LT or all-cause mortality.

TOP-362-YI
Safety and efficacy of Upadacitinib in patients with primary sclerosing cholangitis and associated colitis
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Background and aims: PSC is closely associated with the occurrence of inflammatory bowel disease (IBD). Tofacitinib (selective Janus Kinase [JAK] 1/3 inhibitor [i]), approved for the treatment of ulcerative colitis (UC), led to an improvement in colitis activity in the majority of PSC-IBD patients. There were no safety concerns in relation to PSC. In addition, there was a decrease in alkaline phosphatase in the subgroup that responded to tofacitinib with regard to their bowel disease (Schregel et al., 2023). Upadacitinib (Upa), a novel and potent orally administered selective JAK1 inhibitor, has been approved for the treatment of IBD in 2022/23 (Sandborn et al., 2020; Danese et al. 2022). Our aim was to assess safety and efficacy of Upadacitinib on liver and bowel disease in patients with PSC-IBD.
Method: Multicenter clinical data collection was conducted retrospectively at baseline, after 3, 6, 12 months follow-up (m-FU) and annually thereafter. Patients post liver transplantation were excluded.
Results: Forty (70% male) patients with a median age of 21 years from 9 centers were included of whom 31 had a complete 3-months follow-up. Of all patients, 87.5% presented with UC and 12.5% with Crohn's disease phenotype. 77.5% received at least two biologicals prior to Upa, 15% another JAKi. Adverse events occurred in 10 cases (3× elevated Transaminases, 3× (peri-)anal fissure/abscess, 3× respiratory infections, 1× low WBC). Upa was discontinued in 20%, mostly due to lack of efficacy. In those still on Upa, ALP levels non-significantly dropped from a mean of 348 at baseline to 270 U/l at 3m-FU (p = 0.068) while mucosal appearance as assessed by Mayo Endoscopic subscore significantly improved by a median difference of −1 (p = 0.015) between baseline and 6m-FU (median 2 vs 1). Transient elastography (TE) (p = 0.237; mean of 6.6 to 7.4 kPa at 6m-FU), and AST-levels remained stable between baseline and 3m-FU (144 vs 118 U/l, p = 0.597).
Conclusion: Updacitinib led to a decreased activity of PSC-associated IBD and a non-significant decrease in serum ALP levels. Additional studies are warranted to monitor safety of JAK inhibition in PSC.

THURSDAY 08 MAY

THU-271
Evolution of the United Kingdom's national immunoglobulin G4-related disease multidisciplinary meeting in guiding diagnosis and management of complex cases
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Background and aims: Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory disorder, with frequent pancreatic and hepatobiliary involvement. A UK National IgG4-RD multidisciplinary meeting (MDM) was introduced to improve diagnostic pathways and streamline management of patients with suspected IgG4-RD. We sought to appraise the evolution of this MDM and its value in management.
Method: Data were retrospectively collected from all patients discussed in the IgG4-RD MDM, from November 2016 to October 2024. Core specialists included Gastro-Hepatology, Rheumatology, Radiology and Histopathology with various visiting specialists (n = 14). Baseline characteristics, reason for referral, referring specialty, affected organs, medications and outcome were among the data fields collected. Patients were classed as definite, probable or not IgG4-RD based on consensus diagnostic criteria and MDM opinion.
Results: 1165 cases were discussed over eight years. Referrals came from 125 centres nationwide and 33 medical and surgical specialties, predominantly Gastroenterology (21.3%), Hepatology (18%) and Rheumatology (11.7%). The caseload rose annually (except one-year of the COVID pandemic), summating 233 discussions in the last year. Over half (58%) of all referrals sought diagnostic confirmation, 14% required review of active disease and 22.9% requested management advice, including 5.1% on relapse. Notably, the complexity of questions increased over time. 801 patients had full datasets; 543 (67.8%) referrals were new, 258 (32.2%) were follow-up. Overall, 645 (80.5%) were considered to have definite or probable IgG4-RD. 59.3% had two or more organs involved. Median organ involvement was

two (range 1–8); most frequent were pancreatic (45.8%), biliary (28.1%) and lymph nodes (22.6%). In the 645 patients with definite or probable IgG4-RD and full datasets, 18 combinations of IgG4-RD medications were prescribed at referral. 260 (40.3%) were on steroids; 169 (26.2%) on any immunosuppressant, 60 (9.3%) had used rituximab (third-line as per NHS England). MDT outcomes - further investigations requested in 433 (67.1%), change of drug recommended in 278 (43.1%), escalation of current drug dose in 20 (3.1%) cases. 101 referrals specifically requested escalation to rituximab; the MDM agreed in 91 (90.1%) cases. Concurrent malignancy was confirmed in 33 of the 645 cases: lymphoma in 25 and pancreatic cancer in four.

Conclusion: The UK National IgG4-RD MDM is an integral pathway for clinicians to facilitate advanced case discussion surrounding complex IgG4-RD, with its value demonstrated by a growing volume and complexity of referrals. Diagnostic uncertainty remains the principal reason for referral, with 80% receiving a diagnosis of probable or definite IgG4-RD, supporting the need for ongoing education in this rare disease.

THU-272

Appraising improvement in prediction of clinical outcomes based on different response criteria and liver stiffness measurements in patients with primary biliary cholangitis treated with second-line therapies

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Background and aims: The confirmation of clinical benefit for second-line therapies that showed efficacy on surrogate biomarkers may be difficult in the context of primary biliary cholangitis (PBC). For this reason, EMA suggested to adopt more stringent cut-offs of biochemical parameter used to define response criteria in forthcoming clinical trials, and also to consider the variation of liver stiffness measurements (LSM). The aim of the present study was to appraise the improvement in prediction of liver-related events (LRE) based on the adoption of different response criteria and LSMs in patients with PBC treated with second-line therapies.
Method: Data were from the Italian RECAPITULATE cohort, including PBC patients treated with Obeticholic acid (OCA) in centres belonging to the Italian PBC Registry and to the CLEO PBC Study group. After excluding patients with <6 months' observation or with Child-Pugh B/C cirrhosis or previous hepatic decompensation, response to therapy was evaluated by liver enzymes and/or follow-up LSM, or by the following dichotomous criteria: ALP/ULN<1.5 with at least 40% reduction (ALP40); normal total bilirubin (TB) and ALP/ULN<1.67 with at least 15% drop (POISE); normalization of ALT, ALP and TB (normal range, NR); normalization of ALP and ALT and TB<0.7 (DEEP). LRE were defined as the occurrence of hepatic decompensation, liver transplantation or liver-related death. Cause-specific Cox regressions were fitted including the abovementioned response parameters as time-dependent covariates. Associations were evaluated through hazard ratios (HR), while predictive abilities through the c-statistics and log-partial-likelihood.
Results: 677 PBC subjects (mean age 58, women 88%, cirrhotics 29%) were followed for a median of 30 months, and 31 LRE were registered. A sub-sample of 519 individuals with available LSM (total 946 LSMs) was also analysed. TB was the most strongly associated factor with LRE (HR 2.42, 95%CI 1.94–3.02, p < 0.001) along with LSM (HR 1.06, 95%CI 1.04–1.08, p < 0.001). ALP/ULN was associated with LRE only in subjects with TB < 0.7 (HR 1.80, 95%CI 1.17–2.79, p 0.008). ALP40, POISE, NR and DEEP response criteria showed progressively larger effect size (HR ranging from 0.67 to 0.25, respectively). TB and LSM were the most predictive markers of LRE (c-statistics 0.73 and 0.83 respectively; log-likelihood test < 0.001). A multivariable model including ALP+TB+LSM reached a c-statistics of 0.85. LSM significantly improved predictivity of all the dichotomous response criteria (log-likelihood test <0.001 for all).
Conclusion: In this large cohort of PBC patients treated with second-line therapies, the adoption of more stringent response criteria was not mirrored by an improved prediction of LRE. LSM was strongly associated and predictive of LRE, both when used alone and when added to other response criteria. These findings emphasize the importance of integrating LSM to current response criteria for conducting clinical trials to inform on clinical outcomes.

THU-273

Evaluation of the association between biomarkers and patient-reported outcomes in patients with primary biliary cholangitis

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Background and aims: This analysis evaluated associations between liver stiffness, patient-reported outcomes (PROs), and liver biochemistries in patients (pts) with primary biliary cholangitis (PBC).
Method: This retrospective, observational study reflects the experience of pts with physician-confirmed PBC receiving care at Beth Israel Deaconess Medical Center with available PRO and laboratory data through October 2022. Laboratory data (2018–2022) included alkaline phosphatase (ALP), aspartate aminotransferase, alanine aminotransferase, total bilirubin, and gamma-glutamyl transferase (GGT). Transient elastography (TE) was used as a noninvasive measure of liver stiffness. PRO instruments included the EQ-5D-3L, PBC questionnaire (PBC-40), Chronic Liver Disease Questionnaire (CLDQ), and pruritus visual analog scale (VAS). Correlations between biomarkers, TE, and PROs from the first date available were analyzed using Spearman's rank correlation. The median time between lab tests, TE, and PRO assessments was 0 months.
Results: Of the 113 pts with available data, the mean (SD) age at diagnosis was 53.2 (12.2) years; most were White (85.8%), female (92.0%), and had private/commercial insurance (54.0%), followed by Medicare (36.3%) and Medicaid (7.1%). Most pts (96.5%) were current users of ursodeoxycholic acid. Mean (SD) test results were 9.3 (13.2) kPa for TE, 91.0 (140.1) IU/L for GGT, and 169.5 (213.7) IU/L for ALP. Among pts with ≥1 PRO assessment, the mean (SD) total scores were 6.4 (1.5) for the EQ-5D-3L (n = 92), 84.6 (30.7) for PBC-40 (n = 97), 31.5 (6.8) for CLDQ (n = 99), and 1.5 (2.3) for VAS (n = 104). Some biochemistries had low correlations (0.24–0.44) with certain domains of the PRO instruments. ALP had low correlations (0.26–0.38) with 4 of the 6 domains of the PBC-40, including the emotional, social, and itch domains. Similarly, ALP had low but negative correlations with the CLDQ emotional function (–0.25) and worry (–0.34) domains. TE measurements showed low correlations with the EQ-5D-3L mobility (0.37) and usual activities (0.32) domains and a low negative correlation with the CLDQ worry domain (–0.26). GGT had a slightly higher correlation with the EQ-5D-3L self-care domain (0.44) and low correlations with the EQ-5D-3L usual activities (0.25), PBC-40 emotional (0.25), and CLDQ worry (-0.25) domains. Similar domains from different PRO instruments showed moderate to high correlations: PBC-40 fatigue and CLDQ fatigue (-0.84), CLDQ

emotional and PBC-40 emotional (-0.58), and VAS and PBC-40 itch (0.56).
Conclusion: Consistent with published literature, liver biomarkers of disease severity were not strongly correlated with the different domains of PRO instruments. However, similar domains from different PROs show moderate to high correlations and can be used as complementary tools to assess pts' emotional and physical well-being.

THU-274
Efficacy and safety of seladelpar in patients previously treated with fibrates or OCA
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Background and aims: Seladelpar is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in patients (pts) with an inadequate response to UDCA or as monotherapy in pts unable to tolerate UDCA. RESPONSE was a Phase 3, randomised, placebo-controlled clinical trial of seladelpar in pts with inadequate response/intolerance to UDCA. Pts completing RESPONSE were eligible to roll over into ASSURE (NCT03301506), an ongoing, open-label, long-term, Phase 3 safety trial. Here we describe data from month 18 (month 6 of ASSURE) in pts with or without prior use of fibrates or obeticholic acid (OCA) who rolled over from RESPONSE into ASSURE.
Method: Pts received 10 mg seladelpar orally daily or placebo in RESPONSE; pts received open-label 10 mg seladelpar in ASSURE. Fibrates and OCA were prohibited during the study period and a 6-week washout was required prior to entry in RESPONSE. Data are described for pts in ASSURE with or without prior use of fibrates/OCA and based on whether they received seladelpar (continuous seladelpar pts) or placebo (crossover pts) in RESPONSE. Efficacy included the percentage of pts achieving a composite biochemical response (CBR; alkaline phosphatase [ALP] <1.67 × upper limit of normal [ULN], ALP decrease ≥15%, and total bilirubin ≤ULN). Safety assessments included adverse events (AEs) and laboratory parameters.
Results: Among pts who continued into ASSURE from RESPONSE (158), 16 continuous seladelpar and 11 crossover pts reported prior use of fibrates/OCA (total, n = 27; 17%); 88 continuous seladelpar and 43 crossover pts reported no prior use of fibrates/OCA (total, n = 131; 83%). At month 18, among continuous seladelpar pts, 9/15 (60%) pts with prior fibrate/OCA use achieved a CBR vs 54/87 (62%) pts without prior fibrate/OCA use. Among crossover pts, 7/11 (64%) pts with prior fibrate/OCA use vs 32/41 (78%) pts without prior fibrate/OCA use achieved a CBR at month 6 of ASSURE. From ASSURE initiation to month 6, incidence of AEs was similar across continuous seladelpar and crossover pts, regardless of prior OCA/fibrate use; no treatment-related serious AEs were reported.
Conclusion: In this interim analysis of continuous seladelpar and crossover pts from ASSURE, pts who reported prior use of fibrates/OCA achieved a similar sustained biochemical response with seladelpar compared with pts who reported no prior use. Seladelpar appeared safe and well tolerated in this subgroup.

THU-275
Terminology, diagnosis and management of primary biliary cholangitis-autoimmune hepatitis variant syndrome (PBC-AIH): results from an international Delphi consensus process
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Background and aims: Heterogeneity in definition, diagnosis and treatment of primary biliary cholangitis-autoimmune hepatitis variant syndrome (PBC-AIH) is present in guidelines and daily practice. This initiative aimed to bring together global experts to achieve consensus on the terminology, diagnosis and management of PBC-AIH.
Method: The initiative was endorsed by the ERN RARE-LIVER, the Global PBC Study Group and the IAIHG. The Delphi process included two rounds of voting, and followed a modified approach according to the "RAND/UCLA Appropriateness Method." A core group of experts identified the unmet needs and areas of uncertainty, identified panelists worldwide, drafted the first set of statements, analyzed and discussed the results of the first round, organized a physical meeting at EASL 2024 in Milan, and drafted a second round of statements restricted to those areas that did not reach consensus after the first round.
Results: The first round included 92 participants, while 82 took part in the second one, representing a geographically diverse panel of 78 hepatologists and 14 liver pathologists. Consensus was reached on definition (variants), suspicion criteria (incomplete response to UDCA with disproportionate elevation of transaminases compared to cholestasis), liver biopsy indications to diagnose PBC-AIH (mandatory in PBC patients, need for revision of the index biopsy in AIH patients first). The panel agreed that diagnosis should be periodically re-evaluated, since features can occur sequentially, and that PBC-AIH is associated with worse prognosis as compared to PBC alone. Severe interface hepatitis in patients with PBC would require immunosuppression, but age, comorbidities, stage and patient preferences should be considered.
Conclusion: This Delphi initiative successfully convened PBC and AIH experts to establish consensus in a complex, understudied area lacking evidence-based guidelines. The resulting statements offer a basis for prospective studies and standardized clinical protocols, aiming to enhance consistent management of PBC-AIH.

THU-276

Introduction of an advanced pharmacist clinic leads to improved assessment and treatment of patients with PBC

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Background and aims: The UK-PBC Audit identified multiple shortcomings in assessment and management of PBC nationally and within our clinics. To improve care, we introduced an Advanced Pharmacist PBC clinic (APC) in May 2023, and from June 2024 combined this with an electronic PBC template. We sought to examine the impact of this by performing an audit of APC clinic attendances using our local UK-PBC audit data as the baseline comparator.
Method: Data prospectively collated electronically from the APC, between 27/06/2024 and 01/12/2024 was compared to our 2021 UKPCA audit of patients attending standard care clinics (SCC). Continuous variables were compared using Mann-Whitney U test. Categorical variables were compared using chi-square.
Results: 438 patients (129 APC, 309 SCC) were included for analysis. Patients attending APC were representative of the SCC in terms of age (Median 65.5 v 66 years, $p = 0.823$), sex (Female 113 (87.6%) vs 276 (89.3%), $p = 0.729$), presence of cirrhosis (14 (10.9%) vs 56 (18.1%), $p = 0.058$) and prescription of ursodeoxycholic acid (urso) (119 (92.2%) vs 285 (92.2%), $p = 0.996$). Urso treated patients attending the APC clinic were more likely to be on 13–15 mg/kg of urso (112 (94.1%) vs 124 (43.8%), $p < 0.001$), and rates of second line therapy use were also numerically higher (34 (26.4%) vs 58 (18.7%), $p = 0.076$). Paris response criteria were more likely to be met in the APC cohort (117 (90.7%) vs 241 (78.0%), $p = 0.002$), though ALP normalisation rates were similar (48 (37.2%) vs 126 (40.8%), $p = .486$). Assessments of pruritis (122 (94.6%) vs 217 (70.2%), $p < 0.001$), fatigue (122 (94.6%) vs 213 (68.9%), $p < 0.001$) and bone health (112 (86.8%) vs 240 (72.9%), $p = 0.028$) were all more likely to have been documented as taking place in the APC. Additionally, patients in the APC were more likely to be on treatment for pruritis (36 (27.9%) vs 55 (17.8%), $p = 0.017$). Prospective data continue to accrue, and a further 4 months of data will be presented at conference.
Conclusion: The introduction of an Advanced Pharmacist PBC clinic, incorporating an electronic clinic template, has led to substantial improvements in the care of patients with PBC. Benefits include increased assessment of PBC-related symptoms and bone health, improved optimisation of urso dose, and higher rates of therapy for pruritus. APC attendees were significantly more likely to meet Paris response criteria.

THU-277

Psychometric evaluation of the pruritus numeric rating scale in patients with primary biliary cholangitis with moderate-to-severe pruritus

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Background and aims: Pruritus Numeric Rating Scale (NRS) is a patient-reported outcome (PRO) previously validated and used to assess severity of itch in various diseases. However, the Pruritus NRS measurement properties have not been assessed in Primary Biliary Cholangitis (PBC) patients who experience cholestatic pruritus in a clinical trial setting. The psychometric properties of the NRS following US FDA PRO and PFDD Draft Guidance (2009, 2023) were evaluated using the RESPONSE (NCT03602560) study, a placebo-controlled Phase 3 trial of seladelpar in patients with PBC.
Method: The 11-point Pruritus NRS (range: 0–10; no itching–worst imaginable itching) was completed daily for 6 months. Patient-reported outcomes used to support the Pruritus NRS validation included the Patient Global Impression of Severity of pruritus (PGI-S, 7-day recall), Patient Global Impression of Change of pruritus (PGI-C, start-of-study recall), 5-D Itch (2-week recall), and PBC-40 (4-week recall) and were administered at study visits. Reliability, validity, and ability to detect change analyses for the Pruritus NRS were conducted in trial participants with moderate-to-severe pruritus NRS (MSPN) (≥4 on NRS) at baseline, the target population of interest.
Results: Of the 193 RESPONSE trial participants enrolled, 72 were included in the MSPN psychometric analysis (mean [range] age: 47.1 [27–68] years; 97.2% female). Test-retest reliability of the Pruritus NRS was acceptable for itch (ICC = 0.48) in subjects with stable 5-D Itch Degree scores between Day 1 and Week 4. Convergent validity of the Pruritus NRS was supported based on moderate-to-strong correlations with 5-D Itch Degree score at Day 1, Week 4, Week 12, and Week 26 ($r = 0.60, 0.50, 0.64$ and 0.68, respectively) and the PBC-40 Itch domain score at Day 1, Week 4, Week 12, and Week 26 ($r = 0.59, 0.40, 0.49$ and 0.62, respectively). Known-groups validity was confirmed and differed significantly for comparisons between none, mild, moderate, severe levels of itch when evaluated based on 5-D Itch Degree ($p < 0.0001$) and PGI-S severity ($p < 0.0001$). Responsiveness was demonstrated by incrementally larger decreases in Pruritus NRS scores (improvement) across PGI-S ($p < 0.0001$) and PGI-C ($p < 0.0001$) levels over time.
Conclusion: Findings confirm that the Pruritus NRS utilized in RESPONSE to assess itch is a valid and reliable measure for use in detecting anti-pruritic treatment efficacy in patients with PBC-related pruritus.

THU-278

Clinical diagnostics of autoimmune hepatitis enabled by mass spectrometry-based proteomics

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Background and aims: Autoimmune hepatitis (AIH) is a rare, chronic liver disease sometimes difficult to diagnose and distinguish from other chronic liver diseases like metabolic dysfunction-associated steatotic liver disease (MASLD). We performed mass spectrometry (MS)-based proteomics of paired liver-plasma samples from AIH

patients to improve our understanding of the pathophysiology and uncover potential new biomarkers.
Method: We recruited 19 newly diagnosed AIH patients, 17 MASLD patients, and 19 healthy controls. Snap-frozen liver tissue and plasma were collected. MS-based tissue and plasma proteomics were performed using PASEF-DIA on Bruker timsTOF instrument. Differential abundance analysis was conducted using a linear model. A protein was considered differentially abundant if a false discovery rate adjusted p-value by Benjamini-Hochberg was < 0.05. For the classification of AIH versus MASLD and healthy, machine learning analyses were performed employing logistic regression models on liver and plasma proteome data. Data were validated by the Olink proteomics platform in United Kingdom Biobank (UKB).
Results: There were 2,589 and 227 differentially abundant proteins in liver and plasma, respectively, when comparing AIH with healthy, 58 of these were significant in both liver and plasma. Metabolic dysregulation and systemic immune activation were characteristics of the AIH liver and plasma proteome, respectively. When combining both the liver and plasma proteome to classify AIH versus MASLD and healthy, we achieved an average ROC-AUC of 0.95 (standard deviation 0.06). Validation in the UKB was possible for 8 of 20 predictive plasma proteins and showed consistent directional changes, with three proteins (C7, ICAM1, cAST) significantly different between AIH and MASLD/healthy, and 6 of 8 proteins (C7, ICAM1, cAST, IGFBP3, TIMP1, TTR) being significantly different between AIH and MASLD/healthy when adjusting for age and sex.
Conclusion: MS-based proteomic analyses of paired liver-plasma samples from AIH patients enabled discovery of numerous proteins with high diagnostic potential. Validation in UKB confirmed consistent directional changes for key predictive proteins. However, further validation in larger cohorts is needed to confirm these results and enhance diagnostic accuracy. Overall, proteomics holds promise as a novel non-invasive diagnostic tool for AIH.

THU-279
One-year efficacy and safety of tacrolimus in chronic autoimmune hepatitis

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Background and aims: Treatment of Autoimmune hepatitis (AIH) in patients difficult-to-treat or intolerant to standard of care (SOC) can include Tacrolimus (TAC) but evidence on its efficacy and safety is still limited. We aimed to evaluate the efficacy and safety of TAC in difficult-to-treat (DTT) and SOC-intolerant AIH patients.
Method: Patients with AIH followed at Fondazione IRCCS San Gerardo dei Tintori, Monza, for 12 months of follow-up since initiating TAC were included in the study. Biochemical parameters (AST, ALT, GGT, bilirubin, albumin, IgG) were monitored at treatment initiation and during follow-up at 1, 3, 6, and 12 months.
Results: Twenty-seven AIH patients, 22 refractory and five intolerant to SOC, were included. Median age was 46 years (IQR 37, 57), with 63% female. Regarding ethnicity, 23 were Caucasian, three patients were Hispanic and one was Asian. The median bilirubin at enrollment was 0.73 (0.60, 1.39) times the upper limit of normal (ULN), median albumin was 3.71 mg/dl and median gamma globulins were 1.02 (0.72, 1.62). After 12 months of TAC therapy, a significant reduction in AST levels (from 1.8 to 0.8 times ULN) and ALT levels (from 2.5 to 0.7 times ULN) was observed, with the greatest improvements occurring within the first three months. In the 22 DTT cases, AST levels declined from 2.4 times ULN to 0.9 times ULN, and ALT levels declined from 2.7 × ULN to 0.8 times ULN. Adverse events were observed in 67% of patients. Nine patients experienced an infection, of whom one died due to pneumonia. Four patients experienced arthralgias and three experienced headache. Tacrolimus was never discontinued due to adverse events.
Conclusion: TAC can be a viable therapy for DTT or SOC-intolerant AIH patients in the chronic setting, significantly improving biochemical markers within 12 months. Side effects are frequent and require monitoring. Multicenter, randomised controlled studies are needed to better assess efficacy and safety of TAC in this sub-cohort of patients.

THU-280-YI
Efficacy, safety and long-term clinical outcomes of a low-dose versus high-dose prednisolone induction in autoimmune hepatitis: a propensity score matched analysis

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Background and aims: Different corticosteroid dosing regimens are used in the management of autoimmune hepatitis (AIH). We aimed to compare the efficacy of a low versus high-dose prednisolone induction regimen in achieving biochemical response in AIH.
Method: In this retrospective review of a prospectively maintained database, treatment-naive AIH patients treated with prednisolone were categorised into two groups: low-dose (≤20 mg/day) and high-dose (>20 mg/day). The primary outcome was the biochemical response, defined by the normalisation of serum transaminases within six months of treatment initiation. Secondary outcomes were index or further decompensation in compensated and decompensated patients respectively, mortality, complete biochemical response (CBR) within six months and steroid-related adverse effects. Propensity score matching (PSM) was done in a 1:1 ratio. Kaplan-Meir survival analysis was used to compare index or further decompensation, and mortality.
Results: A total of 128 patients were included, with 48 and 80 patients in the low- and high-dose groups, respectively. Median follow up duration was 34 (21–65) months. Azathioprine was used in 83.3% and 82.5% of patients, while Mycophenolate Mofetil was used in 6.3% and 8.8% of patients in the low-dose and high-dose groups, respectively. After PSM, each group consisted of 46 patients. The median starting dose was 20 (12.5–20) mg in low-dose group and 40 (40–40) mg in high-dose group. Biochemical response rates were similar between the two groups (60.9% vs. 63.0%; p = 0.830). Patients with cirrhosis had lower response than those without cirrhosis (51.2% vs. 79.1%; p = 0.002). However, within each subgroup (cirrhosis and no cirrhosis), response rates did not vary with low-dose or high-dose

prednisolone. CBR was evaluated in 75 patients, rates of which were similar between low-dose and high-dose groups (22.5% vs 20.0%, p = 0.792). Index decompensation among compensated (HR 1.07; 95% CI 0.33–3.50; p = 0.910) and further decompensation among previously decompensated patients (HR 1.65; 95% CI 0.68–4.05; p = 0.270) was similar in low-dose compared to high-dose group. No difference in mortality was present between the low-dose and high-dose groups for both compensated patients (HR 0.62; 95% CI 0.07–5.25; p = 0.665) and decompensated patients (HR 1.12; 95% CI 0.32–3.88; p = 0.857). There was a trend towards fewer steroid-related adverse effects in the low-dose group (27.1% vs. 42.5%; p = 0.080). Most common side effects were cosmetic (25%) followed by dysglycemia or diabetes mellitus (7.0%) and infection (4.7%).
Conclusion: Low-dose prednisolone induction results in similar biochemical response and clinical outcomes with possibly lower steroid-related adverse effects compared to a high-dose regimen in AIH. Thus, low-dose prednisolone induction may be appropriate where minimization of adverse effects is a high priority.

THU-285
Prognostic factors in autoimmune hepatitis: a french multicenter study
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Background and aims: Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by liver inflammation that can progress to fibrosis and cirrhosis. Few studies have assessed factors associated with major hepatic events such as death, liver transplantation, or hospitalizations. However, these data are critical for risk stratification and personalized patient management.
Method: This multicenter French retrospective study included 239 AIH patients who underwent liver biopsy between 2010 and 2023. Patients on corticosteroids for >5 days at biopsy or with >50% missing data were excluded. Logistic regression identified factors associated with treatment response at 6 and 12 months, excluding variables with >30% missing data. Cox regression assessed factors linked to hepatic events (death, transplantation, or hospitalization), excluding variables with >20% missing data.
Results: A total of 239 patients were included (median follow-up: 52.2 months (IQR 26–87)). At diagnosis, 72% of patients were presented with acute disease, 13% with acute-on-chronic disease, and 16% with chronic disease. Women represented 67% of the cohort (mean age of 50.9 years (SD 18.23)). Cirrhosis was present in 31%, 35% had a non-hepatic autoimmune disease. Median serum ALT activity was 550 IU/L [IQR 237–1097], and IgG concentration was 19.4 g/L [IQR 16–28]. ANA antibodies were positive in 83%, smooth muscle antibodies in 46%, and anti-actin antibodies in 52 patients. Induction therapy consisted of budesonide in 31 patients and prednisone/prednisolone (mean dose 0.7 mg/kg/day [SD 0.4]) in 202. Azathioprine was the first-line treatment (mean dose 1.2 mg/kg/day, SD 0.6) in 208 patients (87%). Second-line therapy was initiated in 58 patients (47 received MMF), and 23 required third-line therapy. Complete response at 6–12 months was achieved in 71% of patients. Corticosteroid dependence occurred in 15%, and 35% of initial responders experienced relapse after 6 months of treatment. Immunosuppression was stopped without relapse in 29 patients (median time from initiation to discontinuation: 38 months [IQR 23–52]). Refractory AIH was observed in 13%. A total of 39 patients experienced hepatic events (HCC: 2, death: 12, liver transplantation: 9, liver disease-related hospitalizations: 16). Variables independently associated with complete response included baseline IgG levels (OR 0.9, 95% CI 0.86–0.94, p = 0.001) and ALT levels (OR 1.6, 95% CI 1.1–2.4, p = 0.018). Significant predictors of hepatic events included refractory hepatitis (HR 6.7, 95% CI 2.5–18.0), and cirrhosis at biopsy (HR 1.6, 95% CI 1.2–2.2).
Conclusion: Achieving treatment response is critical to improving outcomes in AIH patients, particularly those with cirrhosis. New therapeutic strategies are urgently needed for patients who fail standard treatments.

THU-286
Seladelpar treatment of patients with primary biliary cholangitis improves the GLOBE score and predicts improved transplant-free survival
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Background and aims: The GLOBE score is a validated risk assessment tool that provides an estimate of transplant-free survival for patients (pts) with primary biliary cholangitis (PBC). Seladelpar is a first-in-class delpar (selective PPAR-delta agonist) with anticholestatic, anti-inflammatory, and antipruritic activity indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in pts intolerant to UDCA. This analysis evaluated the change in GLOBE score in pts with PBC on seladelpar from the pivotal, placebo-controlled Phase 3 RESPONSE (NCT04620733) trial and the subsequent open-label extension (ASSURE; NCT03301506).
Method: Pts with PBC who received UDCA for ≥12 months (M) or were intolerant to UDCA and had alkaline phosphatase (ALP) ≥1.67× the upper limit of normal (ULN) and total bilirubin (TB) ≤2× ULN were enrolled into RESPONSE and randomised 2:1 to receive daily seladelpar 10 mg or placebo. After 1 year (Y), pts were eligible for ASSURE. At this time, pts on placebo could cross over to seladelpar (crossover) and pts on seladelpar continued treatment (continuous). The change in GLOBE score was assessed for pts who received continuous or crossover seladelpar after placebo. The predicted transplant-free survival was assessed for pts who received continuous seladelpar up to 2Y or placebo up to 1Y. The contributions of ALP, TB, albumin, and platelets to changes in GLOBE score were evaluated.
Results: A total of 193 pts were enrolled. Baseline (BL) characteristics were balanced between treatment groups; 95% were female; mean (SD) age and duration of PBC were 57 (9.7) and 8 (6.6) years. Mean (SD) BL values were 314 (120.9) U/L for ALP, 0.76 (0.31) mg/dL for TB, 4.1 (0.26) g/dL for albumin, 242 (80.6) × 10^3/uL for platelets, and 0.32 (0.68) for GLOBE score. Mean (SD) changes in GLOBE score from BL at 3M and 1Y for pts on seladelpar were −0.38 (0.21) and −0.34 (0.39), respectively, vs −0.07 (0.28) and −0.01 (0.32) for pts on placebo. At 2Y, GLOBE score changes were −0.39 (0.33) and −0.42 (0.50) for pts on continuous or crossover seladelpar, respectively. For pts on seladelpar, the greatest changes in GLOBE score were attributable to the ALP component (3M, −0.20; 1Y, −0.21; 2Y, −0.19), followed by the TB component (3M, −0.11; 1Y, −0.09; 2Y, −0.13). Seladelpar treatment for 3M, 1Y, and 2Y led to predicted changes in transplant-free survival with hazard ratios (95% CIs) of 0.7 (0.7–0.7), 0.8 (0.7–0.9), and 0.7 (0.6–0.8) compared to BL, respectively. The hazard ratios (95% CIs) for pts on placebo at 3M and 1Y were 1.0 (0.9–1.0) and 1.0 (1.0–1.1). At 2Y, pts on crossover seladelpar had similar results to those on continuous seladelpar.

Conclusion: Seladelpar treatment resulted in an early decrease in GLOBE score for pts with PBC, which was maintained over 2Y and was associated with improved predicted transplant-free survival.

THU-287
Alberta has the highest prevalence of primary biliary cholangitis in North America

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Background and aims: Reported incidence and prevalence of primary biliary cholangitis (PBC) in Calgary, Alberta, Canada was among the highest worldwide. In this study, we assessed changes in the incidence and prevalence of PBC in the whole province of Alberta, Canada (4.8 million, 2023) and examined age and sex epidemiological trends.
Method: All adult (≥18 years) individuals in Alberta who fulfilled a validated administrative databases-driven case-definition of PBC (positive predictive value 78%) between 2002 and 2022 were included in the study. We used multiple population-based administrative databases (inpatient, ambulatory care, physician claims, and Alberta registry) to identify patients with PBC. A washout period between 2002 and 2005 was considered to calculate incidence. Temporal trends of annual incidence and prevalence rates per 1 million at-risk population were assessed using Joinpoint regression analysis software. Average annual percent change (AAPC) was reported according to sex. Inflection points were evaluated during the study time. Rates were adjusted and standardized according to the Canadian population (2021).
Results: Between 2002 and 2022, we identified 3,250 patients with PBC in Alberta (71.6% female; median age 58 years). Median age at diagnosis was similar between females and males (58 vs. 59 years, $p = 0.10$). Age-adjusted incidence rate among males significantly increased during the study period and peaked in 2010 which was an inflection point (65.9 per million before trending down to 23.3 per million in 2020). Age-adjusted incidence rate among females significantly increased and peaked in 2010 [inflection point] at 88.8 per million and remained stable (82.2 per million in 2020). In 2021, age-adjusted point prevalence of PBC was 1,024 per million for females and 286 per million for males. AAPC for female PBC prevalence rate was 55.3% (95% CI: 53.0–57.4) between 2002 and 2012; and 40.5% (95%CI: 38.6–42.5) between 2012 and 2020. However, AAPC for male PBC prevalence rate was 14.2% (95%CI: 12.8–15.6%) between 2002 and 2008; 49.9% (95%: 32.1–66.1%) between 2008 and 2011; and 5.5% (95%CI: 3.3–7.6%) between 2011 and 2019 before remaining steady in the last two years of the study. There were multiple inflection points of PBC prevalence rates for both sexes in our study duration.
Conclusion: The province of Alberta has the highest reported adjusted prevalence rate in North America. While PBC prevalence rates remained stable over the last decade for males, there has been a significant increase among females. The high prevalence rates of PBC in Alberta are likely the result of early diagnosis and improved survival.

THU-288
Prognostic value of liver stiffness dynamics in patients with autoimmune hepatitis

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Background and aims: Liver stiffness measurement (LSM) is a well-established non-invasive test to estimate the risk of fibrosis and clinically significant portal hypertension (CSPH). However, most evidence for the prognostic value of LSM is derived from viral and metabolic liver disease, while data from autoimmune hepatitis (AIH) patients are limited. In this study we investigated the prognostic value of repeated LSMs for (i) progression to hepatic decompensation, as defined by the occurrence of ascites, hepatic encephalopathy and/or variceal bleeding, and (ii) transplant-free survival (TFS).
Method: Patients presenting with AIH between Q1/2005 and Q4/2023 at the Medical University of Vienna were identified through a systematic database query. Patients with a confirmed diagnosis of AIH, based on an IAIHG Score of ≥6 were included. Clinical information was extracted from individual medical records.
Results: 236 AIH patients (mean age: 43.2 ± 18.9 years, 76.8% female) were retrospectively studied for a median follow-up of 8.1 (IQR 3.6–13.1) years. Median LSM at diagnosis was 8.7 (IQR: 5.9–14.9) kPa, 102 (43%) had advanced disease (ACLD), suggested by LSM ≥10 kPa, and in 38 (16%) CSPH was assumed by LSM ≥20 kPa. At 6 months (n = 203) and 1.5 years (n = 152) after/on AIH treatment, median LSM declined to 7.4 (IQR 5.3–11.6) kPa and 7.6 (IQR 5.3–11.8) kPa, respectively. In a ROC analysis, LSM at 6 months (M6-LSM) performed best to predict decompensation (AUC: 0.806 CI-95% [0.713–0.899]) and TFS (AUC: 0.719 [CI-95%: 0.543–0.869]). We further observed that a M6-LSM ≥10 kPa cut-off identified patients at high risk for decompensation (sensitivity: 75.0%, specificity 73.1%) and transplantation/death (sensitivity 66.7%, specificity 69.1%). Based on M6-LSM, patients with <10 kPa had a 0.8% 10Y-cumulative incidence of decompensation and a 97.8% 10Y- TFS, while 10Y-cumulative incidence of decompensation was 23.3% in patients with 10–19.9 kPa and 30.8% in patients with ≥20 kPa. 10Y-TFS was 100.0% in patients with 10–19.9 kPa but declined to 92.3% in patients with ≥20 kPa. Interestingly, the absolute and relative change between baseline and M6-LSM was neither a good predictor of decompensation (AUC: 0.425) nor of TFS (AUC: 0.429).
Conclusion: In AIH patients, LSM and particularly LSM at 6 months after immunosuppressive treatment initiation provide important prognostic information regarding decompensation and transplant-free survival. On-treatment M6-LSM ≥10 kPa identifies AIH patients at risk for progressing to decompensated liver disease, while M6-LSM ≥20 kPa indicates an increased risk of death or need for LTX.

THU-289
Efficacy of tioguanine and mycophenolate mofetil as second-line immunosuppressive treatment in autoimmune hepatitis management

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Background and aims: Azathioprine or 6-mercaptopurine is commonly used as a first-line maintenance treatment in the management of autoimmune hepatitis (AIH). When either intolerance or inadequate response to first-line therapy occurs, a second-line agent such as mycophenolate mofetil (MMF) is used. Tioguanine is commonly used in New Zealand to treat inflammatory bowel disease, and its use for autoimmune hepatitis has recently increased. This study aims to compare the effectiveness of tioguanine and MMF as second-line treatments for achieving biochemical remission in autoimmune hepatitis (AIH).
Method: Patients in Canterbury who fulfilled the Simplified AIH Diagnostic Criteria and were treated with tioguanine or MMF were identified. Cases were included if tioguanine or MMF were commenced as a second-line but excluded if commenced as a first- or third-line agent. Biochemical remission is defined as ALT<30 U/L. Flare is defined as elevation of ALT after achieving biochemical

remission. Statistical comparisons were conducted using Chi-square or Fisher's exact test for sample sizes <5.
Results: A total of 356 AIH patients were identified. MMF and tioguanine were commenced as a second-line agent in 42 and 10 patients, respectively. Their first-line treatments ceased because of intolerance in 67% and inadequate response in 33%. Comparing tioguanine with MMF, biochemical remission was achieved in 40% versus 57% at 6 months and 78% versus 68% at 12 months. MMF had significantly more flares than the tioguanine group (38% vs 0%; p = 0.016). Subgroup analysis showed that in patients with inadequate response to first-line treatment, the tioguanine group had significantly higher biochemical remission in 12 months (100% vs 45.5%; p = 0.037). Adverse effects were rare for both groups, only resulting in one MMF patient withdrawing treatment.
Conclusion: This is the first study comparing tioguanine against MMF in AIH management. Both tioguanine and MMF had high and comparable efficacy in achieving biochemical remission in AIH patients as a second-line agent. Tioguanine was well tolerated even in patients intolerant to azathioprine and may perform better than MMF in patients with inadequate response to first-line treatment.

THU-290
Addressing primary biliary cholangitis symptoms during consultations: an international survey of those who see patients

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Background and aims: Symptom assessment is not prioritised in current international clinical guidelines for primary biliary cholangitis (PBC), with recommendations being inconsistent or absent. This survey aims to understand healthcare professionals' (HCPs) perceptions of the discussions they have with their patients with PBC regarding symptoms.
Method: A survey of HCPs (physicians and nurses) who treat patients with PBC was conducted to capture the content of discussions throughout the patient's journey. Questions focused on symptom assessment, monitoring and access to a broader team of allied HCPs and support groups. Gastroenterologists, hepatologists, registered nurses and hepatology nurse specialists with a range of clinical experience were targeted from a database of HCPs covering North America, Europe and Asia.
Results: A total of 151 HCPs (physicians N = 121; nurses N = 30) with experience in managing PBC participated in the survey in August 2024. Overall, 95% of HCPs reported proactively asking patients about symptoms at the first consultation, when the diagnosis of PBC is established. Itch and fatigue were the symptoms most commonly discussed with all patients at this consultation (80% and 75%, respectively). Although HCPs did not commonly ask patients about symptoms in advance of a routine appointment, 97% reported proactively discussing symptoms during these consultations. The proactive discussion of itch and fatigue was less commonly reported at these interactions (72% and 67%, respectively). Over 90% of HCPs reported discussing with patients that symptoms may change over the disease course; however, only 46% always highlighted to patients that control of PBC may not correlate with an improvement in symptoms. Symptom severity was reported to be assessed using both quantitative and qualitative measures by 42% of HCPs, while 13% used only quantitative measures and 45% used only qualitative measures. To assess changes in symptoms over time, 50% of HCPs reported using both quantitative and qualitative measures, 10% used only quantitative measures and 36% used only qualitative measures. Only 54% of HCPs reported familiarity with any formal tools or scales to measure symptoms and/or the impact of PBC on patients. Regarding symptom management, 81% of HCPs prioritised specific symptoms for management (as opposed to all that are identified) and 64% reported changing their approach to symptom management depending on the stage of PBC.
Conclusion: Despite the majority of HCPs reporting that they routinely evaluate symptoms in patients with PBC, there is inconsistency in which specific PBC symptoms are proactively or routinely discussed with patients, how they are assessed (quantitatively and/or qualitatively) and how this relates to the control of their PBC. Additional guidance on symptom assessment would be beneficial to improve patients' experience.
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THU-291
Clinical meaningful change of pruritus numeric rating scale in adults with primary biliary cholangitis with moderate-to-severe pruritus

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Background and aims: Cholestatic pruritus affects people with primary biliary cholangitis (PBC) and can be extremely debilitating. The Pruritus Numeric Rating Scale (NRS) can evaluate treatment effects. This analysis followed US FDA PRO and PFDD Draft Guidance (2009, 2023) and examined the meaningful within-person change (MWPC) in the Pruritus NRS that PBC patients with pruritus perceive as a beneficial treatment effect.
Method: Data from the phase 3 RESPONSE (NCT04620733) trial of seladelpar were analyzed for participants with moderate-to-severe pruritus NRS (MSPN) (NRS ≥4) at baseline (key secondary endpoint). The NRS (range: 0–10; no itching–worst imaginable itching) was administered daily for 6 months. Two anchor measures, the 7-day recall Patient Global Impression of Severity of pruritus (PGI-S) and the Patient Global Impression of Change of pruritus (PGI-C) were administered at study visits. MWPC threshold estimates using anchor-based methods were supported by distribution-based methods and empirical cumulative distribution function (eCDF) curves. Qualitative interviews evaluated meaningful change on the Pruritus NRS in PBC adults with pruritus (NRS ≥4) outside of the trial.
Results: Of the 193 participants enrolled in the RESPONSE trial, 72 were included in the MSPN analysis (mean [range] age: 47 [27–68] years; 97% female). There was a strong relationship between change in the Pruritus NRS and PGI-S ($r = 0.50$, $p < 0.0001$) and PGI-C ($r = -0.52$, $p < 0.0001$) scores at month 6 supporting their use as anchor measures in evaluating clinically meaningful change in the MSPN population. Anchor-based analyses demonstrated MWPC estimates of ≥3-points on the Pruritus NRS corresponding to "moderate improvement" for PGI-C and 1-category improvement for PGI-S. eCDF curves had good separation between Pruritus NRS change scores and anchor categories between baseline and month 6. Distribution based analyses (comparison of NRS change score to measures of variability, like the standard error of measurement) suggested a lower threshold for score change in Pruritus NRS (0.72). Half (n = 6/12, 50%) of the interview participants supported a 3-point improvement as minimum meaningful change on the NRS.
Conclusion: Triangulation of anchor, eCDF, distribution-based analyses, and qualitative interviews of patient perception of benefit suggest a 3-point improvement in Pruritus NRS as seen with seladelpar in RESPONSE is meaningful to PBC patients with moderate-to-severe itch.

THU-292

Serum levels of IL-31 and autotaxin are independently associated with pruritus severity in patients with primary sclerosing cholangitis

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Background and aims: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease with no approved treatment and few effective off-label therapies to reduce the symptom burden. We previously reported that over 1/3 of patients with PSC experience moderate-to-severe pruritus. However, little is known about biomarkers of pruritus in patients with PSC. The aim of this analysis was to prospectively identify biomarkers of pruritus in PSC.
Method: Patients aged 18 and older, diagnosed with PSC and without a liver transplant were enrolled at 7 academic medical centers from July 2021 to March 2024. Itch numeric rating scale (NRS), 5-D Itch, PSC-PRO, and SF-36 were completed and serum collected at the time of enrollment. For the NRS, patients reported their average and worst itch (WI) in the past 24 hours, 7 days, and 6 months. Colitis activity was assessed in patients with inflammatory bowel disease (IBD) by the Simple Clinical Colitis Activity Index (P-SCCA). Total serum bile acids (TSBA), liver biochemistries, IL-31, and autotaxin were measured. Spearman rank correlation, general linear models, and area under the receiver operator curve were used to examine the relationships between the WI in the past 7 days (WI-NRS) and serum biomarkers.
Results: A total of 200 patients were enrolled (51% male; mean (SD) age of 44.6 (16.1) years; 71% White, 11% Black/African American; 15% cirrhosis). Most patients (77%) had large duct PSC while 4% had small duct PSC and 2% had PSC-AIH. IBD was present in 70% (50% ulcerative colitis/17% Crohn's disease/3% indeterminate). WI-NRS was reported as moderate or severe (WI-NRS 4–7 or 8–10, respectively) by 48 (24%). Alkaline phosphatase (ALP) ($r = 0.26$), GGT ($r = 0.18$), ALT ($r = 0.15$), AST ($r = 0.20$), total ($r = 0.25$) and direct bilirubin ($r = 0.26$), albumin ($r = -0.18$), total serum bile acids ($r = 0.21$), autotaxin ($r = 0.28$), and IL-31 ($r = 0.40$) all correlated with WI-NRS (all p-values <0.05). Among patients with IBD, P-SCCA also correlated with WI-NRS ($r = 0.41$, $p < 0.0001$). General linear modeling demonstrated that log AST (b = –3.2), log direct bilirubin (b = 1.4), log autotaxin (b = 1.9), and IL-31 (b = 0.6) independently associated with WI-NRS (all p-values <0.05). Among patients with IBD, log autotaxin (b = 4.0, p = 0.0006) and P-SCCA (b = 1.5, P = 0.002), but not IL-31 (b = 0.5, p = 0.15) remained independently associated with WI-NRS. The area under the receiver-operator curve (AUROC) for WI-NRS <4 vs ≥4 was 0.68 (0.57–0.78) for autotaxin and 0.67 (0.56–0.79) for IL-31. Combining autotaxin and IL-31 did not improve the AUROC [0.70 (0.60–0.80)].
Conclusion: Both autotaxin and IL-31 independently associated with pruritus severity in patients with PSC. However, only autotaxin remained an independent predictor of pruritus severity after adjusting for colitis activity in patients with concomitant IBD.
This study was supported by GSK (214524).

THU-293

Disparities in treatment response and liver decompensation by race and ethnicity in primary biliary cholangitis: results from the ELLA-PBC cohort

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Background and aims: Alkaline phosphatase (ALP) normalization predicts outcomes in primary biliary cholangitis (PBC). However, the impact of race, ethnicity, and insurance access on treatment response remains poorly understood. This study aims to evaluate disparities in treatment response, decompensation rates, and transplant-free survival (TFS) among racial/ethnic groups with PBC.
Method: The East Los Angeles Latinx PBC (ELLA-PBC) cohort includes predominantly Hispanic PBC patients presenting to Keck Medical Center of USC and Los Angeles General Medical Center (2006–2022). PBC was confirmed by Paris criteria. Patients with prior transplant were excluded. Kaplan-Meier 5-year TFS and cumulative incidence of progression to cirrhosis or decompensation were estimated. Complete biochemical remission (CBR; ≤1 × ULN) at 1-year post-ursodeoxycholic acid (UDCA) initiation was analyzed using logistic regression.
Results: Of 427 patients, 96 (22.5%) were White and 331 (77.5%) were non-White, including 282 Hispanic patients. Non-White patients were more often foreign-born (51.1% vs. 10.4%; $p < 0.001$) and underinsured (68.9% vs. 17.7%; $p < 0.001$). Over a median follow-up of 3.3 years, 88 patients underwent transplant or died. The 5-year TFS rates were similar for White (74.9%, 95% CI 61.7–84.1) versus non-White patients (77.1%, 95% CI 71.1–82.0; $p = 0.45$) and the Hispanic subgroup (76.1%, 95% CI 69.6–81.5; $p = 0.35$). Among patients compensated at baseline (N = 275), 51 experienced decompensation. The 5-year cumulative incidence of decompensation was higher in non-White (23.5%, 95% CI 17.4–31.3; $p = 0.20$) and Hispanic patients (25.5%, 95% CI 18.6–34.2; $p = 0.14$) versus White patients (16.4%, 95% CI 7.7–32.9). In UDCA-naïve patients (N = 158), baseline ALP levels were 231 U/L (IQR 128–565) in White, 275 (IQR 180–443; $p = 0.25$) in non-White, and 285 (IQR 193–464; $p = 0.21$) in Hispanic patients. At 1-year, CBR rates were 20.7% in White, 4.7% in non-White, and 4.3% in Hispanic patients, corresponding to a 78% and 77% lower response for non-White ($p < 0.001$) and Hispanic patients ($p = 0.001$) versus White patients. After adjusting for PBC-AIH variant and insurance status, CBR remained 65% lower in non-White ($p = 0.04$) and 55% lower in Hispanic patients ($p = 0.13$) compared to White patients.
Conclusion: Non-White and Hispanic UDCA-naïve patients with PBC had near 80% lower CBR rates at 1-year compared to White patients, with non-White differences persisting after adjusting for insurance status. Hispanic patients demonstrated a 10% higher decompensation rate compared to White patients, though not statistically significant potentially due to the smaller sample size of White patients. Given insurance status attenuated the effect of Hispanic ethnicity on CBR rates, more studies are needed to separate the effect of socioeconomic and healthcare-related disparities from race and ethnicity to improve equity in PBC outcomes.

THU-294

Change in pruritus in patients with primary biliary cholangitis and moderate-to-severe pruritus: a pooled analysis from the Response and Enhance studies

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Background and aims: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune, cholestatic liver disease. Pruritus may occur in up to 70% of patients (pts) with PBC during the course of disease and can greatly reduce quality of life. Seladelpar (SEL) is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as a monotherapy in pts unable to tolerate UDCA. In two Phase 3, placebo (PBO)-controlled trials (ENHANCE [NCT03602560] and RESPONSE [NCT04620733]), SEL significantly reduced pruritus among pts who had moderate to severe pruritus at baseline (defined as numerical rating scale [NRS] ≥4). Here, we present pooled pruritus outcomes across different measures of itch in pts with PBC from RESPONSE and ENHANCE with NRS ≥4 at baseline.
Method: Pts with PBC with an inadequate response/intolerance to UDCA were randomised 1:1:1 to daily SEL 5 mg, SEL 10 mg, or PBO for 52 weeks in ENHANCE and 2:1 to daily SEL 10 mg or PBO for 52 weeks in RESPONSE (ENHANCE terminated early with key endpoints amended to month [M] 3). Pooled data from pts with NRS ≥4 at baseline who received SEL 10 mg or PBO in RESPONSE and at least 6 months in ENHANCE were analysed. In a post-hoc analysis, changes across several measures of itch up to M6 (NRS, PBC-40 itch domain, and the 5-D itch scale) were assessed.
Results: Of the 126 pts with moderate to severe pruritus, 76 and 50 received SEL 10 mg and PBO, respectively, in RESPONSE or ENHANCE. Most pts at baseline were <50 years old at age of PBC diagnosis (73/126) and had a history of pruritus (122/126) and fatigue (77/126). NRS, PBC-40 itch domain, and 5-D itch scale scores were similar between the SEL and PBO groups at baseline. At M6, pts who received SEL experienced greater improvements in NRS scores (mean change from baseline of −3.12 vs −2.09 for SEL and PBO, respectively, p = 0.0004), PBC-40 itch domain scores (mean change from baseline of −2.26 vs −1.37 for SEL and PBO, respectively, p = 0.0227), 5-D itch total scores (mean change from baseline of −4.85 vs −2.30 for SEL and PBO, respectively, p < 0.0001), and 5-D itch degree domain scores (mean change from baseline of −0.96 vs −0.54 for SEL and PBO, respectively, p = 0.0005). The overall safety profiles in pts with pruritus in the SEL and PBO groups were similar in this pooled analysis. Adverse events occurred in 58/76 (76.3%) SEL and PBO 40/50 (80%) PBO patients.
Conclusion: In agreement with previous studies, this pooled analysis indicates that up to 6 months of SEL treatment reduced pruritus to a greater extent vs PBO in pts with PBC who had moderate to severe pruritus when assessed across 3 different measures of itch. SEL was well tolerated in this pt population.

THU-296

Evaluation of response to Ursodeoxycholic acid (UDCA) in a nationwide population with primary biliary cholangitis

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Background and aims: Alkaline phosphatase (ALP) and total bilirubin (TB) are usually evaluated after 1 year of ursodeoxycholic acid (UDCA) when add-on second-line therapy for patients with primary biliary cholangitis (PBC) is considered. Both biochemical parameters are also included in various biochemical response criteria, which have been associated with clinical outcome in predominantly tertiary cohorts. We aimed to assess ALP and TB after one year of UDCA and their relation to long-term clinical outcome in a large nationwide cohort.
Method: The retrospective Dutch PBC Cohort Study (DPCS) includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019–2023) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. Patients were included in case of available biochemistry after one year of UDCA monotherapy. Where needed and feasible, imputation was performed using joint model multiple imputation. Laboratory values are presented in upper limits of normal (ULN). Response rates at one year of UDCA and liver transplant (LT)-free survival (LTFS) were assessed according to ALP and TB cut-offs.
Results: In total, 3089 patients were included. At baseline, the median age was 57.7 (IQR 49.6–66.9) years, 2705 (87.6%) were female, 201 (6.5%) had cirrhosis, median ALP was 1.9 (IQR 1.3–3.2) and median TB was 0.5 (IQR 0.4–0.8). After one year of UDCA, the median ALP was 1.2 (IQR 0.9–1.6) and median TB was 0.5 (IQR 0.4–0.7). During a median follow-up duration of 8.3 years (IQR 4.0–13.5), 74 (2.4%) patients underwent LT and 522 (16.9%) died (all-cause mortality). In multivariable analyses, both log ALP (aHR 1.8 95% CI 1.5–2.1, p < 0.001) and log TB (aHR 3.0, 95% CI 2.5–3.6, p < 0.001) were associated with the hazard of LT or death. The cumulative 10-year LTFS was 77.4% (95% CI 73.2–81.8), 84.4% (95% CI 82.1–86.7), and

88.4% (95% CI 86.2–90.9) in those with ALP >2 (n = 489), ALP 1–2 (n = 1500) or ALP≤1 (n = 1056), respectively (p < 0.001). The 10-year LTFS was 56.8% (95% CI 50.5–63.9), 83.2% (95% CI 80.0–86.6), and 89.5% (95% CI 87.7–91.4) in those with TB >1 (n = 267), TB 0.6–1 (n = 694) or TB≤0.6 (n = 1811), respectively (p < 0.001). Patients with an ALP≤1.5 and normal TB at one year (1781/2758, 64.6%; of whom 95.2% also had an AST≤1.5) showed a 10-year LTFS of 88.7% (95% CI 86.8–90.6). Among the 642/2758 (23.3%) patients with ALP≤1.0 and a TB≤0.6 (deep response) the 10-year LTFS was 91.0% (95% CI 88.2–93.9).
Conclusion: In this nationwide cohort, including every patient with PBC from all Dutch treatment centers, ALP and TB after one year of UDCA were independently associated with clinical outcome. Almost a quarter of patients reach a deep response to UDCA alone, which was associated with the best LT-free survival.

THU-300
Long term efficacy, effectiveness and side effects of third line therapies in autoimmune hepatitis
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Background and aims: Evidence demonstrating the long-term efficacy and safety of third-line agents is limited. We aimed to evaluate the long-term outcomes of autoimmune hepatitis (AIH) patients treated with third-line agents.
Method: We conducted a retrospective review of 704 AIH patients treated at our tertiary liver centre between 1975 and May 2024. Patients who received third-line therapy for at least six months were included in the analysis. Clinical event-free survival was defined as the absence of ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, liver transplantation, or death.
Results: Of the 93 included patients, 74 (79.6%) were female, with a median age of 47 years (IQR 30–63.7). Twenty-seven percent of patients were cirrhotic at diagnosis. Ninety patients (96.8%) received steroid maintenance therapy (12% budesonide; 88% prednisolone). Sixty-six patients (71%) were treated with azathioprine (AZA); 46 discontinued due to side effects, 13 due to lack of efficacy, one achieved remission. Nine patients were treated with mercaptopurine (MP) (10.1%) as first/second line therapy; all of whom discontinued due to side effects. Twenty-eight percent of patients did not receive AZA or MP. Mycophenolate mofetil (MMF) was initiated in 68 patients (73.1%). MMF treatment was discontinued in nine patients due to side effects, seven for family planning, and three due to lack of efficacy. In one patient, MMF was switched to rituximab to treat co-existing vasculitis. Median follow-up time on MMF was 168 months (23.1–168). Tacrolimus (TAC) was used in 51 patients (54.8%); four discontinued treatment (in one patient due clinical trial enrolment, one due to HPV-related cervical intraepithelial neoplasia, one for inefficacy, and one due to cytopenia), with a median follow-up time of 59.4 months (14.2–62.8). Rituximab was administered to six patients (6.5%). Triple therapy was used in 18 patients (19.4%), most commonly a combination of TAC, steroids, and MMF, with a median treatment duration of 62.4 months (26.4–139.6). Median ALT levels improved from 149 U/L (49–312) pre-third line treatment to 32 U/L (21–47) at last visit. Median IgG levels decreased from 17.5 g/L (12.6–24.3) pre-third line treatment to 13.8 g/L (11.2–17.9) post-treatment. Median clinical event-free survival was 148.3 months (48–189.3) in patients treated with MMF (n = 42, including 14 not exposed to AZA), 53.5 months (18.5–85.2) in patients treated with TAC (n = 33, including 5 not exposed to AZA) and 59.7 months (22.2–119.1) in patients treated with triple therapy (n = 18).
Conclusion: In this single-centre cohort, primarily comprising difficult-to-treat AIH patients, third-line therapies demonstrated favourable long-term clinical outcomes with significant improvement in biochemical parameters, prolonged clinical event-free survival, and a good safety profile.

THU-301
Fibrates in primary sclerosing cholangitis: a multicenter retrospective observational study
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Background and aims: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease with no effective medical treatment. EASL Guidelines recommend bezafibrate as a first-line treatment for pruritus. Preliminary evidence from small patient cohorts has suggested that bezafibrate and fenofibrate may improve liver function tests (LFTs), and a randomized clinical trial is currently underway in France to validate this. Data on the safety of fibrates in PSC remains limited. This study aimed to evaluate the safety profile and impact of fenofibrate and bezafibrate on LFTs and liver stiffness measurements (LSM) in a multicenter cohort of PSC patients across Europe and the United States.
Method: Patients with a confirmed diagnosis of PSC who were treated with either bezafibrate or fenofibrate at university hospitals in Monza, Milan, Yale, Hamburg, and Oxford, with at least six months of follow-up, were retrospectively included. LFTs and LSM were evaluated at baseline and during follow-up. Safety was assessed based on treatment discontinuation rates and the occurrence of adverse clinical outcomes (liver-related death, liver transplantation).
Results: Seventy-two PSC patients were included: 40 (55.6%) received bezafibrate, 32 (44.4%) fenofibrate; 70 (97.3%) were already on ursodeoxycholic acid therapy. The median age at diagnosis was 30.5 years (IQR 23.8–45.3); 48 (66.7%) were male. Fifty-two (72.2%) had IBD, and 14 (9.4%) had a variant with autoimmune hepatitis. The primary indication for therapy was cholestasis (58.3%), pruritus (31.9%), or both (9.7%). Over a median follow-up of 20.1 months (IQR 12.1–43.8) ALP levels showed a significant median reduction of 42.9% at six months (IQR 12.1–54.2, p < 0.0001) and remained stable thereafter. ALP normalization was achieved by 30.0%, 32.6%, and 33.3% of patients at six, 12, and 24 months, respectively. No significant differences in ALP reduction over time were observed between bezafibrate and fenofibrate (p = 0.6262). Median LSM at baseline was 8.9 kPa [IQR 6.77, 11.45] and remained stable after 12 months (p > 0.05). Twenty patients (27.8%) discontinued treatment: 7 (35%) due to inefficacy (3 on pruritus, 3 on cholestasis improvement, 1 on both), 5 (25%) due to adverse events, 5 (25%) due to clinical outcomes, and 3 (15%) by personal choice or inclusion in clinical trials. Among them, 12 (60%) and 3 (15%) discontinued treatment after 6 and 12 months, respectively.
Conclusion: In PSC patients, fibrates demonstrated significant ALP reduction, with 30.0% of patients achieving normalization in 6 months with no difference between fenofibrates and bezafibrate.

LSM remained stable at 12 months. Safety was acceptable, with discontinuation driven mainly by inefficacy and in the first 6 months of treatment. Fibrates may be valuable for improving cholestasis in addition to pruritus in PSC, warranting further prospective studies.

THU-302

Impact of social determinants of health on outcome of autoimmune liver diseases: insights from the european reference network on hepatological diseases (ERN RARE-LIVER)

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Background and aims: Social Determinants of Health (SDOH) are conditions in which people grow, work, and age. Studies highlight the influence of SDOH on the development and progression of various chronic diseases. However, little is known about the influence of SDOH on autoimmune liver disease (AILD). We aim to explore the relation between SDOH and quality of care, treatment and outcome parameters of AILD.

Method: An international multicentre cross-sectional questionnaire is distributed among adults with AILD between October 2024 and January 2025. The questionnaire covers well-established instruments evaluating SDOH as defined by the World Health Organization, including sociodemographics, income, education, work environment, food insecurity, housing, early childhood development, social support and access to health services. As outcome variables, parameters of treatment and disease progression were assessed. The questionnaire was revised by patient representatives of ERN RARE-LIVER. Data collection will be completed by January 2025. Regression models will be employed to analyze the association between SDOH and AILD.

Results: After 7 weeks of data acquisition, 957 patients from 15 European countries answered the questionnaire. 176 (19%) of the patients had primary sclerosing cholangitis, 309 (33%) had autoimmune hepatitis, 380 (40%) had primary biliary cholangitis, and 81 (9%) had variant syndromes. 741 (77%) were female, and most were between 50 and 60 years old. Overall, 95 (11%) participants screened positive for food insecurity. Of those, 60 (63%) and 33 (33%) reported additional expenses for liver medication and additional private health insurance, respectively. In total, 141 (16%) individuals reported having liver cirrhosis. The prevalence of cirrhosis was 29% (25/89) among those who primarily spoke a non-native language at home, and 14% (116/798) among those who spoke the dominant language of their country ($p = 0.001$).

Conclusion: This interim analysis highlights the high prevalence of food insecurity and out-of-pocket expenses for liver-related healthcare among patients with AILD and suggests significant negative health outcomes in individuals facing language barriers. These findings emphasize the necessity to address SDOH in clinical practice to reduce health inequities and improve clinical outcomes in AILD care.

THU-303-YI

Prevalence and impact of extrahepatic autoimmune disease in patients with primary biliary cholangitis

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Background and aims: Primary Biliary Cholangitis (PBC) is associated with several extrahepatic autoimmune diseases (EHAID), but reliable prevalence estimates are scarce. We aimed to assess the occurrence and impact of EHAID in a nation-wide population with PBC.

Method: The retrospective Dutch PBC Cohort Study (DPCS) includes every identifiable patient with PBC in the Netherlands from 1990 up to last data collection (2019–2023) in all 71 Dutch hospitals. Clinical data were obtained through medical chart review. Logistic regression and survival analyses were used to assess whether EHAID is associated with biochemical response and liver transplant-free survival among patients who were treated with ursodeoxycholic acid (UDCA) alone. Multivariate analyses were adjusted for age at diagnosis, cirrhosis at baseline, use of immunosuppressive drugs, sex, year of diagnosis and biochemical parameters.

Results: In total, 4293 patients were included of whom 1239 (28.8%) were diagnosed with EHAID during the course of disease, 138 (3.2%) patients underwent LT and 806 (18.8%) patients died during a median follow-up of 8.3 years (IQR 3.7–14.3). Hypothyroidism was the most

prevalent EHAID 428/1239 (34.5%), followed by Sjögren's Syndrome 217/1239 (17.5%). EHAID was already present at baseline in 932/1239 (75.2%) patients. Patients with EHAID at baseline were more frequently female (91.6% vs 87.0%, p < 0.001) and had cirrhosis less frequently (5.5% vs 7.3%, p = 0.046) as compared to those without EHAID, while median age (56.7 years, IQR 49.0–66.7 vs 56.8 years, IQR 48.3–66.4, p = 0.548), median ALP (1.83×ULN, IQR 1.27–2.99 vs 1.94×ULN, IQR 1.31–3.23, p = 0.202) and median AST (1.52×ULN, IQR 1.03–2.26 vs 1.53×ULN, IQR 1.06–2.33, p = 0.682) were similar. After one year on UDCA alone, the PARIS-II response rate was 391/595 (65.7%) among patients with baseline EHAID vs 1329/2265 (58.7%) in those without EHAID (p = 0.002), but EHAID was not independently associated with the UDCA response (PARIS-II) (aOR 0.93, 95CI% 0.72–1.20, p = 0.564). Among 3243 patients with at least 6 months follow-up, the 10-year LT-free survival was 85.7% (95% CI 82.2–88.9) in those with EHAID at baseline vs 85.5% (95% CI 83.9–87.1) in those without (p = 0.758). This absent association between EHAID and long-term clinical outcome remained in multivariable Cox regression analysis (aHR 1.08, 95%CI 0.84–1.39, p = 0.554).

Conclusion: In this nationwide cohort, almost 30% of patients with PBC are affected by extrahepatic autoimmune diseases (EHAID), which are observed more frequently in females. At PBC diagnosis, cirrhosis was less common in patients with EHAID, suggesting EHAID may contribute to earlier diagnosis. Presence of EHAID was not related to the biochemical response to UDCA or the long-term clinical outcome of PBC.

THU-304-YI

Non-invasive prediction of clinically significant portal hypertension in patients with compensated advanced primary biliary cholangitis

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Background and aims: Primary biliary cholangitis (PBC) is a progressive cholestatic disease that can lead to portal hypertension. PBC patients with compensated advanced chronic liver disease (cACLD), defined according to the Baveno VI criteria based on a liver stiffness measurement (LSM) ≥10 kPa, are at risk of developing clinically significant portal hypertension (CSPH). Identifying cACLD patients with CSPH is essential for implementing therapeutic strategies. We aimed to non-invasively stratify the CSPH risk in PBC patients with cACLD using the Baveno VII criteria, also implementing spleen stiffness measurement (SSM), and the NICER model (PMID 39326431).

Method: Multicentric study including 88 PBC patients with cACLD from 5 tertiary centres for liver diseases (Novara, Milan, Palermo, Istanbul, Vienna) who underwent vibration-controlled transient elastography (VCTE)-based LSM and SSM. The Baveno VII criteria were applied, along with the single SSM cut-off (≤40 kPa vs. >40 kPa) and the dual SSM cut-offs (≤25 kPa and SSM ≥55 kPa). The NICER model was computed as published: Logit = –6.40032480 + ln(SSM) × 1.96952565 + ln(LSM) × 1.83093447 – BMI × 0.12882190 – platelets (PLT) × 0.01850461. Esophagogastroduodenoscopy (EGD) was performed per Baveno VI recommendations and proposed to all patients with SSM > 40 kPa.

Results: Among the 88 PBC patients, 72 (82%) were women, 79 (90%) on ursodesoxycholic acid monotherapy, median age was 65 (IQR 55–74) years, median BMI 25.1 (IQR 23.1–26.9) kg/m2, median disease duration 3.4 (IQR 1.3–10.3) years, median ALP 1.3 (IQR 1.0–2.3) × ULN, median total bilirubin 0.7 (IQR 0.5–1.1) mg/dL, median LSM 17.3 kPa (IQR 11.9–35.8), median SSM 51.5 kPa (IQR 32.8–68.7). Thirty-seven (51%) out of the 73 patients with available EGD had oesophageal varices, of which 15 (20%) had high-risk oesophageal varices. Applying the Baveno VII criteria: CSPH was ruled-out in 30 (34%) and ruled-in in 29 (33%) patients, while 29 (33%) remained in the grey zone. Using the Baveno VII-SSM criteria with a single cut-off: 38 (43%) patients were at low risk for CSPH, 44 (50%) at high risk, 6 (7%) in the grey zone. Using the Baveno VII-SSM with dual cut-offs: 31 (35%) patients were classified as low risk, 36 (41%) as high risk, and 21 (24%) in the grey zone. Based on the NICER model, CSPH risk distribution was: <25% 36 patients (41%), > 75% 48 patients (54%). Among the 73 patients who underwent EGD, esophageal varices were found in 1 (1%) of patients with a CSPH risk <25% and in 34 (46%) of patients with a CSPH risk > 75% (p < 0.001).

Conclusion: The addition of SSM to the Baveno VII criteria reduces the diagnostic grey zone in PBC patients with cACLD, particularly using the single-SSM cut-off at > 40 kPa. The SSM-containing NICER model provides valuable and accurate non-invasive CSPH risk assessment information also in PBC patients.

THU-305

Quantitative morphometric analysis via artificial intelligence-driven image analysis in autoimmune hepatitis: a multi-center study

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Background and aims: Clinical-pathological correlations in autoimmune hepatitis (AIH) remain challenging due to significant variability in clinical and pathological presentations and diverse subtypes. This study employed computer vision on digital slides to derive quantitative morphometric parameters, aiming to improve diagnostic accuracy and strengthen correlations with clinical markers.

Method: Clinical data and hematoxylin and eosin (H&E)-stained histological slides from diagnosis were collected from two Italian and one German tertiary referral centers. Images were processed with tissue and portal tract segmentation, and a nucleus classifier to differentiate hepatocytes and inflammatory cells. For each case, ten morphometric parameters, six classical histological metrics (mhAI and Ishak fibrosis scores), and over fifty clinical parameters were analyzed.
Results: The study includes a cohort of 128 patients with confirmed AIH; mean age at diagnosis was 54 ± 17 years, with 66% females. After feature selection, the following morphometric parameters were prioritized for clinico-pathological correlations: 'inflammatory cell-to-hepatocyte ratio', 'mean distance between inflammatory cells', 'functional liver area' and 'cell density in portal tracts'. The 'inflammatory cell-to-hepatocyte ratio' in the lobule ($p < 0.01$) and the 'mean distance between inflammatory cells' ($p < 0.01$) showed strong correlations with mhAI score. When compared to traditional histological mHAI and Ishak Fibrosis scores, morphometric parameters demonstrated stronger correlations with AST and ALT levels in multiple linear regression. Patients with higher values of AST and ALT at diagnosis showed significantly higher values of 'inflammatory cell-to-hepatocyte ratio' ($p < 0.001$) and lower values of 'mean distance between inflammatory cells' ($p = 0.02$). The 'functional liver area' and 'cell density in portal tracts' were higher in patients with lower platelets ($p < 0.01$ and $p = 0.01$, respectively).
Conclusion: Artificial intelligence-driven image analysis enables more reproducible quantification of histological parameters and enhances the correlation with clinical findings, complementing existing semi-quantitative scoring systems.

THU-306
Efficacy and safety of odevixibat in adult patients with progressive familial intrahepatic cholestasis: results from the 72-week PEDFIC2 phase III, open-label study

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Background and aims: Long-term treatment with odevixibat (ODX) was well tolerated and led to sustained and clinically meaningful improvements in pruritus, as well as reductions in serum bile acid (sBA) levels in patients of any age across progressive familial intrahepatic cholestasis (PFIC) types in the PEDFIC 2 study (NCT03659916) [1]. We conducted an analysis focusing on patients > 18 years of age to further characterize the clinical benefit of long-term ODX therapy in adults with any PFIC type.
Method: PEDFIC 2 included enrolment of patients of any age and PFIC type. Patients received ODX 40 µg/kg/day or 120 µg/kg/day. Efficacy endpoints: change from baseline (BL) in sBA to last assessment; sBA response (≤70 µmol/L or reduced ≥70% from BL) at Week 72; and patient-reported pruritus response (scratching score ≤1 or ≥1-point drop in pruritus score from baseline to a given time point). Long-term safety was evaluated throughout the study.
Results: 7 adult patients received ODX in PEDFIC 2 (120 µg/kg/day, n = 6; 40 µg/kg/day, n = 1) with 5 completing 72 weeks treatment (median treatment duration: 84 weeks [range, 24–119 weeks]). Ages ranged from 18 to 26 years at BL; 3/7 patients had FIC1 deficiency, 2/7 had BSEP deficiency, and 2/7 had episodic cholestasis. At last assessment, 5/5 patients (FIC1 deficiency, n = 3) and BSEP deficiency, n = 2) had reductions in sBA with ODX. At Week 72, sBA response was reported in 2/5 patients (FIC1 deficiency, n = 1 and episodic cholestasis, n = 1). 3/5 patients (FIC1 deficiency, n = 2) and BSEP deficiency, n = 1) achieved a pruritus response with ODX (BL itching score: 3 vs ≤1 at last assessment); in 2/5 patients itching score was similar to BL at the last assessment. 2 patients with episodic cholestasis had low sBA and minimal pruritus at BL; neither patient reported a symptom flare during treatment with ODX (treatment exposure: 14 and 20 months, respectively). Patient level data will be presented at the congress. 5/7 patients transitioned to commercial product, 1 patient withdrew consent to participate after 6 months of treatment, and 1 patient was lost to follow-up. Most treatment-emergent adverse events were mild/moderate in severity and assessed as unrelated to ODX; most common was diarrhea (n/N = 3/7) and vitamin D deficiency (n/N = 3/7). 2/7 patients had mild GI disturbances considered possibly/probably related to ODX and 3/7 patients had serious AEs (SAEs), i.e., streptococcal septic arthritis, gastroenteritis-induced dehydration, and acute pancreatitis. All SAEs were assessed as unrelated to ODX.
Conclusion: Clinically meaningful improvements in pruritus and reductions in sBA were achieved with long-term ODX in adults with PFIC. Although based on a small sample size, present data indicate the efficacy and safety profile of ODX in adults with PFIC is consistent with previous results and that additional clinical investigation in this population is warranted.

Reference

Thompson RJ, *et al.* AASLD 2024. Abstract 5045 (Poster).

THU-307
Analysis of histopathological diagnosis and clinical diagnosis of 1,752 patients undergoing liver biopsy

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Background and aims: To investigate the histopathological diagnosis, clinicopathological features and etiological components of liver biopsy, and to provide guiding value for clinical diagnosis and treatment.
Method: The clinicopathological data of 1,752 patients who underwent liver biopsy in Ningbo No. 2 Hospital from January 2015 to December 2023 were included in this study. The consistency of demographic traits, clinical diagnosis, pathological diagnosis, and the severity of liver histopathology were analyzed.
Results: Among the 1,752 patients, 1,589 (90.70%) had a definite diagnosis of the disease, and the top three were hepatitis B virus (HBV) infection (45.04%), metabolic dysfunction-associated steatotic liver disease (MASLD) (12.61%), autoimmune liver diseases (11.64%), and 163 cases (9.30%) without a clear disease diagnosis, involving 22 diseases. Multiple liver illnesses were present concurrently, such as autoimmune liver disease and drug-induced liver damage (DILI), autoimmune liver disease and MASLD, HBV infection and MASLD, etc. and with HBV infection combined with MASLD being the most predominant (67.14%). Hepatic occupations were mainly liver primary or metastatic malignant tumors of the liver (3.82%). The patients with HBV infection, concomitant combination of two or more liver diseases, and liver primary or metastatic malignant tumors were mainly males, while the patients with MASLD, autoimmune liver disease, DILI, and undiagnosed diseases were mainly females, and the composition was statistically significant ($P < 0.001$), and the statistical differences between the two were significant ($P < 0.05$). There was a significant statistically significant difference in age

between the groups ($P < 0.001$), with the lowest age of patients with HBV infection and the highest age of patients with primary or metastatic hepatic malignancies. Except for 2017, the composition of diseases was dominated by HBV infection until 2021, whereas the composition ratio of non-infectious liver diseases showed a yearly increasing trend from 2022 onwards, reaching 96.82% in 2023 (especially for MASLD, which reached 44.09%). The autoimmune liver disease group had the most severe hepatic pathological damage, including the mean Ridit value of liver inflammation grade and fibrosis stage, and the composition ratio of significant hepatic inflammation (≥G2)/significant hepatic fibrosis (≥S2)/cirrhosis (S4), especially in patients with autoimmune hepatitis-primary biliary cholangitis overlap syndrome.

Conclusion: The etiology and clinicopathological features of liver diseases are highly heterogeneous, and the demand for liver pathology caused by HBV infection is gradually decreasing, while liver pathological diagnosis is necessary for non-infectious liver diseases, especially autoimmune liver diseases.

THU-308-YI

Long-term evaluation of controlled attenuation parameter for steatosis monitoring in autoimmune hepatitis

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Background and aims: The controlled attenuation parameter (CAP) has demonstrated usefulness in detecting steatosis in individuals with autoimmune hepatitis (AIH), but its role in long-term monitoring of these patients remains unclear. The aims of this study were: 1) to evaluate the utility of CAP for detecting steatosis during follow-up; 2) to identify predictive factors for steatosis development; and 3) to assess the effects of corticosteroids (CS) and metabolic comorbidities on steatosis progression in AIH patients.

Method: This was a retrospective, multicenter study that included 293 patients with biopsy-confirmed AIH who had undergone at least one CAP measurement. Patients with concomitant liver diseases or AIH variants were excluded. A CAP threshold of 275 dB/m was used to confirm the presence of steatosis. To assess longitudinal changes in CAP during follow-up, a mixed-effects model for repeated measures (MMRM) was applied. Predictive factors for cirrhosis development, as well as event-free survival (EFS) related to decompensation, death, or transplantation, were also analyzed.

Results: The cohort consisted mainly of women (n = 206, 70%), with a median age of 55 years (IQR: 42–64). At the time of AIH diagnosis, 64 patients (22%) had dyslipidemia, 33 (11%) had diabetes mellitus (DM), and 27 (9%) had a body mass index (BMI) ≥30 kg/m². Sixty patients (20%) had steatosis as identified by liver biopsy and/or abdominal ultrasound at baseline, and 73% of these met the criteria for metabolic-associated steatotic liver disease (MASLD). Among those with steatosis, there was a higher prevalence of DM (23% vs. 9%, p = 0.004) and a higher BMI (30 vs. 25 kg/m², p < 0.01). Of the 234 patients without steatosis at baseline, 31 (14%) developed steatosis (CAP ≥275 dB/m) after a median follow-up of 9 years (IQR 6–13). These patients had a higher CAP value (242 vs. 205 dB/m, p <0.01) at the first transient elastography (TE) performed at a median of 24 months (IQR 5–71), and there was a significant increase in CAP values during follow-up, as determined by MMRM ($F_{(1, 208)} = 58.44$, $p < 0.01$). BMI (OR 1.54, p = 0.05) and CAP value (OR 1.01, p < 0.01) at the time of the first TE were significant predictors of steatosis development. The initial dose and duration of CS treatment were not correlated with BMI and were not linked to an increased risk of steatosis. The presence of steatosis, DM, or MASLD at diagnosis or during follow-up did not correlate with poorer treatment response or an increased risk of cirrhosis development. The low number of events in this cohort prevented further evaluation of the impact of steatosis on EFS.

Conclusion: CAP is a valuable tool for detecting steatosis in AIH. Corticosteroid dose, treatment duration, and metabolic comorbidities did not contribute to the development of steatosis. Elevated BMI and CAP emerged as the most significant predictors of steatosis development in AIH patients during follow-up.

THU-309-YI

Liver steatosis prevalence in primary sclerosing cholangitis

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Background and aims: The rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), driven by the obesity epidemic, has made its co-occurrence with other primary liver diseases increasingly common. Primary sclerosing cholangitis (PSC) is a rare immune-mediated cholestatic liver disease, and there is a gap in research aiming to evaluate the prevalence and impact of liver steatosis in PSC. We aimed to evaluate the prevalence of liver steatosis in patients with PSC using controlled attenuation parameter (CAP) measurements, acquired during transient elastography.

Method: Patients with PSC were enrolled from an ongoing multicenter phase III study of simvastatin (PiSCATIN). Clinical, laboratory, liver MRI data, CAP and liver stiffness measurement (LSM) values (Fibroscan, Echosens, Paris, France) were collected at baseline. Liver steatosis was defined by a median CAP value of ≥254 dB/m, as validated by Steinman et al. in their study on CAP accuracy for detecting steatosis in autoimmune liver diseases. Baseline characteristics were compared between non-steatotic and steatotic patient groups using frequencies or median and IQR. The association between CAP values and these parameters was assessed with uni- and multivariable linear regression models. A 2-tail significance level of p < 0.05 was chosen.

Results: A total of 220 patients with valid CAP values were included, 153 (69.5%) males. The median CAP was 227 dB/m (IQR 80) with a point prevalence of liver steatosis (CAP ≥254 dB/m) of 29% (95% CI 23–35). Patients' age, sex, PSC type or duration did not differ significantly between steatotic and non-steatotic groups. In both groups the prevalence of IBD was 80%, IBD duration did not differ significantly. Median body mass index (BMI) was 24.1 kg/m² (IQR 5.3) in the non-steatotic group and 27.8 kg/m² (IQR 5.8) in the steatotic group, with fewer lean individuals (BMI <25) in the steatotic group (17% vs. 55%, $p < 0.05$). Cholesterol and triglyceride levels were higher ($p < 0.05$) in steatotic group, with medians of 5.5 mmol/L (IQR 1.25) and 1.2 mmol/L (IQR 0.7), compared to 5 mmol/L (IQR 1.6) and 0.9 mmol/L (IQR 0.45) in the non-steatotic group. The median LSM value was 6.9 kPa (IQR 5.3), with no significant association between CAP and LSM values ($p > 0.05$). Multivariable linear regression showed BMI, triglycerides, and diabetes independently associated with CAP ($p < 0.05$), but no significant association was found between CAP and MRI findings of advanced liver disease (e.g., liver deformity, ascites, spleen enlargement, and varices).
Conclusion: Although the potential importance of steatosis in PSC prognosis is yet to be determined, the prevalence of liver steatosis in patients with PSC was within the range expected in the general population. Higher BMI and plasma triglyceride levels, but not a more advanced disease stage, are associated significantly with higher CAP values.

THU-310

Pruritus is not a clinical feature of early-onset primary sclerosing cholangitis during late teenage years

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Background and aims: Primary sclerosing cholangitis (PSC) is a rare chronic liver disease which can present at any age, including during childhood, adolescence and early adulthood. Earlier age at diagnosis of PSC is often initially associated with overlapping autoimmune features and patients can develop a dominant biliary phenotype over time, although the natural history and symptom burden of subgroup is not well characterized. There are no licensed treatments for PSC, and in the United Kingdom the currently accessible clinical trial is for patients with PSC and severe pruritus. We sought to describe the prevalence of pruritus in early-onset PSC, and factors associated with pruritus.
Method: This was a single centre retrospective study of patients with PSC who attended our clinical service over a 1-year period. We included patients with PSC aged 16–28 years, and excluded patients who did not attend or who had undergone liver transplantation. We collected variables including demographics, clinical parameters, presence of pruritus, and blood tests.
Results: We identified 107 patients with PSC. There were 58 males (54.2%) and median age at appointment was 23.2 years (IQR, 20.2–25.8). The median age at diagnosis was 13.9 years (IQR, 10.4–17.3), and 78 (72.9%) had overlapping autoimmune features. Ursodeoxycholic acid (UDCA) was used in 71 (66.4%). Current pruritus was noted in 19 (17.8%) of the cohort: 2 (1.9%) were on rifampicin for pruritus, 1 (0.9%) was on a clinical trial for pruritus, no patients were on bezafibrate. Pruritus was reported in 0/13 patients aged 16–18, 8/48 (16.7%) aged 19–23, and 11/46 (23.9%) aged 24–28. Pruritus was more common in males (27.6% v 6.1%, $p = 0.004$) and in patients without overlapping autoimmune features (34.5% v 11.5%, $p = 0.006$). In patients with pruritus there was a trend towards older age at diagnosis (15.2 v 13.9 years, $p = 0.09$) and current age (24.8 v 23.1 years, $p = 0.08$). They had higher alkaline phosphatase (488 v 102, $p < 0.001$) and gamma glutamyl transferase (426 v 57, $p < 0.001$), but there was no difference in platelet count (261 v 277, $p = 0.73$).
Conclusion: In our cohort of patients with early-onset PSC, pruritus was not a significant symptom in patients in their late teenage years, but was more common during early adulthood. Pruritus was associated with biochemical markers of biliary damage, suggesting it develops in more advanced stages of cholangiopathy. Further work is required to fully characterize this subgroup of patients, and to discover therapeutic options to ideally prevent progressive cholangiopathy.

THU-311-YI

Uncovering novel therapeutic targets for autoimmune hepatitis (AIH): detection via omics integration and validation in proof-of-concept clinical trial

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Background and aims: Standard immunosuppression for autoimmune hepatitis (AIH) is non-specific with corticosteroids as drug of choice for remission induction. An improved understanding of the underlying pathophysiology is needed and could enable a tailored therapeutic approach and avoid side effects associated with standard therapy. This study aims to provide insight into the inflammatory network by identifying key players and their interactions as well as to evaluate them in the clinical context of AIH.
Method: Liver biopsies from patients with AIH and PBC were analyzed by mRNA sequencing. Transaminase levels and histological features were correlated with gene expression. Key immune contributors of this inflammatory signature within AIH were further characterized by single cell and spatial sequencing. Functional validation was performed using ex vivo cytotoxicity assays. Results were further evaluated in the clinical context as part of a phase II, proof-of-concept trial, assessing the effect of infliximab, a monoclonal antibody targeting TNF, in patients with previously untreated AIH.
Results: In livers of patients with AIH, activated transcription factor modules such as NFKB1/STAT1, along with pathways like TNF, exhibit differential expression and correlate with transaminase levels and histological inflammation. Computational and functional analyses reveal that IL-15, produced by dendritic cells and macrophages, enhances the cytotoxic potential of liver-resident CD8+ T cells. This cytotoxic pathway is fully activated by TNF, secreted by clonally expanded tissue-resident CD4+ T cells. In AIH, hepatocytes increase the expression of adhesion molecules for CD8+ T cells and MHC class II molecules in response to TNF, rendering them vulnerable to damage from both CD8+ and CD4+ T cells, thereby sustaining the inflammatory cycle. Steroid-free blockade of TNF using infliximab in patients with previously untreated AIH markedly reduces serum ALT levels and liver stiffness, indicating an amelioration of the inflammatory activity in vivo.
Conclusion: This study provides a comprehensive and unique insight into the cellular and molecular basis of AIH pathogenesis. Targeting TNF, one of the key players identified, is a feasible therapeutic

alternative to corticosteroid-based standard therapy in patients with untreated AIH.

THU-312

Clinical outcomes of primary sclerosing cholangitis associated with inflammatory bowel disease after liver transplantation: a systematic review and meta-analysis

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Background and aims: Primary sclerosing cholangitis (PSC) can recur after liver transplantation (LT), and its association with inflammatory bowel disease (IBD) adds complexity to clinical outcomes, given the variable course of IBD post-LT. This study aims to comprehensively estimate the incidence rates (IR) of key outcomes in PSC-IBD patients following LT, including recurrent PSC (rPSC), colorectal cancer (CRC) or high-grade dysplasia (HGD), bowel surgeries, IBD exacerbations, and newly diagnosed IBD.
Method: Online databases were searched from January 2000 till October 2024 for studies reporting on patients who underwent LT for PSC with IBD diagnosed either before or after LT. The pooled IR were calculated with the "meta" package (R Studio [V.4.2.764]) using a random effects model.
Results: Of 4,381 studies initially identified, 80 underwent full-text review, and 27 retrospective cohort studies were included in the meta-analysis. These cohorts reported on 3,425 patients underwent LT for PSC, of whom 65% had concomitant IBD at the time of LT. The mean follow-up period across studies ranged widely from 3 years to 17 years. The recurrence rate of PSC in PSC-IBD patients, based on data from 18 studies, was 30.8 cases per 1,000 person-years (95% CI 23.4–38.2), compared to 23.8 cases per 1,000 person-years (95% CI 8.6–39.1) in PSC-only patients from 7 studies. Though the recurrence rate was higher in PSC-IBD patients, the difference was not statistically significant ($p = 0.42$). A pooled analysis of 12 studies reporting on colorectal neoplasia in PSC-IBD patients post LT reported an overall IR of CRC/HGD of 6.1 cases per 1,000 person-years (95% CI 3.7–8.4). The rate of IBD clinical exacerbation, defined as worsening of IBD symptoms, increased inflammatory activity at endoscopy, or required optimization of IBD treatment post-transplantation, was 35.8 cases per 1,000 person-years (95% CI 22.7–48.9), though heterogeneity was high ($I^2 = 80\%$). The overall bowel surgery rate post-LT was 19.5 cases per 1,000 person-years (95% CI 16.1–22.9) within 17 studies. Additionally, 12 studies reported on newly diagnosed IBD in PSC patients without pre-existing IBD at LT, with pooled IR of 16.7 cases per 1,000 person-years (95% CI 10.4–22.9).
Conclusion: This meta-analysis reveals that the IR of rPSC is considerable among PSC patients with and without concomitant IBD. In patients with PSC-IBD, strict endoscopic surveillance post LT is indicated to mitigate the risk of CRC/HGD. Furthermore, PSC-only patients remain at risk of developing IBD after LT. These findings underscore the need for a tailored follow-up strategy involving both hepatologists and gastroenterologists to optimize care for PSC patients post-transplantation.

THU-313

Treatment with elafibranor has no impact on bone health in patients with primary biliary cholangitis

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Background and aims: Patients (pts) with primary biliary cholangitis (PBC), a rare, cholestatic liver disease, have a higher risk of osteoporosis and fractures. Risk of fracture is noted for peroxisome proliferator-activated receptor agonists. We present bone mineral density (BMD) and bone serum biomarkers assessed to Week (Wk) 52 in the phase III ELATIVE® trial.
Method: In ELATIVE® (NCT04526665), 161 pts with PBC were randomised 2:1 to elafibranor 80 mg or placebo. The frequency of bone fractures was assessed. BMD was assessed by dual energy X-ray absorptiometry (DEXA) scan for the femoral neck, lumbar spine and total hip regions, reported as T scores. Bone turnover was assessed via two serum biomarkers: carboxy terminal crosslinked telopeptides of type 1 collagen (CTX), a marker of bone resorption, and type 1 procollagen peptide (P1NP), a marker of bone formation. Changes from baseline (CfB) in BMD T scores and CTX and P1NP levels were assessed to Wk 52.
Results: In total, 63, 64 and 59 pts receiving elafibranor and 27, 26 and 24 pts receiving placebo had baseline and Wk 52 BMD T scores for the femoral neck, lumbar and total hip regions, respectively. Distribution of BMD T scores at baseline suggested osteopenia and osteoporosis in both groups, particularly in patients who received elafibranor. Imbalances were also seen in the underlying medical history for osteoporosis (elafibranor: 19.4%; placebo: 3.8%) and osteopenia (elafibranor: 19.4%; placebo: 17.0%) for the overall trial population. No significant differences were seen in CfB of mean BMD T scores in the femoral neck and lumbar spine regions. A significant difference in CfB of BMD T scores in the total hip regions was seen between the elafibranor and placebo groups (Least Square [LS] means: elafibranor: 0.020; placebo: −0.305 $p = 0.0186$). Overall, 81 pts receiving elafibranor and 32 pts receiving placebo had baseline and Wk 52 CTX and P1NP data. An increase in CTX and a decrease in P1NP was observed in both groups; no meaningful between-group differences were reported for either marker. The increase in CTX in the elafibranor group was numerically smaller than in the placebo group (LS means difference vs placebo: −11.0 pg/mL [95% confidence interval (CI): −91.3; 69.3]; $p = 0.787$). The decrease in P1NP in the elafibranor group was numerically smaller than in the placebo group (LS means difference vs placebo: 3.5 µg/L [95% CI: −6.7; 13.7]; $p = 0.495$). Seven (6.4%) pts receiving elafibranor and no patients receiving placebo had bone fractures. Six of the pts with bone fractures had an associated accidental fall and all pts had a confounding medical history.
Conclusion: Biomarkers of bone turnover and rates of fractures in patients with PBC receiving elafibranor or placebo suggest that elafibranor has no negative impact on bone health. Elafibranor's efficacy and safety profile favours its use in the treatment of PBC.

THU-314

The Mayo-risk model predicts postsurgical transplant-free survival in patients with Primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a devastating chronic liver disease. The pathogenesis is not fully understood and considered to be multifactorial. The Mayo-Risk Score (MRS) and Amsterdam-Oxford Score (AOS) have been established to estimate progression and outcome. Due to chronic inflammation in bile ducts and high prevalence of inflammatory bowel disease in PSC patients, risk of tumor development is high. Thus, surgery is often indicated in these patients. However, data on surgical risk and postsurgical outcomes with associated predictors are scarce.
Methods: In this single-cohort, retrospective study, 257 consecutive patients from 2004 to 2023 with PSC, treated in a specialized tertiary center for autoimmune liver diseases, were screened. 72 patients were identified that underwent a non-transplantation, surgical procedure. The time of index surgery was defined as baseline. Detailed data on surgery type, postoperative complications and follow-up were recorded. Primary endpoint was transplant-free survival. Predictors for outcome were assessed using cox regression. The whole cohort of 257 patients was then stratified in two propensity matched cohorts at the time of first diagnosis of PSC at our center; a cohort undergoing non-transplantation surgery at any time at follow-up within 5 years vs. a cohort without. Survival analysis was performed between the two cohorts.
Results: 72 patients were included into the analysis, 27 with liver cirrhosis. IBD was present in 80%. Most patients (82%) were treated with ursodeoxycholic acid. 60% received visceral procedures, with partial hepatectomies and cholecystectomies as predominant surgery types, followed by IBD associated surgery. Regression analysis revealed that cirrhosis was a strong predictor for postsurgical 1-year TFS. AOS (HR 3.59; 95% CI 1.88–6.87; $p \leq 0.001$) and MRS (HR 2.04; 95% CI 1.49–2.87, $p \leq 0.001$) were strongly associated to postsurgical TFS with excellent AUC in ROC-analysis (AOS: AUC 0.821 and MRS 0.896; $p \leq 0.001$ respectively) with MRS performing superior to AOS and MELD (AUC 0.824, $p \leq 0.001$). In the propensity matched cohorts, non-cirrhotic patients undergoing surgery at any timepoint within 5 years of first diagnosis did not have impaired survival vs. non-cirrhotic patients with no surgery at follow-up.
Conclusion: Cirrhosis is a strong predictor for postsurgical 1-year TFS in patients with PSC. Predictive scores in the context of PSC (MRS/AOS) excellently performed in predicting 1-year TFS, with the MRS performing superior to AOS and MELD. The use of MRS/AOS may be considered as predictors for preoperative risk stratification. If non-cirrhotic, patients with PSC receiving surgery seem not to have an impaired survival compared to PSC patients without any surgical procedure within 5 years.

THU-315

Misclassification of UDCA treatment response in patients with primary biliary cholangitis (PBC) in the real-life setting

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Background and aims: In patients with primary biliary cholangitis (PBC) ursodeoxycholic acid (UDCA) treatment response is classified after 12 months by Paris II criteria (alkaline phosphatase (ALP) and aspartate-aminotransferase (AST) ≤1.5× upper limit of normal (ULN), with bilirubin <1 mg/dL). The German PBC registry recruited patients into sub-groups of UDCA adequate and inadequate Paris II responders. We analyzed how frequently clinical judgement and Paris II criteria aligned and how many cases were misclassified.
Method: Clinical judgement of UDCA treatment response was compared to formal assessment of Paris II criteria. Differences were tested by Fisher's Exact or Mann-Whitney U tests.
Results: Clinical judgement and formal definition differed in 48/383 (12.5%) cases: 4/130 (3.1%) were falsely classified as inadequate UDCA responders, 44/253 (17.4%) as adequate although being inadequate responders with ALP or AST levels > 1.5 × ULN in 57% and 23%, and bilirubin > 1 mg/dL in 28% after 12 months of therapy. Incorrectly classified responders occurred in 22/168 (13%) and 22/85 (26%) cases at academic and non-academic centers ($p = 0.014$). At non-academia, ALP levels at diagnosis were 3.6 ± 3.0 × ULN vs. 1.7 ± 0.9 × ULN in incorrectly vs. correctly classified responders ($p < 0.001$). They declined to 2.3 ± 1.2 × ULN vs. 0.9 ± 0.3 × ULN after 12 months of therapy ($p < 0.001$). Differences of minor extent were also observed for AST ($p = 0.029$ and 0.019) or bilirubin after 12 months of UDCA ($p = 0.031$). At academia, AST levels at diagnosis were 5.1 ± 9.2 × ULN vs. 2.4 ± 5.9 × ULN in incorrectly vs. correctly classified responders ($p = 0.008$). They declined to 1.2 ± 0.7 × ULN vs. 0.8 ± 0.2 × ULN after 12 months ($p = 0.001$). Bilirubin levels at diagnosis were 1.8 ± 3.3 × ULN vs. 0.9 ± 2.7 × ULN in incorrectly vs. correctly classified responders ($p < 0.001$). They declined to 1.2 ± 1.8 × ULN vs. 0.4 ± 0.2 × ULN ($p < 0.001$). No relevant differences in ALP levels were observed.
Incorrectly and correctly classified responders did not differ in terms of cirrhosis, transient elastography > 8 kPa, age <62 years at PBC diagnosis, or mean UDCA dosage after 12 months of therapy.
Conclusion: Clinical judgement of UDCA treatment response and Paris II criteria differ in a relevant proportion of cases, especially at non-academic centers. Higher baseline ALP levels and ALP kinetics may lead to assumption of adequate treatment response although Paris II criteria are formally not met.

THU-316

Evidence-based digital support in hepatology: retrieval-augmented generation's role in autoimmune liver diseases management

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Background and aims: Autoimmune liver diseases (AILDs) present significant management challenges, given their complex manifestations. Following our initial evaluation of Large Language Models (LLMs) in AILD management, which demonstrated promising but limited capabilities, we developed and assessed three specialized Retrieval-Augmented Generation (RAG) systems. They incorporated comprehensive clinical guidelines and medication safety information to enhance decision-support accuracy. Our aim was to evaluate the effectiveness of RAG-AI systems in providing evidence-based recommendations for AILD management.
Method: We engineered three RAG systems: HepaChat (customGPT from the OpenAI platform), RAG-ChatGPT (Model: gpt4o), and RAG-Claude (Model: claude 3.5 sonnet). Each system integrated 13 international clinical guidelines, including protocols from EASL, AASLD, AWMF, APASL, and BSG, spanning autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) management. Additionally, we incorporated a comprehensive database containing 12,465 FDA medication warnings to ensure safety. Ten liver specialists (six European, four American) evaluated system responses to 56 standardized clinical questions using a 1–10 Likert scale. Questions addressed disease comprehension, therapeutic approaches, and clinical decision-making across all three major AILDs.
Results: Our analysis showed HepaChat's better performance (mean score 7.70 ± 1.37) with 35 best-rated responses, compared to RAG-ChatGPT (7.38 ± 1.51, 20 best-rated) and RAG-Claude (7.31 ± 1.44, 9 best-rated). Geographic stratification unveiled variations in evaluation patterns (Americas: 8.01 vs Europe: 6.79). Disease-specific analysis demonstrated HepaChat's suitability in AIH (Europe: 7.20, Americas: 8.33) and PSC (7.34 and 8.31, respectively), and AIH in America (8.42), only surpassed by RAG-ChatGPT for PBC in Europe (7.11 vs 7.01). All three systems showed marked advancement over conventional LLMs (2023 benchmark: 6.93 ± 1.53).
Conclusion: This study demonstrates that custom chatbots and RAG systems incorporating clinical guidelines could enhance AILD management. HepaChat's performance and accessibility through the OpenAI platform offers accessible support for healthcare providers in underserved communities; the use of chain-of-thought reasoning may explain its advantage over standard RAG architectures. Geographic variations in assessment highlight the importance of regional clinical perspectives in AI development. These findings establish a foundation for novel clinical support tools, potentially incorporating multi-modal data integration and specialized agent architectures. Future developments should focus on clinical workflow integration and adaptation to various healthcare settings while maintaining safety protocols.

THU-317-YI
The differential, but significant, burden of pruritus, fatigue, and sicca across cholestatic liver diseases

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Background and aims: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are cholestatic liver diseases with a high symptom burden. We sought to explore symptom profiles and their associations.
Method: English-speaking adults with PBC or PSC at the Autoimmune and Rare Liver Disease programme in Toronto, Canada were prospectively recruited to self-administer electronic surveys on socioeconomic details, symptoms, and quality of life with clinic visits. Liver stiffness measurements by transient elastography as a disease stage surrogate were recorded. Surveys included the numeric rating scale (NRS), 5-D itch scale, visual analog fatigue scale (VAFS), modified fatigue impact scale (MFIS), and Primary Sjogren's Symptom Quality of Life (PSS-QoL). Comparisons were made with Kruskal-Wallis for continuous values and Chi-square/Fisher's Exact for categories. Spearman's rank (R) correlation coefficients were calculated.
Results: A total of 221 consented individuals completed baseline surveys (106 PBC [95% women], 115 PSC [62% men]). Daily itch (by NRS) was experienced by two-thirds of PBC and half of PSC respondents. More women experienced moderate-severe itch (24% women vs. 0% men in PBC; 23% women vs. 5.6% men in PSC, $p = 0.008$). Itch localization (by 5-D) differentially affected those with PBC compared to PSC. Moderate-severe fatigue affected 90% of women in both diseases, contrasting to 69% of PSC ($p = 0.022$) and 50% of PBC men ($p = 0.017$). Worse physical fatigue subscores (by MFIS) were seen in PBC than PSC; no differences were seen in cognitive or psychosocial subscores. No differences in itch or fatigue were noted amongst same gendered individuals stratified by disease. Moderate-severe Sjogren's symptoms (by PSS-QoL) was noted in 53% of PBC and 50% of PSC women; this contrasted to 0% of PBC ($p = 0.002$) and 26% of PSC men ($p = 0.036$). PSC men experienced higher Sjogren's symptom severity than PBC men ($p < 0.001$). Sicca was prevalent in PBC with skin (63%), eye (60%), and mouth dryness (58%). In PSC, sicca was common, with skin (47%), mouth (35%), and eye dryness (30%). Fatigue (by VAFS) and Sjogren's (by PSS-QOL) had the strongest correlation (R 0.68); itch (by NRS) and Sjogren's had moderate correlation (R 0.45), while itch and fatigue had weak correlation (R 0.32; $p < 0.001$ for all). Minimal to very weak correlations existed between symptom burden with household income, marital status, and education. Liver stiffness was weakly correlated with fatigue (by VAFS) (R 0.30, $p = 0.005$) and Sjogren's (by PSS-QoL) (R 0.34, $p = 0.001$) amongst PBC but not in PSC; there were no correlations with pruritus (by NRS).
Conclusion: Across cholestatic liver diseases, women experience higher symptom burden and severity than men. Fatigue and Sjogren' symptom scores are strongly correlated. Symptoms do not correlate with socio-economic status and are only weakly correlated with liver stiffness.

THU-318

Epidemiological trends of autoimmune hepatitis in South Korea: a population-based study from 2010 to 2023

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Background and aims: The epidemiology of autoimmune hepatitis (AIH) has shown geographic and temporal variation. There are few longitudinal studies on the epidemiology of AIH in Korea. This study aimed to identify temporal trends in the epidemiology and outcomes of AIH in Korea from 2010 to 2023.
Method: We obtained data from the Korean National Health Insurance Service database and the Rare Intractable Disease Registry for AIH, identified by the International Classification of Diseases, 10th Revision code K75.4, from 2010 to 2023. We calculated the prevalence and incidence of AIH by age and sex, and analyzed temporal trends using Joinpoint regression.
Results: During 2010–2023, a total of 10,055 patients aged 20 years and older were newly identified with AIH (female-to-male ratio 5.3, mean age 59 years). The average age- and sex-adjusted incidence rate from 2010 to 2023 was 17.7 per million per year, and the annual incidence rate tended to increase with an average percent change of 6.5% until 2017, when it plateaued. During the COVID-19 pandemic, from 2020 to 2022, AIH incidence rates were stable. The increasing trend in AIH incidence was consistent among both sexes and in the 30+ age group, and was more pronounced in the 70+ age group. Age- and sex-adjusted prevalence rates increased from 92.3 per million population in 2010 to 284.8 in 2023, an average percent change of 10.8%. The increasing trend in AIH prevalence was more pronounced in those aged 70 years and older. The annual case-fatality ratio was 1.95%, significantly higher in men than women (2.72% vs 1.81%).
Conclusion: From 2010 to 2023, the average incidence of AIH was 17.7 per million per year, with an upward trend that has recently plateaued. The prevalence of AIH in South Korea has increased to 284.8 per million in 2023, which is comparable to the prevalence of AIH reported in Western countries.

THU-319

Sebepliase alfa improves lipid metabolism and liver outcomes in pediatric patients with lysosomal acid lipase deficiency

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Background and aims: Lysosomal acid lipase deficiency (LAL-D) is a lipid metabolism disorder that causes substantial liver damage. Children and adults with LAL-D present with dyslipidemia, indicated by abnormal low- and high-density lipoprotein cholesterol levels (LDL-C, HDL-C) and elevated serum alanine and aspartate aminotransferase (ALT, AST) levels. The aim of this analysis was to quantify baseline lipid and liver parameters in patients with LAL-D and examine if these values changed in patients treated with the LAL enzyme replacement therapy sebelipase alfa (SA).
Method: This observational analysis included patients enrolled in the International LAL-D Registry (NCT01633489) who were alive at enrollment, including a subset who were diagnosed with LAL-D before 18 years of age. Patients were included in the registry regardless of whether they were treated with SA. Patients were excluded if they started SA treatment at <6 months of age (indicating rapidly progressive LAL-D) or used lipid-modifying medications during the analysis period.
Results: A total of 310 patients were enrolled in the International LAL-D Registry. Of 99 patients included in the pediatric subset analysis, 88 were treated with SA. Among 71 patients with both lipid and liver results, 68 (96%) had abnormalities in both lipid and liver parameters at baseline. Median (interquartile range) baseline concentrations of LDL-C and HDL-C were 210 mg/dL (158, 236; n = 80) and 35 mg/dL (29, 44; n = 78), respectively. Among 83 patients with both ALT and AST results, 2 (2%) had both values within normal limits (WNL) and 72 (87%) had elevations in both measures at baseline. Among 86 patients with ALT results, 22 (26%) had ALT results > 3 × the upper limit of normal at baseline. Among treated patients with LDL-C results at baseline and at least one follow-up, median LDL-C concentrations were 212, 151, 179, and 169 mg/dL at baseline and 1, 2, and 3 years of follow-up, respectively. Median HDL-C concentrations improved continuously from 35 mg/dL at baseline to 42 mg/dL at 3 years. Sixty treated patients had ALT results at baseline and at least one follow-up measure. ALT levels were WNL in 3 of 60 (5%) patients at baseline and in 21 of 46 (46%) patients at 1 year, 19 of 51 (37%) patients at 2 years, and 16 of 45 (36%) patients at 3 years of follow-up; AST results were similar over time. Among treated patients, 66% reported ≥1 adverse events, most of which were mild or moderate. Fourteen patients experienced serious adverse events (SAEs), including one death (roadway accident). All SAEs were deemed unrelated to treatment.
Conclusion: Patients with LAL-D diagnosed before age 18 years had substantial signs of liver injury and dysregulation of lipid metabolism, with ~75% of patients meeting the LDL-C criterion of familial hypercholesterolemia. Treatment with SA may improve lipid metabolism (LDL-C, HDL-C) and parameters of liver injury (ALT, AST) in this population.

THU-320

Diagnostic distribution of patients positive for anti-mitochondrial antibodies (subtype), anti-sp100, and anti-gp210: pathological examination is necessary of PBC diagnosis: a retrospective study based on liver biopsy

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Background and aims: Primary biliary cholangitis (PBC) is the most common chronic cholestatic autoimmune disease with an increasing prevalence worldwide. Serum biomarkers including anti-mitochondrial antibodies (AMAs) AMA-M2, anti-gp210 and anti-sp100, are the classical diagnostic antibodies for PBC in clinic. However, these antibodies also exist in other autoimmune diseases, and antibodies-positive patients with transient elevations in alkaline phosphatase (ALP) are insufficient for PBC diagnosis. In this condition, pathological examination may be necessary for PBC diagnosis. The aim of this study is to explore the diagnostic distribution of antibodies-positive patients in the cohort of patients who underwent liver biopsy, especially those who did not meet the PBC diagnostic criteria at baseline according to APASL.

Method: A retrospective analysis was conducted at the Second Hospital of Nanjing, between January 2017 and December 2023. Patients (n = 745) underwent liver biopsy, and the relation of serum antibodies including AMA/AMA-M2, AMA-M4, AMA-M9, anti-gp210, and anti-sp100, and the final PBC diagnosis were examined.
Results: A total of 745 patients were included, and 780 liver biopsies performed in this study. Among them, 713 patients underwent a single biopsy (713 biopsies), and 32 patients underwent repeated biopsies (67 biopsies), including 29 patients with two biopsies (58 biopsies) and 3 patients with three biopsies (9 biopsies). The serum diagnostic distribution of patients positive for anti-mitochondrial antibodies (AMAs) and its subtypes (AMA-M2, AMA-M4, AMA-M9), anti-gp210, and anti-sp100 was analyzed. Among the single biopsy group, 562 patients (78.8%) were diagnosed with PBC, while 151 patients (21.2%) were non-PBC. In the repeated biopsy group, 58 of 67 biopsies (corresponding to 30 patients) confirmed PBC, while 9 biopsies (corresponding to 5 patients) identified as non-PBC. Among these, 3 non-PBC patients were later diagnosed with PBC during follow-up after repeated biopsies. Overall, 592 patients (79.4%) were diagnosed with PBC after liver biopsy, including 4 patients confirmed during follow-up. Analysis of antibody distribution among the 780 liver biopsies showed 526 AMA-positive cases, 491 AMA-M2-positive cases, 241 anti-gp210-positive cases, 188 anti-sp100-positive cases, 9 AMA-M4-positive cases, and 5 AMA-M9-positive cases. Among non-AMA/AMA-M2/AMA-M4/AMA-M9-positive patients (148 cases), 40 were anti-gp210-positive (14 non-PBC, 2 later diagnosed as PBC during follow-up), and 77 were anti-sp100-positive (39 non-PBC). All 5 cases with dual positivity for anti-gp210 and anti-sp100 were diagnosed with PBC, while all 4 cases with triple positivity for AMA, anti-gp210, and anti-sp100 were non-PBC.
Conclusion: Antibody positivity alone is insufficient for PBC diagnosis. Comprehensive evaluation, including liver biopsy pathology, alkaline phosphatase levels, and other clinical indicators, is essential to avoid misdiagnosis.

THU-321

Real-world assessment of standard of care trends in primary biliary cholangitis and cholestatic pruritus in Europe

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Background and aims: Primary biliary cholangitis (PBC) is a chronic, progressive liver disease characterised by the immune-mediated destruction of intrahepatic bile ducts, leading to cholestasis and subsequent liver fibrosis. One of the most challenging and distressing symptoms experienced by patients with PBC is pruritus, which affects up to 89% of patients and is clinically significant in up to 53% of patients. Despite the prevalence of pruritus and its significant impact on patients' quality of life, it is often undertreated. There are limited real-world data from Europe regarding the use of medications for cholestatic pruritus. This study assessed the use of medications related to PBC and cholestatic pruritus among patients with PBC in France, Germany, Italy and Spain from 2015 to 2023/4.
Method: This study was a multinational retrospective study of patients (>18 years) with PBC using existing electronic medical record data from France, Germany, Italy and Spain. All databases were standardised to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. Patients with PBC were identified based on two or more diagnosis codes for PBC on separate clinical visits within a 1-year period. We evaluated prescriptions for PBC-specific therapies (ursodeoxycholic acid [UDCA], obeticholic acid [OCA], fibrates) and guideline-suggested medications for cholestatic pruritus (cholestyramine, rifampicin, oral opiate antagonists, selective serotonin reuptake inhibitors [SSRIs], gabapentin). All analyses were descriptive, and results are reported overall and stratified by country.
Results: Overall, 2612 patients with PBC were identified (France: 583; Germany: 891; Italy: 752; Spain: 386). Mean age at baseline was 63.1 years and 83.5% of the cohort was female. Documented pruritus was present in 2.3% of patients. Most patients (85.2%) had a prescription for UDCA over the study period; there was a declining trend in UDCA prescriptions over the years across all countries, most pronounced in Germany (92.1%– 66.7%). Few patients reported OCA (<2%) or fibrates use (6.7%). Use of guideline-suggested antipruritic medications across all countries over the study period was low (cholestyramine 4.9%; rifampicin 0.8%; oral opiate antagonists <1%; SSRIs 12.1%; gabapentin 2.7%).
Conclusion: These analyses, based on a typical cohort of patients with PBC, demonstrate low real-world usage of guideline-suggested therapies for cholestatic pruritus. The proportion of patients with documented pruritus was low, suggesting underreporting of this symptom. Given that prior literature shows that most patients with PBC experience pruritus at some point in their disease, a considerable proportion of patients are not receiving guideline-suggested pruritus therapies. This underscores a clear unmet patient need for licensed treatments to address cholestatic pruritus in PBC.
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THU-322

The risk of psychiatric disorders in patients with autoimmune hepatitis: a nationwide registry-based follow-up study

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Background and aims: Patients with autoimmune hepatitis (AIH) may have impaired quality of life and symptoms of depression and anxiety. Little is known about the long-term risk for psychiatric disorders. We conducted a population-based follow-up study on the risk of psychiatric disorders in patients with AIH and compared with the general population.
Method: From nationwide registries we identified all Danish patients diagnosed with AIH, 1994–2022, and matched population comparators. Based on hospital diagnoses and medical prescription data, we estimated the prevalence of psychiatric disorders at AIH diagnosis. Patients and comparators were followed through 2022, and we compared the risk of subsequent diagnoses of psychiatric disorders.
Results: We included 1371 patients with AIH and 13,556 comparators with a median age of 54 years at AIH diagnosis. In the patients with AIH, 207 developed a psychiatric disorder during 13,798.6 years of follow-up (median follow-up: 8.8 years). One third of these patients developed more than one psychiatric disorder. The absolute risk for overall psychiatric disorders was 12.4% (95% confidence interval [CI] 10.6–14.4) 10 years after AIH diagnosis. Depressive and anxiety disorders comprised the highest 10-year risk of 11.4% and 3.6%, respectively, and the same pattern applied to comparators. The overall 10-year risk of psychiatric disorders was similar in patients and comparators with an adjusted relative risk of 1.0 (95% CI 0.7–1.6), and this was the case for all psychiatric disorders.
Conclusion: This nationwide study showed that the risk for psychiatric disorders was similar in patients with AIH and in population comparators.

THU-323

A larger decline of IgG after initiation of treatment in patients with AIH is associated with complete biochemical response despite having normal baseline IgG levels

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Background and aims: A minority of patients with autoimmune hepatitis (AIH) present without elevation of immunoglobulin G (IgG) levels at diagnosis. The International Autoimmune Hepatitis Group (IAIHG) consensus criteria define complete biochemical response (CBR) as normalisation of both transaminases and IgG within the first six months of treatment, and this intermediate endpoint correlates with superior liver-related survival. In AIH patients presenting without elevation of IgG at diagnosis, determination of CBR thus mainly relies on normalisation of transaminases alone. We aimed to investigate differences in IgG evolution under immunosuppression according to biochemical response status.
Method: We investigated the evolution of IgG values at baseline before treatment and after 6 months of treatment in subjects with IgG within normal range at diagnosis, from a multicentric cohort in Belgium consisting of one tertiary care centre and seven secondary care centres. Mean differences of IgG at baseline versus after 6 months of treatment were then compared between subjects attaining CBR and those with insufficient response (IR).
Results: Out of 213 AIH patients in our cohort, 49 (23.0%) presented without IgG elevation at presentation. No difference was recorded between this group and the rest of the cohort in terms of baseline demographic and biochemical variables except for IgG. In the subgroup without IgG elevation, mean IgG value at baseline was 12.15 (±2.38) g/L. Thirty-five subjects (71.4%) achieved CBR and showed a mean IgG decline after six months of 2.43 (±2.57) g/L, whereas the remaining fourteen subjects demonstrated a mean IgG decline of 0.24 (±3.46) g/L ($p = 0.019$).
Conclusion: We demonstrate that AIH patients without IgG elevation at diagnosis achieving CBR have a substantially larger IgG decline after six months of treatment. Further investigation of this finding in larger studies of this particular subset of AIH patients could elucidate the value of IgG decline and its potential relationship to survival endpoints.

THU-324

Does steatotic liver disease influence treatment response and clinical outcomes in primary biliary cholangitis?

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Background and aims: Steatotic liver disease (SLD) affects over one-third of the global population. The controlled attenuation parameter (CAP) by vibration-controlled transient elastography (VCTE) is a reliable measure to assess the presence of SLD. Elevated alkaline phosphatase (ALP) is associated with more advanced fibrosis in patients with SLD and primary biliary cholangitis (PBC). This international multicentre study aimed to determine whether SLD can influence treatment response and clinical outcomes in patients with PBC.
Method: From an international registry of the GLOBAL PBC, 820 patients with at least one CAP value were retrospectively analyzed. SLD was defined as CAP≥280 dB/m. Patients with prior liver transplantation (LT) or hepatocellular carcinoma (HCC) were excluded. The biochemical response was based on conventional criteria (Paris-2, Toronto, GLOBE score), and the deep response was defined as normal ALP and Bilirubin<0.6xULN. The influence of SLD on clinical outcomes (hepatic decompensation (HD), HCC, LT or death) was estimated using Cox regression analysis, allowing for non-linear associations with restricted cubic splines.
Results: Among the patients included, 729 were females (88.9%), the mean age was 61.6 ± 12.0 years, and 186 (22.7%) had SLD. Patients with SLD had a higher BMI (31.7 ± 6.4 vs. 25.6 ± 5.0 kg/m^2, p < 0.001) and higher frequencies of diabetes mellitus (25.8% vs. 7.9%, p < 0.001) and hypertension (45.8% vs 26.8%, p < 0.001). Patients with SLD had similar liver stiffness measurement (LSM, 13.7 ± 14.5 vs. 11.4 ± 12.1, p = 0.073) and frequency of cirrhosis by VCTE (LSM≥14.0 kPa, 24.5% vs. 19.0%, p = 0.129), but had lower FIB-4 and APRI scores (1.6 ± 1.3 vs. 2.1 ± 1.9, p = 0.001, and 0.52 ± 0.48 vs. 0.72 ± 0.99, p < 0.001, respectively) compared to those without SLD. A higher proportion of patients with SLD achieved treatment response according to Paris-2 (62.9% vs 47.1%, p = 0.001), and Toronto criteria (70.8% vs 53.5%, p < 0.001), GLOBE score (79.0% vs. 69.6%, p = 0.032), ALP normalization (43.8% vs 30.6%, p = 0.001), and deep response (30.2% vs 17.0%, p < 0.001). Over a median follow-up of 7.6 ± 6.4 years, 6.0% (n = 49) developed HD, 0.2% (n = 2) HCC, 2.0% (n = 16) required a LT and 3.9% (n = 32) died. SLD was not associated with a higher risk of HD (HR 0.26, 95%CI 0.06–1.18, p = 0.082) or need for LT and mortality (HR 0.85, 95%CI 0.41–1.75, p = 0.654).
Conclusion: In PBC patients, the presence of SLD evaluated with CAP by VCTE is common but does not seem to have a negative impact on response to treatment and clinical outcomes. Future studies with a larger sample size are warranted.

THU-325-YI

The PSC-DM: development and validation of a clinical diagnostic model to aid the diagnosis of primary vs. secondary sclerosing cholangitis

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Background and aims: Sclerosing cholangitis is a chronic cholestatic biliary disease, characterised by inflammation and fibrosis of the bile ducts, stricture formation and progressive destruction of the biliary tree leading to biliary cirrhosis. It may be primary (immune-mediated) or secondary to a variety of insults. Diagnostic uncertainty between the aetiology can impact on cancer surveillance, clinical trial validity, and patient outcomes. This study aimed to develop and validate a clinical diagnostic model to help differentiate PSC from SSC.
Method: Retrospective review of 388 adult clinical case records with sclerosing cholangitis. Derivation cohort from three tertiary liver centres in Italy; validation cohort from one tertiary centre in the UK. Patients were classified as PSC or SSC according to EASL guidelines. We performed a multivariate logistic regression analysis in the derivation cohort to identify predictors of PSC diagnosis and validated it in the external cohort.
Results: In the derivation cohort of 244 patients (159 PSC and 85 SSC), six variables were associated with an increased likelihood of PSC over SSC. These were younger age (p < 0.0001), presence of IBD (p < 0.0001), no history of abdominal surgery (p < 0.0001), absence of pancreatic involvement (p = 0.0508), presence of autoimmune comorbidities (p = 0.0393), and a family history of autoimmune diseases (p = 0.0202). The variables were used to develop a predictive model for PSC diagnosis (PSC-DM) with an area under the receiver operating characteristic curve (AUROC) of 0.98 (95% confidence interval (CI) 0.97–0.99). In the external cohort of 144 patients (99 PSC and 45 SSC), the AUROC of the model was 0.95 (95% CI 0.92–0.98).
Conclusion: We derived and externally validated a model based on routinely available clinical parameters that accurately discriminate between patients with PSC and SSC. This would enhance patient's referral, tailored management and appropriate selection for clinical trials.

THU-326

Epidemiological and clinical differences in primary sclerosing cholangitis between men and women in Spain: a multicenter analysis of 697 patients

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Background and aims: Primary Sclerosing Cholangitis (PSC) is a rare immune-mediated liver disease strongly associated with inflammatory bowel disease (IBD) and exhibiting a higher prevalence in men. Unlike other autoimmune liver disorders, there is a lack of updated, gender-specific epidemiological and clinical data on PSC in Spain. Additionally, prior studies suggest that the association between PSC and IBD in Spain may be weaker compared to northern Europe. Aims: To compare the epidemiological and demographic characteristics, IBD association, and clinical progression of PSC between men and women in Spain.
Method: This observational, cross-sectional, multicenter study included prevalent cases of PSC across 47 Spanish hospitals. A total of 697 patients were analyzed using anonymized surveys and data from the Spanish Registry of Cholestatic and Immune Liver Diseases (COLHAI).
Results: The cohort included 697 PSC patients, of whom 428 were men (61.4%) and 269 were women (38.6%), with median current ages of 50.3 and 53.6 years, respectively. Among them, 458 (65.8%) had IBD (50% ulcerative colitis, 13.5% Crohn's disease, and 2.4% indeterminate colitis). Diagnosis of IBD preceded PSC in 52.5% of cases, occurred simultaneously in 32.7%, and followed PSC in 14.7%, with no gender-based differences. PSC was diagnosed at a younger mean age in patients with IBD compared to those without (37.7 vs. 46.2 years; $p < 0.001$). Men reported a higher frequency of active alcohol consumption (9.7% vs. 1.5%, $p < 0.001$). At diagnosis, jaundice was more common in men (24.1% vs. 16.8%; $p = 0.03$), whereas fatigue was more frequent in women (25% vs. 15.9%; $p = 0.04$). No significant differences were observed in cholestasis, pruritus, or other digestive symptoms. IBD prevalence was significantly higher in men (70.6% vs. 58.2%, $p < 0.001$). Hepatic decompensation (ascites, encephalopathy, or upper gastrointestinal bleeding due to portal hypertension) occurred more frequently in men than in women (13.8% vs. 7.1%; $p = 0.006$), although the time from PSC diagnosis to decompensation did not differ significantly (7.35 years for men vs. 9.5 years for women). Approximately 14.6% of patients experienced cholangitis, with no gender-based differences. During follow-up, 133 patients underwent liver transplantation (95 men and 38 women; 22.2% vs. 14.1%, $p = 0.01$), with a comparable mean time from PSC diagnosis to transplantation (9.4 years in men vs. 8.7 years in women; p = NS).
Conclusion: This study highlights significant gender differences in the clinical course of PSC, with men exhibiting a worse prognosis, higher risk of complications, and greater need for liver transplantation. These findings underscore the importance of considering gender in risk stratification and management of PSC and emphasize the need for longitudinal studies to further investigate gender-based differences in disease progression.

THU-327

Rituximab therapy for autoimmune hepatitis cirrhosis is associated with a high rate of complete biochemical response and improvement in MELD score

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Background and aims: data on safety and efficacy of third-line therapies for autoimmune hepatitis (AIH) is scarce. Recently, results from patients treated with rituximab or infliximab have been published, but the number of cirrhotic patients was limited, despite the fact that 1/2 of children and 1/3 of adults have cirrhosis at AIH diagnosis. Our aim was to analyse the impact of rituximab treatment in cirrhotic patients with AIH.
Method: retrospective study that included all patients from the ColHai registry and IAIHG hospitals with AIH diagnosed by biopsy (simplified criteria ≥6), who had cirrhosis and received rituximab. Biochemical response (BR) was defined as normal AST and ALT, and complete biochemical response (CBR) if IgG was also normal.
Results: 29 cirrhotic adults from 12 hospitals were included, 24 (82.8%) were women with a median age of 46 (IQR 33–61) years, 26 AIH and 3 AIH variants (1 PBC and 2 PSC). Criteria for rituximab was: 24 (82.8%) refractory AIH, 3 (10.3%) intolerance to prior treatments and 2 (10%) concomitant systemic/haematological disorder. Nineteen (65.5%) patients had cirrhosis at diagnosis and 10 developed cirrhosis during follow-up (FU). At the start of rituximab, 4 (14.2%) patients were decompensated, 20 (69.0%) had signs of portal hypertension, including 5 (17.2%) with oesophageal varices. Overall, MELD score was 10 (7–13). Only 2 (6.9%) patients achieved CBR before starting rituximab that was prescribed due to a concomitant disorder. After rituximab, 22 (75.9%) patients achieved CBR within a median time of 8 (IQR 3–13) months. Seven out of 22 (31.8%) patients who achieved CBR presented ≥1 flare, with no cases of ACLF. However, 1 (3.4%) patient required liver transplantation due to decompensation. Flares were managed by increasing or restarting corticosteroids and in 4/7

patients a new cycle of rituximab. Overall, 4 (14.8%) patients developed adverse reactions, 11 (37.9%) infections, and 2 (7.1%) skin tumours. Two (6.9%) patients died due no-related liver causes.
The majority of patients (24, 85.7%) underwent periodical doses of rituximab. Median doses of rituximab were 2 (1–5). Rituximab was associated with a reduction in corticosteroid doses in 20 (71.4%) patients and suspension of ≥1 immunosuppressant in 13 (46.5%). Median FU was 23 (13–37) months. At last FU, 15 (51.7%) patients were still on rituximab, 21 (72.4%) in BR, and 15 (55.2%) in CBR. The comparison between pre-rituximab and last FU showed an improvement in all liver tests, including a significant improvement in MELD score (10.8 vs 8.8, p = 0.006).
Conclusion: rituximab is an effective treatment for AIH cirrhosis with 3 out of every 4 patients achieving CBR. Besides, its use is associated with an improvement in liver functions tests, including MELD. AIH flares were not associated with any case of ACLF, and managed with corticosteroids and new doses of rituximab.

THU-328

Utility of splenic stiffness as a predictor for varices needing treatment in autoimmune hepatitis and primary biliary cholangitis

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Background and aims: Baveno VII (BVII) guidelines recommend performing endoscopy for variceal screening in patients intolerant or with contraindications to beta-blockers, and liver stiffness (LS) ≥20 kPa, platelet count ≤150,000, or splenic stiffness (SS) ≥40 kPa. However, these criteria have not been validated in patients with autoimmune hepatitis (AIH) or primary biliary cholangitis (PBC). This study aimed to evaluate the ability of SS and the BVII criteria in predicting varices needing treatment (VNT) in AIH and PBC patients.
Method: This multicenter, cross-sectional study included 70 AIH and 45 PBC patients with cirrhosis, confirmed by liver biopsy and/or ultrasound (nodular margins and/or signs of portal hypertension). All patients underwent LS and SS measurement using Fibroscan®. Laboratory and endoscopic data (±12 months) were collected. Sensitivity (S), specificity (Sp), and accuracy (AUC) of BVII criteria and SS in predicting VNT were analyzed, along with the false-negative rate (FNR), which represents the percentage of missed VNT cases.
Results: Most patients were female (PBC 87%; AIH 71%), with median ages of 66 years (IQR 58–75) for PBC and 63 years (IQR 53–70) for AIH and were in biochemical response at SS measurement (PBC 66%; AIH 77%). In PBC patients, median LS and SS were 15 kPa (IQR 11–24) and 42 kPa (IQR 32–57), respectively. Eleven patients (24%) had VNT, with a median LS and SS of 16 kPa and 62 kPa, respectively. BVII criteria showed moderate accuracy in predicting VNT (AUC 0.66; S 100%; Sp 32%; FNR 0%). Among the BVII components, platelet count (AUC 0.86; S 100%; Sp 41%; FNR 0%) outperformed LS (AUC 0.68; S 36%; Sp 65%; FNR 12%). SS (AUC 0.87; S 100%; Sp 56%; FNR 0%) showed better predictive ability than BVII but was comparable to platelets. Combining platelets and SS yielded the best predictive capacity (AUC 0.94; S 100%; Sp 71%; FNR 0%). In AIH patients, median LS and SS were 10 kPa (IQR 7–14) and 32 kPa (IQR 26–41). Thirteen patients (19%) had VNT, with median LS and SS in these patients being 15 kPa and 43 kPa, respectively. BVII criteria showed good accuracy in predicting VNT (AUC 0.86; S 92%; Sp 65%; FNR 8%), mainly due to the strong predictive capacity of platelet count (AUC 0.88; S 92%; Sp 70%; FNR 8%). In contrast, LS and SS showed moderate predictive capacities with AUCs of 0.76 (S 38%; Sp 88%; FNR 14%) and 0.75 (S 66%; Sp 77%; FNR 10%), respectively. Adding SS to the platelet count did not enhance its predictive capacity (AUC 0.90; S 54%; Sp 88%; FNR 11%).
Conclusion: AIH patients with VNT had lower LS and SS values than PBC patients. BVII criteria effectively predicted VNT in patients with PBC and AIH. However, in PBC, the combination of platelet count ≤150,000 and SS ≥40 kPa provided excellent accuracy and enhanced BVII criteria for predicting VNT. In AIH, a platelet count ≤150,000 was the most reliable predictor of VNT, outperforming SS, LS, and BVII criteria, which showed low sensitivity and higher FNR.

THU-333

Non-invasive tests for liver fibrosis are stable in patients with primary biliary cholangitis with two years of treatment with elafibranor

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Background and aims: Primary biliary cholangitis (PBC), a rare cholestatic liver disease, causes progressive biliary fibrosis. Liver stiffness measurements (LSM) and Enhanced Liver Fibrosis (ELF) are non-invasive tests (NITs) for fibrosis. The phase III ELATIVE® trial (NCT04526665) assessed elafibranor, a peroxisome proliferator-activated receptor (PPAR) agonist exerting effects on PPAR alpha

and delta, in patients (pts) with PBC. PPAR alpha activation has been associated with positive effects on fibrosis. LSM and ELF in pts treated with elafibranor and placebo in ELATIVE® to 52 weeks have been reported previously. Here, we assess the effect of elafibranor on NITs for fibrosis and biochemical markers in ELATIVE® to Week 104; NITs are also stratified by disease stage.

Method: In pts with LSM and ELF from baseline (BL) to Wk 104, proportions of pts with LSM > 8 kPa and > 10 kPa and changes ≥0.5 kPa, and ELF ≥7.7 and ≥9.8 and changes ≥0.19, were assessed at visits to Wk 104. LSM and ELF changes were assessed in early and advanced stage disease; advanced disease was defined as BL LSM > 10 kPa and/or advanced fibrosis/cirrhosis on histology. Changes from BL (CfB) to Wk 104 were assessed for alkaline phosphatase (ALP), total bilirubin (TB), albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT).

Results: At data cutoff, 48 pts receiving elafibranor in ELATIVE® had LSM and 41 had ELF from BL to Wk 104. LSM increased and decreased by ≥0.5 kPa in similar proportions of pts across study visits to Wk 104 (36.2–40.0% and 42.6–47.9%). A consistent proportion of patients had LSM > 8 kPa and > 10 kPa from BL (54.2% and 33.3%) to Wk 104 (50.0% and 29.2%). Of the 16 pts with LSM > 10 kPa at BL, 6 (37.5%) had LSM ≤10 kPa at Wk 104; of the 32 with LSM ≤10 kPa at BL, 4 (12.5%) had LSM > 10 kPa at Wk 104. ELF increased and decreased by ≥0.19 in similar proportions of pts across visits to Wk 104 (24.4–41.5% and 32.5–41.5%). All pts had ELF ≥7.7 at every visit. Comparable proportions of pts had ELF ≥9.8 at BL and Wk 104 (48.8% vs 39.0%). At Wk 104, in pts with early stage disease, LSM increased and decreased by ≥0.5 kPa in 35.5% and 45.2% of pts, and ELF increased and decreased by ≥0.19 in 44.4% and 37.0% of pts. In pts with advanced stage disease, LSM increased and decreased by ≥0.5 kPa in 47.1% and 52.9%, and ELF increased and decreased by ≥0.19 in 35.7% and 50.0% of pts. In pts with LSM, mean CfB in ALP and GGT to Wk 104 were −124.0 U/L and −25.1 U/L, respectively. In pts with ELF, CfB in ALP and GGT to Wk 104 were −116.9 U/L and −22.8 U/L, respectively. TB, ALT, AST and ALB were relatively stable in both subsets. Elafibranor was well-tolerated in this subset to Wk 104, consistent with the overall safety profile in ELATIVE®.

Conclusion: With two years of elafibranor treatment, predictors of liver fibrosis and key biochemical markers remain stable in pts with PBC, including those with advanced stage disease.

THU-334

Cholestasis as a predictor of PSC in inflammatory bowel disease: insights from a romanian cohort study

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Background and aims: Primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD) often coexist, with PSC prevalence in IBD patients ranging from 3–8%. Approximately 80% of PSC patients also have IBD. Thus, chronic cholestasis in an IBD patient necessitates further investigation. The study aimed to evaluate the significance of cholestasis syndrome in patients with IBD.

Method: We conducted a retrospective study at Fundeni Clinical Institute, evaluating 3,767 patients suspected of ulcerative colitis (UC) or Crohn's disease (CD) from 2011 to 2022. Of these, 1,386 had confirmed UC, and 1,116 had confirmed CD. PSC was diagnosed in 1.37% (19) of UC patients and 1.34% (15) of CD patients. Data included IBD type, disease severity, extent, treatment, age at IBD and PSC diagnosis, liver disease presence, biochemical cholestasis (ALP > 120 U/L or GGT > 55 U/L), and MRCP performance.

Results: Biochemical cholestasis was observed in 14.4% of IBD patients, with mean ALP levels of 142 U/L in UC and 187 U/L in CD, and mean GGT levels of 121 U/L in UC and 125 U/L in CD. Among these, 65% of UC patients and 78% of CD patients underwent MRCP for PSC diagnosis/exclusion. Liver disease was present in 21% of cholestatic UC patients and 47.8% of cholestatic CD patients. Diagnoses included cholangiocarcinoma (3.2%), hepatocellular carcinoma (3 patients), PSC (9%), primary biliary cholangitis (2 patients), and liver cirrhosis (9%). Mean ALP and GGT levels were significantly elevated in PSC patients compared to cholestatic non-PSC patients (mean ALP: 308.8 U/L vs. 144.2 U/L, $p < 0.001$; mean GGT: 243 U/L vs. 108.4 U/L, $p < 0.001$). In the PSC-UC group, 15 of 19 patients had pancolitis (Montreal classification E3), 3 had left-sided colitis (E2), and 1 had proctitis (E1). Severe disease activity was observed in 2 patients, with 3 requiring biologics. Among PSC-CD patients, 11 of 15 exhibited severe disease activity, and 9 required biologic treatment.

Conclusion: Cholestasis in IBD patients does not always indicate PSC, as other liver diseases may be involved. The phenotypic characteristics of this cohort displayed some variation compared to published data. This is the largest monocentric study in Romania examining IBD patients for PSC diagnosis. PSC prevalence in our long-term IBD cohort was lower than expected. PSC patients exhibited ALP and GGT levels exceeding twice the upper normal limit.

THU-335

CM-101 impacts disease biomarkers in primary sclerosing cholangitis: assessment of the SPRING study pharmacokinetics and pharmacodynamics

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Background and aims: CM-101, a novel monoclonal antibody targeting CCL24, was shown in the SPRING study to be well tolerated and exhibited anti-inflammatory, anti-fibrotic, and anti-cholestatic activities in patients with primary sclerosing cholangitis (PSC). Here we analyze the pharmacokinetics (PK) and pharmacodynamics (PD) data and explore their relationships with biomarkers of efficacy.

Method: The SPRING study was a phase 2, randomized, double-blind, placebo-controlled study of PSC patients. The study design and clinical data have been presented. Patients received 5 doses of CM-101 (either 10 mg/kg or 20 mg/kg) or placebo IV every 3 weeks for 15 weeks. PK parameters were assessed, and target engagement of CCL24 was quantified using a ligand binding assay for total (CM-101-bound and unbound) serum CCL24. PK parameters were correlated with clinical markers of the liver enzymes alanine transaminase (ALT) and alkaline phosphatase (ALP), and liver stiffness as measured by transient elastography (TE).

Results: PK analyses indicated dose-proportional increases in CM-101 concentration with steady-state levels achieved after the fourth dose, resulting in mean C_{trough} values of 63.45 µg/mL when patients were dosed at 10 mg/kg, and 141 µg/mL when patients were dosed at 20 mg/kg. The steady state was maintained throughout the double-blind treatment period (week 15). Increases in C_{max}, $AUC_{0\text{-}168h}$, and AUC_{last} were dose-proportional for both Dose 1 and Dose 5 of CM-101. Total CCL24 levels rose 3.3-fold and 6.7-fold for the 10 mg/kg and 20 mg/kg groups, respectively, and remained elevated throughout the double-blind treatment period. This increase, which was evident only in the CM-101 treated groups, reflects effective antibody-target engagement, and was dose-dependent between the 10 mg/kg and 20 mg/kg groups. The increase in serum CCL24 levels corresponded to the increase in serum CM-101 levels. Linear regression analyses

found trends between increasing exposure (as measured by C_{trough}, C_{max}, and $AUC_{0\text{-}168h}$ parameters) and decreasing TE, ALT and ALP.
Conclusion: CM-101 demonstrates two-compartment, dose-dependent PK with high target engagement in patients with PSC. A dose-dependent trend between the higher dose and reductions in TE and ALP is encouraging. Additional data is expected following a planned phase 3.

THU-336-YI
Direct nerve fiber recordings reveal functional alterations in cutaneous C-fibers linked to itch severity in cholestatic liver diseases

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Background and aims: Chronic pruritus is a common and sometimes difficult-to-treat symptom associated with cholestatic liver diseases that significantly affects patients` quality of life. While several potential pruritogens have been identified, the functional properties and alterations of cutaneous C-fibers mediating pruritic stimuli remain poorly understood. This aim of this study was to objectively assess functionality of C-fibers in patients with and without chronic cholestatic pruritus using microneurography (MNG), a technique for direct recording of nerve fibers.
Method: Sixteen patients with cholestatic liver diseases (primary biliary cholangitis [PBC], n = 7; primary/secondary sclerosing cholangitis [PSC/SSC], n = 4; other causes of chronic cholestasis, n = 5) participated in the study. Validated pruritus questionnaires, including mean itch intensity measured on a numeric rating scale (NRS), were administered. MNG recordings of single C-fibers were obtained via a ultra-thin electrode inserted into the superficial peroneal nerve at ankle level. Standardized mechanical and electrical stimulation protocols as well as chemical stimulation with either lysophosphatidic acid (LPA, 0.1 mM) or a bile acid pool (deoxycholic acid, glycocholic acid, ursodeoxycholic acid) were used to classify C-fibers.
Results: Patients were stratified into high-pruritus (NRS ≥3) and low-pruritus (NRS <3) groups, with no significant differences between the groups in term of age, gender, laboratory parameters, or disease stage. A total of 72 C-fibers were recorded. The high-pruritus group exhibited a greater proportion of functionally abnormal C-fibers (57%) compared to the low-pruritus group (33%). Notably, 50% of patients with high pruritus had more than 50% of their C-fibers classified as pathologically altered, whereas no patients in the low-pruritus group exceeded this threshold. Spontaneous activity, a marker of hyper-reactivity, was observed in 38% of high-pruritus patients but was completely absent in the low-pruritus group. No significant differences were identified in C-fiber activation following stimulation with LPA or the bile acid pool.
Conclusion: Patients with cholestatic liver diseases and high-intensity pruritus exhibit a higher proportion of functionally altered C-fibers, suggesting that chronic cholestasis causes long-term changes in the functionality of cutaneous nerve fibers.

THU-337
Is the POISE really valid as a surrogate endpoint for patients with PBC treated with UDCA and PPAR agonist? – a retrospective validation study from the real-world data in Japan

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Background and aims: In clinical trials evaluating PPAR agonists for primary biliary cholangitis (PBC) with an incomplete response to ursodeoxycholic acid (UDCA), the POISE criteria are commonly used as the primary endpoint. These criteria are defined as achieving an alkaline phosphatase (ALP) level <1.67× the upper limit of normal (ULN) with a ≥15% reduction from baseline, and bilirubin levels within the ULN after one year of treatment. However, the POISE criteria were originally established as a predictor of favorable long-term prognosis in patients treated with UDCA monotherapy, and it remains an area of uncertainty whether these criteria are similarly associated with long-term prognosis in patients receiving combination therapy with UDCA and PPAR agonists. This study aimed to retrospectively evaluate whether the POISE criteria are predictive of long-term outcomes in patients treated with UDCA and bezafibrate (BZF) based on the real-world data from a nationwide survey of PBC in Japan.
Method: We utilized clinical data from the 17th nationwide survey on PBC conducted during 2023–2024, in which 2,051 patients with PBC were registered. Among them, we included patients without missing data on medical treatment or prognosis, and those who received BZF as an add-on therapy to UDCA, had ALP ≥1.5× ULN at the initiation of BZF therapy, and had been followed for at least one year after starting BZF. We excluded patients with concomitant hepatitis B, hepatitis C, or autoimmune hepatitis. Enrolled patients were categorized based on whether they met the POISE criteria one year after initiating BZF therapy. We statistically compared the incidence of liver transplantation (LT) or all-cause mortality, as well as a composite endpoint including LT, all-cause mortality, decompensated events (ascites, edema, hepatic encephalopathy, gastrointestinal bleeding) and hepatocellular carcinoma between the groups.
Results: Of the 2,051 PBC cases, 226 met the inclusion criteria (male/female, 46:180; mean age at BZF initiation, 57.7 ± 12.8 years; mean follow-up duration after BZF initiation, 8.7 ± 5.0 years). Among these, 92 patients met the POISE criteria (POISE-in), while 134 did not (POISE-out). LT or all-cause mortality occurred in 4 POISE-in patients and 16 POISE-out patients, with incidence rates of 5.76 and 9.81 per 10,000 person-years, respectively. The incidence of events including decompensated cirrhosis and HCC was 5 cases in the POISE-in group

and 32 cases in the POISE-out group, corresponding to rates of 4.9 and 28.6 per 10,000 person-years, respectively. Kaplan-Meier analysis showed significant differences between POISE-in and POISE-out for both LT/all-cause mortality (p = 0.032) and the composite endpoint (p = 0.002).
Conclusion: These findings demonstrate that achieving the POISE criteria is significantly associated with improved long-term prognosis in patients receiving UDCA and BZF, strongly supporting the use of the POISE in clinical trials evaluating UDCA and PPAR agonist combination therapy.

THU-338-YI
Health-related quality of life and well-being of young patients with autoimmune hepatitis during transition of care from paediatric to adult site
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Background and aims: Autoimmune hepatitis (AIH) is a chronic liver disease that, in the majority of patients, requires lifelong maintenance therapy. AIH treatment may impact health-related quality of life (HRQoL) and patients' well-being. Treatment adherence is presumed to be lower during the transition of care from paediatric to adult sites. Here, we assessed HRQoL in young adults with AIH during the transition of care in the reference liver diseases adult centre.
Method: Sixty-six patients (66% female) with AIH diagnosed in childhood were assessed at the first visit to the adult centre and during mean follow-up of 4.5 ± 2.2 years. HRQoL was evaluated by SF-12 (generic HRQoL tool), PHQ-9 (depression), and MFIS (fatigue). The HRQoL was compared using paired observation from the first and the follow-up visit at the adult centre. Additionally, the patient's HRQoL at the follow-up visit (66% female, mean age 24.4 ± 3.0 years) was evaluated to sex- and age-matched healthy volunteers (67% female, mean age 25.6 ± 3.1 years).
Results: On the first visit to the adult centre, patients presented at a mean age of 19.8 ± 2.3 years, 18 (27%) patients were referred after the age of 20. At the first visit, mean ALT was 74 ± 80 U/l, IgG 1538 ± 561 mg/dL, and complete biochemical response (CBR) was seen in 33% of patients. During follow-up, mean ALT was 45 ± 51 U/l, IgG was 1517 ± 658 mg/dL, and complete biochemical response (CBR) was achieved in 62% of patients. Compared to the first visit, CBR was achieved more frequently (p < 0.001). During the 4.5 years of follow-up, there were no differences in the physical component scale (PCS, p = 0.059), but the mental component scale (MCS) of HRQoL was lower at the follow-up visit (p = 0.003). The PHQ-9 results were comparable between both time points (p = 0.394), but moderate depression (PHQ-9≥10 points) was found in 28% and 43% of patients during the first and the follow-up visit, respectively. Half of the patients declared psychiatric consultation in medical history, but only 23% received any psychiatric drug. There were no differences in overall fatigue (total MFIS) as well as MFIS subdomains. During the follow-up, there were no differences in HRQoL (PCS and MCS), depression signs and fatigue in terms of liver cirrhosis, steroids use and CBR achievement (all p > 0.05) Compared to controls, young people with AIH had impaired HRQoL in terms of physical (PCS, p = 0.01), mental (MCS, p < 0.001) as well as depressive signs (PHQ-9, p < 0.001), but not overall fatigue and its cognitive subscale in MFIS. Screening for moderate-severe depression (PHQ-9≥15 points) was positive in 25.4% of patients, compared to 10.6% in controls (p = 0.036).
Conclusion: Young adults with AIH are at risk of significant deterioration of HRQoL as well as a higher risk of depression than in the general population. Beside improvement in laboratory result and achieving CBR, HRQoL remained impaired or, in terms of mental aspects, deteriorated. These findings stress the need for psychological consultation during the transition of care, also in adult clinics.

THU-339-YI
UK validation of the simple cholestatic complaints score: a patient reported outcomes measure in primary sclerosing cholangitis
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Background and aims: Primary sclerosing cholangitis (PSC) is a rare cholestatic disease with significant symptom burden. A reliable patient reported outcome measure (PROM) is of key importance in the development of symptom-directed therapies. The Simple Cholestatic Complaints Score (SCCS) was developed as a 4-item questionnaire that is quick and easy to complete, assessing principal cholestatic symptoms (pruritus, fatigue, abdominal pain and fever). The SCCS has been tested and validated in a Dutch cohort of PSC patients. The aim of this cross-sectional study was to externally validate the SCCS in a cohort of PSC patients from the UK.
Method: Adults with PSC (aged > 16, non-transplant) were invited to complete the SCCS questionnaire alongside additional health related quality of life (QoL) assessments: the chronic liver disease questionnaire (CLDQ), EuroQol-5 Dimension 5-level (EQ-5D 5L) questionnaire, the 5D itch score and the itch numerical rating scale (NRS). Clinical and laboratory data were captured in parallel at the same timepoint. Validity was determined using Spearman correlation coefficient between SCCS and other QoL assessment tools, where both overall and item specific scores were compared.
Results: Between Nov 2022 and Feb 2023, 139 patients with PSC were recruited (median age 40yrs, 79 men, median MELD score 7.0), of whom 91% (127/139) had large duct disease, 94% (130/139) had inflammatory bowel disease (IBD) and 17% (23/139) had cirrhosis. Total SCCS was greater in those with more advanced liver disease (3.0 in cirrhosis vs 2.0 in no cirrhosis, p = 0.002) and those with a history of acute cholangitis (5.0 vs 2.0, p = 0.003), alongside positive correlations with MELD scores (rho 0.30, p = 0.001) and transient elastography (rho 0.21, p = 0.022). No significant differences in total SCCS were seen between sexes, presence of IBD, and extent of ductal involvement. The total SCCS values exhibited strong negative correlations with overall CLDQ scores (rho −0.76, p < 0.001) and EQ-5D 5L VAS scores (rho −0.65, p < 0.001) and index values (rho −0.65, p < 0.001). With respect to item specific scores, the pruritus domain of the SCCS very strongly and positively correlated with the 5D itch score (rho 0.86, p < 0.001) and itch worst NRS (rho 0.89, p < 0.001). The fatigue domain of SCCS exhibited strong correlation to the CLDQ fatigue domain (rho −0.78, p < 0.001); and the abdominal pain SCCS item a strong correlation with the abdominal symptom domain of CLDQ (rho −0.60, p < 0.001).
Conclusion: Herein, we show that the SCCS is reliable in capturing the impact of item specific symptoms, consistent with what is reported in other QoL assessments. The SCCS provides a quick, simple and easy to use PROM, which should be utilized in both clinical care and as an outcome measure in symptom specific PSC clinical trials.

THU-340
Validation of the clinical global impression severity scale for primary biliary cholangitis: a clinical trials outcome tool
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Background and aims: Primary biliary cholangitis (PBC) is a cholestatic disease that can cause disabling symptoms such as fatigue, cognitive dysfunction and emotional distress. These symptoms are captured by patient reported outcome measures (PROM) such as the PBC-40. However, for clinical research, PROMs are limited by personality or contextual influences causing bias (under or over reporting of symptoms). In contrast the Clinical Global Impression (CGI) scale utilizes expert judgement on syndrome severity to provide objective ratings following comprehensive symptom evaluation. CGIs are widely used in CNS indications and accepted by regulators as a primary efficacy endpoint. The newly developed CGI-S-PBC™ consists of a semi-structured interview covering the 6 symptom domains in the PBC – 40 (itch, fatigue, subjective cognition, psychosocial, emotional and somatic symptoms). This validation study aims to measure interrater agreement of the CGI-S-PBC™ among expert hepatologists and its correlation with the PBC-40.
Method: Adults with PBC (n = 13, all female) completed PBC-40 questionnaires and were then interviewed remotely (online) regarding symptoms, by a trained hepatologist. The videoed interviews were then rated independently by n = 12 blinded expert hepatologists. Raters used the CGI-S-PBC™ anchors to score symptoms on a Likert scale (1–7) for each symptom domain and provide a global rating. Statistical analyses (Krippendorf alpha) measured the level of rater agreement between expert ratings. The ratings and their association with the self-completed PBC - 40 scores were also examined (Spearman correlation).
Results: There was strong interrater agreement found amongst most domains, with the highest agreement for itch (alpha 0.93 (95% CI 0.92–0.95) and limited agreement seen for the somatic symptom domain (alpha 0.65, 95% CI 0.61–0.69). Strong agreement was exhibited for fatigue (alpha 0.82, 95% CI 0.80–0.84), subjective cognition (alpha 0.80, 95% CI 0.77–0.82), psychosocial (alpha 0.79, 95% CI 0.76–0.82), emotional (alpha 0.90, 95% CI 0.89–0.92) and the overall global score (alpha 0.81, 95% CI 0.78–0.84). The average score amongst raters had significant strong positive correlations with the PBC - 40 measures. The correlation coefficients were 0.90 for itch, 0.65 for fatigue, 0.79 for subjective cognition, 0.86 for psychosocial, 0.95 for emotional, 0.79 for somatic symptoms, and 0.88 for the overall global score ($p < 0.01$ for all).
Conclusion: The CGI-S-PBC™ is a valid and reliable rating instrument for PBC symptoms, crucial in really understanding the impact on patients. It is an integral tool for the approval of treatments that aim to improve symptoms, critical due to the number of novel symptom-directed therapies in development presently. The CGI-S-PBC™ is currently being used in training PBC-expert hepatologists for application in a randomized controlled trial.

THU-341
Implementation of a clinical global impression severity scale for primary biliary cirrhosis: results of a hepatologist focussed training programme

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Background and aims: Primary Biliary Cholangitis (PBC) is a cholestatic liver disease with high symptom burden. Symptoms such as fatigue and cognitive concerns are not captured by laboratory measures, and therefore additional tools are needed to facilitate the testing of symptom directed therapies. A Clinical Global Impression Severity scale for PBC (CGI-S-PBC™) was recently developed and validated, expanding on the PBC-40 patient reported outcome measure. Commonly used in other disease areas, the use and application of CGI scales is a novel concept in hepatology. Herein we report the application of a CGI training programme developed and administered to hepatologists with PBC expertise, allowing them to apply the tool in clinical trials.
Method: A training programme was developed by clinical hepatologists alongside clinical psychologists with extensive experience in CGI scale development. The training programme consisted of 3 interactive sessions involving education on the CGI scale using didactic instruction, video modelling, interactive discussion, and in vivo practice interviewing. Between each live session and following the final session, trainees watched and scored pre-recorded CGI interviews with PBC patients. Trainees were required to demonstrate >80% accuracy in their scoring against pre-determined gold standards, in order to be certified as successful raters.
Results: To date, 26 hepatologists (19 male) from 8 European countries have completed the training programme. Training sessions were completed in 5 cohorts (maximum of 8 trainees per group). 88% (23/26) achieved ≥80% reliability after the third training session. Only 2 trainees required an additional 1 to 1 training session, following which all trainees achieved >80% reliability on subsequent ratings. Across trainees, the average accuracy of scoring was 86% (cohort 1: 89%, cohort 2: 85%, cohort 3: 85%, cohort 4: 90%, cohort 5: 90%).
Conclusion: This dedicated training programme for the CGI-S-PBC™ scale is proven to be effective and successful in training hepatologists to reliably score PBC specific CGI interviews. Approved raters from this programme are currently participating as central raters in an ongoing phase 2 study of an investigational medication where interrater reliability will be studied in a real-world setting. This training programme complements the recently validated CGI-S-PBC™ scale, for use internationally, where there is an essential need for regulator approved symptom outcome measures, that can be used in clinical trials for novel symptom directed therapeutics in PBC.

THU-342
Efficacy and safety of odevixibat in patients aged ≥10 years with Alagille syndrome: results from the 72-week ASSERT-EXT phase III, open-label extension study

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Background and aims: Robust, long-term data from ASSERT phase III randomized controlled trial (NCT04674761) and ASSERT-EXT

(NCT05035030) open-label extension demonstrate sustained efficacy and tolerability in patients with Alagille syndrome (ALGS) of any age treated with odevixibat (ODX) for ≤96 weeks [1,2]. ODX is US and EU approved for cholestatic pruritus in patients with ALGS aged ≥12 months and ≥6 months, respectively. Here we analyzed efficacy and safety outcomes for patients aged ≥10 years from ASSERT and ASSERT-EXT to characterize the clinical benefit of long-term ODX in older patients.

Method: Patients received ODX PBO for 24 weeks in ASSERT; those who completed were eligible for the 72-week ASSERT-EXT. All patients received ODX 120 μg/kg/day (≤96 weeks for patients randomized to ODX in ASSERT). This integrated analysis includes patients aged ≥10 to <18 years at baseline (BL). Endpoints include mean scratching score (patient-reported); mean serum bile acid (sBA) levels; proportion of patients with clinically meaningful improvement in pruritus (≥1-point reduction); sleep parameters; and growth up to Week 72 timepoint. Safety was evaluated throughout.

Results: 10 patients aged ≥10 years received ODX (PBO/ODX n = 4; ODX/ODX n = 6); median age at BL: 12.2 years (range, 10.9–15.5). 6/10 patients completed ≤96 weeks treatment (median duration: 74 weeks [range, 16–129]); 2 patients withdrew consent prior to Week 72, 1 patient discontinued due to elevated bilirubin, and 1 patient had liver transplant after 110 days of ODX. Pooled mean (SD) pruritus scores at BL (n = 10) and Weeks 69 –72 (n = 4) of ASSERT-EXT were 2.1 (0.8) and 0.4 (0.6), respectively. At Weeks 69–72, 3 patients achieved a ≥1-point reduction in scratching score. Pooled mean (SD) sBAs at BL (n = 10) and Week 72 (n = 6) of ASSERT-EXT were 211.6 (113.4) and 76.8 (50.5) μmol/L, respectively. ODX was associated with improved sleep (mean change [SD] from BL to Week 72 timepoint in difficulty falling asleep: −1.6 [1.5]; difficulty staying asleep: −1.2 [1.2]; and daytime tiredness: −0.9 [1.6]). Height and weight increased over time (mean change [SD] from BL to Week 72 timepoint in height z-score: 0.07 [0.2]; weight z-score: −0.03 [0.4]). Patient-level data will be presented. Most TEAEs were mild/moderate in severity; most common were vitamin D deficiency (n/N = 4/10) and influenza (n/N = 3/10). 3 patients had GI disturbances considered probably related to ODX, 3 had elevated transaminases, and 3 had serious AEs, all unrelated to ODX. 2 patients had diarrhea (n = 1 related to ODX); neither were serious nor led to dose interruption or treatment discontinuation.

Conclusion: ODX was well tolerated with clinically meaningful improvements in pruritus, reductions in sBA, and improvements in sleep outcomes in patients with ALGS aged ≥10 years. Despite sample size, present data indicate the efficacy and safety profile of ODX in this subset of patients is consistent with previous results.

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THU-343

Combination obeticholic acid (OCA) and fibrate therapy is associated with greater probability of biochemical response than switching from OCA to a fibrate in primary biliary cholangitis

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Background and aims: Approximately 40% of patients (pts) with primary biliary cholangitis (PBC) are non-responders to ursodeoxycholic acid (UDCA) and candidates for second-line therapy (SLT). Until recently, the latter consisted of licensed treatment with obeticholic acid (OCA), or off-licensed bezafibrate/fenofibrate (fibrates). Unfortunately, >50% of pts inadequately respond to historic SLT paradigms. Emerging data suggests that combination therapy (OCA+fibrates) is associated with a greater biochemical response rate, although it is not known if 'switching' between SLTs can achieve the same, desired effect. The goal of this study was to compare biochemical response rates combination SLT, to that of a 'switch' regimen, wherein OCA was stopped and substituted for a fibrate in biochemical non-responders.

Method: We conducted a multicentre study across five high volume liver centres in the UK. Our cohort consisted of PBC pts who initiated OCA between 2017–19 with follow-up continuing to 2023. Rates of OCA discontinuation, dates of fibrate initiation, treatment regimen (permutations and combinations of UDCA, OCA and fibrates) were captured; alongside rates of biochemical response according to POISE criteria (alkaline phosphatase values [ALP] <1.67× the upper limit of normal, ALP reduction by >15% of pre-treatment values, and a normal bilirubin). Secondary outcomes included ALP normalisation and the incidence of liver-related clinical events (decompensation, hepatocellular carcinoma, referral for transplantation, death).

Results: In all, we accrued data from 240 pts who initiated OCA as an SLT (median age 46y, n = 48 with cirrhosis). Observing 4-years of follow-up, n = 45 initiated fibrates as add-on therapy to OCA (defined as group 1: n = 31 taking UDCA; n = 41 on OCA+bezafibrate; n = 4 on OCA+fenofibrate). In turn, n = 74 switched from OCA to a fibrate (defined as group 2: n = 51 taking UDCA; n = 57 on bezafibrate; n = 17 on fenofibrate). Follow up of 1, 2, 3, and 4 years was completed by 29, 25, 21 and 22 pts in group 1, respectively, and 57, 47, 38 and 37 in group 2. Biochemical response according to POISE criteria was met in 31%, 44%, 85% and 91% of pts at 1, 2, 3, and 4 yrs, respectively, in group 1. This compared to 16%, 34%, 42% and 43% in group 2 ($P < 0.001$ for all time comparisons). ALP normalisation rates in group 1 vs. group 2 were 3% vs. 0% (p = ns), 4% vs. 7% (p = ns), 25% vs. 13% ($p = 0.01$) and 52% vs. 35% ($p < 0.001$), at 1, 2, 3 and 4 yrs, respectively. A non-significant trend toward greater normalisation rates in all biochemical parameters was observed in group 1 vs group 2: 0% vs. 3%; 7% vs. 3%, 13% vs. 5% and 35% vs. 8%. Five (11%) pts in group 1 experienced a clinical event vs four (5%) in group 2 (hazard ratio: 2.2; IQR 0.5–8.6).

Conclusion: Biochemical response rates under OCA+fibrate treatment are greater than stopping/switching from OCA to fibrates as part of a SLT regimen. Our data support the need for ongoing studies of combination SLT, alongside treatment paradigms associated with greater probability of biochemical response in PBC.

THU-344

Clinical characteristics of a large cohort of primary sclerosing cholangitis patients undergoing liver transplant for primary sclerosing cholangitis and biochemical predictors of recurrence

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Background and aims: Primary sclerosing cholangitis (PSC) is a rare, chronic and progressive cholestatic liver disease, that may progress to liver failure requiring liver transplantation (LT) 10–15 years after diagnosis. Recurrent PSC (rPSC) is a devastating complication that occurs in up to 30% of patients 10 years post LT and is associated with graft loss, need for re-transplantation, and reduced survival. We aimed to describe characteristics of a large PSC cohort undergoing LT and report biochemical predictors of rPSC.
Method: A retrospective cohort study was conducted at the University Health Network in Toronto. 247 PSC patients post LT were identified between January 1, 2000 to December 31,2022. Descriptive statistics were used to define the characteristics of the cohort. Qualitative variables were summarized as proportions and continuous variables as means with standard deviations and medians with interquartile ranges. 174 patients with sufficient data were included in a time-dependent Cox Proportional Hazards model to identify biochemical risk factors for rPSC. A p-value <0.05 was considered statistically significant.
Results: 247 patients with PSC were transplanted during the study period. Mean age at diagnosis was 34.5 (SD 13) years and median follow up time was 16 (IQR 10–20) years. The majority were male (67%, n = 165), had large duct PSC (88.7%, n = 218), associated IBD (79%, n = 194) and were treated with UDCA pre-transplant (70%, n = 174). Mean age at transplant was 43.6 (SD 13.5) years and median MELD was 19 (IQR 13–26). Living donor LT (LDLT) was the most frequent donor type (54%, n = 133) followed by donation after brainstem death (DBD) (44%, n = 103) with donation after cardiac death (DCD) (0.4%, n = 1) and split grafts (1.2%, n = 3) being rarely used. Male (48%, n = 119) and female (49%, n = 122) donors were equally used. The vast majority of patients had a Roux-en-Y hepaticojejunostomy (92%, n = 227). Unidentified cancer pre-transplant was seen on explant in 11% (n = 28) with 4.9% (n = 12) with cholangiocarcinoma, 5.7% (n = 14) with hepatocellular carcinoma and 5% (n = 2) with gallbladder cancer. Biopsy proven rejection episodes were frequent with early (within 1 month) acute cellular rejection (ACR) occurring in 29% (n = 72), late (≥1 month) ACR in 28% (n = 70), and chronic rejection in 6.5% (n = 16). Anastomotic strictures occurred in 19% (n = 46) and rPSC was diagnosed in 26% (n = 63) with median time to rPSC of 3.5 years (IQR 2.3–5.1). Ursodeoxycholic acid (UDCA) was used post-LT in 53% (n = 132). Immunosuppression within the first year was most commonly with tacrolimus (93%, n = 229) and mycophenolate (79%, n = 194), the combination of which continued in the majority beyond 1 year. Higher ALP (HR 1.002, 95% CI 1.0003–1.004, p = 0.02) and creatinine (HR 1.017, 95% CI 1.002–1.031, p = 0.02) were identified as biochemical predictors of rPSC.
Conclusion: rPSC is a frequent complication post-LT and may be predicted by elevated ALP and creatinine. Further evaluation of reliable predictors of rPSC is urgently needed.

THU-349

Risk factors for post-liver transplantation patient and graft survival in autoimmune hepatitis: pioneering insights from a south american cohort

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Background and aims: Autoimmune hepatitis (AIH) is a rare liver disease with regional variations in presentation and genetic associations. About 10% of AIH patients require liver transplantation (LT). Limited studies in non-European cohorts highlight the need for regional data. This study addresses this gap by examining risk factors for post-LT patient and graft survival in a Brazilian cohort.
Method: We conducted a retrospective cohort at a single Brazilian reference center, including AIH LT patients between 2004 and 2024. We excluded patients younger than 14 years-old, those with acute-on-chronic liver failure, and those with fulminant hepatitis. We utilized Kaplan-Meier (KM) estimates for both patient and graft survival post-LT, considering graft loss as either retransplantation or death. Univariate Cox proportional hazards (PH) regression was applied to all relevant variables for predicting patient or graft survival at 5 years, and those with p value <0.05 were further analyzed in a multivariate Cox PH model.
Results: The study included 132 predominantly female (79%) and mixed-race (78%) patients, with a median age of 28.1 years. The most common post-LT immunosuppressive regimen was the combination of an antimetabolite, a calcineurin inhibitor, and a glucocorticoid (52%). The KM survival estimates for patients were 77.5%, 75.2%, and 75.2% at 1, 3, and 5 years post-LT, respectively, while graft survival were 75.6%, 71.3%, and 71.3% at the same intervals. In the univariate analysis for patient survival, higher pre-LT MELD scores (hazard ratio [HR]: 1.1, 95% confidence interval [CI]: 1.0–1.2) was associated with worse outcomes. Conversely, a greater number of immunosuppressive agents (IMSa) was protective (HR: 0.3, 95% CI: 0.2–0.7), as well as the use of any antimetabolite (HR: 0.2, 95% CI: 0.1–0.6). In multivariate analysis, only IMSa number remained a significant predictor of patient survival (HR: 0.2, 95% CI: 0.1–0.8). For graft survival, univariate analysis revealed similar trends, with higher MELD scores (HR: 1.1, 95% CI: 1.0–1.2) negatively associated with outcomes, while a greater number of IMSa (HR: 0.4, 95% CI: 0.2–0.8) and the use of an antimetabolite (HR: 0.2, 95% CI: 0.1–0.6) were protective. Again, in multivariate analysis, only the number of IMSa was a significant predictor (HR: 0.3, 95% CI: 0.1–0.9). Further KM analyses were performed by stratifying patients into those receiving fewer than 3 IMSa and those receiving 3 or more IMSa. Patients receiving at least 3 IMSa had significantly better outcomes, with 5-year patient and graft survival of 92.0% and 90.1%, respectively, compared to 70.6% and 64.7% for patients receiving fewer than 3 IMSa (both p < 0.01).
Conclusion: As far as we know, this is the largest South American cohort of AIH patients undergoing LT reported to date. Given the regional variations in AIH, insights gained from this cohort provide essential data for improving LT strategies in South America.

THU-350-YI

Impact of non-classical phenotypes of primary biliary cholangitis on treatment response and long-term prognosis. Results from the ColHai registry

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Background and aims: Although the classic phenotype of primary biliary cholangitis (PBC) has slow progression and favorable response to treatment, other disease phenotypes characterized histologically by portal inflammation and/or ductopenia are associated with worse prognosis. In this study, we aimed to: 1) catalog the non-classical phenotypes of PBC according to biochemical parameters at diagnosis, 2) identify the impact of non-classical phenotypes on treatment response and disease prognosis, and 3) study the specific prognostic factors in each PBC phenotype.
Method: This multicenter retrospective study included 505 PBC patients who received second-line treatment (2LT) with bezafibrate and/or obeticholic acid. Data were exported from the ColHai registry (Spanish Registry for Autoimmune and Cholestatic Liver Diseases). Patients with PBC variants were excluded from the study. Included patients were classified into 3 groups (G) according to biochemical parameters at diagnosis. G1: alkaline phosphatase (ALP) <4 × upper limit of normal (ULN) and alanine aminotransferase (ALT) <2 × ULN; G2: ALP <4 × ULN and ALT ≥2 × ULN; and G3: ALP ≥4 × ULN. Event-free survival (EFS), defined as absence of decompensation, death or liver transplantation was calculated. The factors associated with prognosis were analyzed in each group.
Results: Most patients (n = 444, 88%) were female, with a median age of 51 years (IQR: 43–58). Sixty-one percent (n = 308) belonged to G1, 33% (n = 163) to G2, and 7% (n = 34) to G3. At diagnosis, G2 and G3 had higher liver stiffness measurements (G1: 5.8, G2: 7.8, and G3: 9.8; p < 0.001) and a higher frequency of pruritus (G1: 28%, G2: 46%, G3: 42%; p < 0.001). At the last follow-up, the percentage of patients with ALP <1 × ULN (G1: 48%, G2: 40%, G3: 20%, p < 0.001), 1.5 × ULN (G1 80%, G2 68%, G3 38%; p < 0.001) and 1.67 × ULN (G1 82%, G2 72%, G3 47%, p < 0.001) were significantly lower in G2 and G3 patients. After a median follow-up of 110 months (IQR: 65–174), G2 patients had lower EFS compared to G1 (p = 0.002). Unlike G1 patients, in G2 patients, ALP was not independently associated with EFS. In this subgroup (G2), only AST (HR: 1.047, p < 0.001 and HR: 1.034, p = 0.027) and platelets (HR: 1.001, p = 0.006 and HR: 1.001, p < 0.001) before and after the initiation of 2LT were independently associated with EFS. In G3, the results were similar to those of G2, but the low number of events prevented multivariate analysis.
Conclusion: Non-classical PBC phenotypes have worse long-term prognosis and lower response to treatment. In patients with PBC and elevated transaminase levels (G2), AST and platelet counts are the main factors associated with prognosis. Further studies are needed to determine the impact of AST normalization on the prognosis of these patients.

THU-351

Advancements in autoimmune hepatitis epidemiology, treatment and complication – a 15-year retrospective study

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Background and aims: Autoimmune hepatitis (AIH) is a rare, heterogeneous liver disease marked by autoantibodies, hypergammaglobulinemia, and distinct histological features. Predominantly affecting women, its incidence and prevalence show significant regional variability globally. Therefore, our aim is to examine the trends of AIH and to assess its demographics, management, and disease progression using an extensive population-based database.
Method: This retrospective, population-based study analyzed data from 2.7 million adults in Clalit Health Services, focusing on autoimmune hepatitis (AIH) diagnoses between 2009 and 2023. Data reordered included demographics, clinical details, and treatment regimens. Key outcomes tracked were the development of cirrhosis and its complications.
Results: This study included 992 AIH patients with a median age of 51.5 years, 80.4% female, and a median follow-up of 6.1 years. Obesity was present in 23.2%, and 10.9% had thyroid disease. At diagnosis, 22.9% had cirrhosis, and an additional 137 patients developed cirrhosis during follow-up, leading to a total prevalence of 36.5%. Among cirrhotic patients, 29.9% experienced decompensation, 25.3% developed ascites, 9.3% had variceal bleeding, and 10.4% developed hepatic encephalopathy. Hepatocellular carcinoma (HCC) occurred in 5.24% of cirrhotic patients, with an incidence rate of 6.32 cases per

1000 patient-years. Overall, 11.2% of cirrhotic patients underwent liver transplantation. The proportion of AIH patients diagnosed with cirrhosis at the time of diagnosis significantly decreased over the study period (p = 0.0028).
Conclusion: This study demonstrates a decreasing trend in AIH patients diagnosed with cirrhosis, suggesting earlier detection and improved management, alongside a lower documented incidence of HCC.

THU-352
The histological activity index is associated with disease severity and treatment response in patients with immune mediated liver injury from checkpoint inhibitors
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Background and aims: Immune mediated liver injury from checkpoint inhibitors (ILICI) is a common adverse event that may require early ICI discontinuation and/or immunomodulatory therapy. The aim of our study was to identify clinical correlates of histological features in ILICI patients seen at a US Drug-Induced Liver Injury Network (DILIN) site and Montpellier, France.
Method: 45 histological features of 67 ILICI patients were scored by 2 expert hepatopathologists. Since the baseline features of the 34 French and 33 DILIN patients were generally similar, the data were merged for analysis. We investigated if hepatic steatosis (>5%), histology activity index (HAI) >5 and granulomas were associated with clinical features, DILIN severity score (1 to 5) and 6-month treatment outcomes.
Results: Median age was 62.5 years, 63% male, 84% Caucasian. Suspect drugs included Ipilimumab/ nivolumab (24%), pembrolizumab (45%) and other ICIs (31%). At ILICI onset, the median drug latency was 72 days, ALT 346 IU/l, Alk P 207 IU/l, T bili 0.8 mg/dl; 52% hepatocellular, 19% mixed, and 28% cholestatic. Biopsy was obtained at a median of 106 days after ICI initiation and prior to corticosteroid initiation in 54%. During follow-up, 92% received corticosteroids, 30% ursodiol, and 27% mycophenolate/ azathioprine; 34% had chronic DILI while 43% died but only 4% from liver failure. Biopsies demonstrated 42% with HAI > 5, 30% with steatosis and 37% with granulomas. Those with HAI > 5 had significantly more granulomas, plasma cells, bridging necrosis and canalicular cholestasis on biopsy ($p < 0.05$). They also had higher initial and peak serum ALT, T bili and INR levels, higher DILIN severity score and were more likely to receive antimetabolites ($p < 0.05$). In contrast, those with histological steatosis were less likely to have severe hepatitis but more likely to have cirrhosis and higher BMI suggesting that the steatosis may have been a pre-existing feature ($p < 0.05$). Histological granulomas were associated with younger patient age, male sex, higher BMI, and lower peak bilirubin levels ($p < 0.05$).
Conclusion: Moderate inflammation, hepatic steatosis and hepatic granulomas are common in ILICI patients. Patients with more severe histological inflammation have higher ALT, bilirubin and INR levels and are more likely to be refractory to corticosteroids. Going forward, liver biopsy data may help clinicians determine optimal management strategies for ILICI patients.

THU-353
Comprehensive exploration of disease-specific autoantigen candidates in autoimmune hepatitis through immunocomplexome analysis
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Background and aims: The disease specific antigens for autoimmune hepatitis (AIH) remain unidentified, yet their discovery could significantly contribute to AIH diagnosis and treatment. Unlike array analysis, this study utilizes immune complexome analysis, which comprehensively examines immune complexes formed in vivo, to identify AIH-specific disease antigens.
Method: This study targeted 53 AIH cases (AIH group) and 64 metabolic dysfunction-associated steatotic liver disease (MASLD) cases (MASLD group), diagnosed through liver biopsy between May 2008 and May 2022. AIH diagnosis was based on pathological evaluation and an international AIH group diagnostic score of ≥11. Using Protein A/G, immune complexes were comprehensively collected from stored serum, then digested into peptides for identification via nano-LC-MS/MS and database searches. Relative antigen abundance was quantified through label-free quantification. Candidates specific to AIH were extracted by comparing the results to the MASLD group, setting the MASLD group's abundance +3SD as the positive antigen cutoff. Relative autoantibody levels against these candidates were analyzed using the Luciferase Immunoprecipitation System (LIPS) assay.
Results: The AIH group had a median age of 62 years, with 42 women (79.3%). Liver fibrosis staging revealed 18/15/6/8 cases at stages F1/2/3/4, respectively. Immune complexome analysis identified 1,218 and 1,216 immune complex-forming antigens in the AIH and MASLD groups, respectively. Setting the MASLD group's cutoff at +3SD, antigens with a significantly higher positive rate in the AIH group, reported expression in hepatocytes, and abundance over 2.5 times the cutoff were selected as autoantigen candidates. Three candidates, SKIL (positive in 22.6% of AIH cases), STAT4 (18.9%), and MAGE-D2 (26.4%), were identified as AIH-specific autoantigen candidates. Furthermore, LIPS assay confirmed increased autoantibody levels against these antigens in AIH-positive cases. AIH cases positive for SKIL and STAT4 exhibited significantly higher AST, ALT, and IgG levels compared to negative cases.
Conclusion: SKIL, STAT4, and MAGE-D2 were identified as novel AIH-specific antigen candidates in a subset of AIH cases. Detailed analysis of these antigens' characteristics as autoantigens, including immunohistochemistry, is ongoing.

THU-355
Predictors of response to steroids in children and adolescents with treatment naïve severe autoimmune hepatitis
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Background and aims: Steroids are indicated in severe autoimmune hepatitis (AIH) to avert liver transplantation (LT). There is limited paediatric data on prediction of response to steroids. The present study was conducted to identify predictors of response to steroids in children and adolescents with severe AIH.
Method: In this retrospective analysis of prospectively maintained database, children and adolescents below 18 years from January 2011 to May 2024 with severe AIH who received steroids were enrolled. Outcome was studied in terms of response to steroids which was defined clinically in terms of survival with native liver (SNL) or not (LT or death) by Day 28.

Results: Fifty children (31 females) with a median age of 11.9 (6.5, 15) years were studied. There were 9 deaths and 3 LT, while 38 (76%) had SNL. On Multivariate cox regression analysis, advance HE (HR 5.2, p = 0.024) and SURFASA score (HR = 1.2, p = 0.029) predicted poor response. SURFASA (AUROC 0.872) and AAPS scores (AUROC 0.827) were found to be superior to CLIF-SOFA (AUROC 0.798) and PELD (AUROC 0.773). A cut-off of SURFASA score of –2.3 differentiated patients with good or poor response.
Conclusion: Response to steroids is seen in three-fourths of children and adolescents with severe AIH. Advance HE and SURFASA score predicted poor response. SURFASA score >/ = –2.3 help in identifying patients in urgent need for LT.

THU-356
Extra-intestinal autoimmune conditions in patients with primary sclerosing cholangitis – does age matter?
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Background and aims: Primary sclerosing cholangitis (PSC) is an immune-mediated liver disease with a genetic predisposition. PSC is associated with inflammatory bowel disease (IBD) and extra-intestinal autoimmune (EIA) conditions, and first-degree relatives also have an increased risk of autoimmune conditions. We aim to evaluate if the phenotype of PSC, including PSC and autoimmune hepatitis overlap (PSC-AIH), presence of IBD and age at diagnosis, is associated with EIA disorders.
Method: All consecutive patients attending Young Adult and Hepatobiliary Medicine clinic with PSC at our centre from October 2023 to August 2024 were identified using electronic patient records. Retrospective data was collected, including phenotype of PSC, age at diagnosis of liver disease, presence of EIA, and family history of autoimmune disorders. Patients with a liver transplant and other cholangiopathies were excluded. Chi-squared tests were used to assess associations between categorical variables. Kruskal wallis was used for non-parametric continuous variables. Logistic regression was used to explore the association between EIAs and liver disease adjusting for confounders (IBD, age, sex).
Results: We included 286 individuals with PSC, with a male predominance of 60.4% and median age at liver disease diagnosis was 26.5 years (Q1: 15.5, Q3: 43). Phenotypes of PSC were: 71% large-duct PSC, 24.8% PSC-AIH and 4.2% small duct PSC. There were 216 (75.5%) patients with IBD, with no significant difference in prevalence based on phenotype (p = 0.25). There were 59 (20.7%) who had an EIA, and the most common EIAs were autoimmune joint condition and thyroid conditions. There was no difference in EIAs based on IBD diagnosis (p = 0.86). After confounder adjustment, there was no significant difference in EIAs by PSC phenotype (odds ratio 0.69; 95% confidence interval 0.31–1.58). For every year increase in age, the odds of having an EIA increased (odds ratio 1.03; 95% confidence interval 1.01–1.05). Of the 231 with available family history, 32 (13.9%) had a first-degree relative with an autoimmune condition. The most common autoimmune disorders in family members were IBD and autoimmune liver disease.
Conclusion: Our results are in line with current literature, and we demonstrated that 21% of patients with PSC had an EIA, and almost 14% had a first-degree relative with an autoimmune condition. The phenotype of PSC with regards to PSC-AIH and PSC-IBD was not associated with presence of EIAs; but increasing age may be a factor. A limitation of our study is the exclusion of patients with more advanced liver disease who underwent liver transplantation. Further work is required to understand which patients with PSC require investigation for EIAs and the potential genetic risk loci underpinning PSC and the association with other autoimmune conditions.

THU-357
The spectrum of adult cholestatic liver diseases related to ABCB4 gene mutations: genotype-phenotype correlation
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Background and aims: Progressive Familial Intrahepatic Cholestasis Type 3 (PFIC3) is an autosomal recessive disorder caused by variants in the ABCB4 gene. PFIC3 is characterized by biallelic variants in ABCB4 that lead to severe gene defects. The presence of monoallelic pathogenic genetic variants of ABCB4 is associated with a range of clinical manifestations such as Low Phospholipid-associated Cholelithiasis (LPAC), Intrahepatic Cholestasis of Pregnancy (ICP), Drug-induced cholestasis Liver Injury (DILI) or recurrent liver biochemistry abnormalities. We aim to characterize patients diagnosed with cholestatic liver diseases (CLD) related to the ABCB4 gene, including genotype-phenotype correlations.
Method: We conducted a retrospective study that included patients with CLD related to the ABCB4 gene mutation diagnosed between 2015 and 2024 in a tertiary care centre. Non-genetic aetiologies were excluded in all patients.
Results: We included 44 adult patients, 26 females, from 38 families with CLD related to ABCB4 gene mutations. The median age at diagnosis was 41 years. The most common initial clinical presentation was recurrent abdominal pain (n = 12) and pruritus (n = 4). Related to phenotype, patients presented PFIC 3 (n = 1), ICP (n = 10), LPAC (n = 14), DILI (n = 2), and recurrent cholestasis or isolated elevation of Gamma-glutamyl transpeptidase (n = 19). Twenty-two patients underwent cholecystectomy, with a median age of 29 years. One patient had cirrhosis and underwent liver transplantation. We identified 17 unique ABCB4 variants and 6 polymorphic susceptibility SNPs; 32 patients had a monoallelic (23 rare, 9 susceptibility SNP) and 12 had a biallelic variant (4 rare, 8 susceptibility SNP). In 7 cases, the rare ABCB4 variant was of uncertain significance but tending towards pathogenicity (VUS-high). We observed no differences in cholestasis or liver injury marker levels when comparing carriers of either monoallelic versus biallelic or rare versus susceptibility variants. When assessing the main phenotype, monoallelic variants were more common in patients with ICP or asymptomatic (either with or without recurrent biochemical changes) (p = 0.040). Susceptibility SNPs (mono or biallelic) were more common in asymptomatic patients, while rare variants were more frequent in ICP and LPAC cases (p = 0.001). Finally, a complete ursodeoxycholic acid (UDCA) response was more common in patients with rare than SNP variants (p = 0.048), suggesting additional genetic/environmental factors that contribute to the phenotype in SNP cases that UDCA does not revert.
Conclusion: Our results indicate that polymorphic susceptibility ABCB4 variants are typically not associated with disease and that monoallelic variants are associated with no disease or ICP, indicating a less severe phenotype. This work establishes for the first time genotype-phenotype correlations for ABCB4 that include both highly penetrant and common susceptibility variants.

THU-358-YI

Epidemiology of primary sclerosing cholangitis in Canterbury, New Zealand, a population-based study

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Background and aims: Primary sclerosing cholangitis (PSC) is an immune-mediated chronic liver disease characterised by inflammation and fibrosis of intrahepatic and extrahepatic bile ducts leading to cirrhosis and its complications. Previous epidemiological studies have shown that the incidence and prevalence of PSC in Canterbury, New Zealand, are among the highest reported worldwide (1)(2). A nationwide population census was conducted in New Zealand in 2023. Therefore, we aimed to report the latest epidemiology of PSC in Canterbury based on the Census 2023 population data.
Method: Patients with a diagnosis of PSC were added to our existing database. Radiology and histopathology reports were also searched to ensure all PSC cases were captured. Those with radiological or histological diagnoses of sclerosing cholangitis without other identifiable causes were included. Incidence and prevalence rates were calculated using Census population data from Statistics New Zealand.
Results: Our database included 142 PSC patients as of 31st December 2023. From 2017 to 2023, 35 new PSC cases were diagnosed in Canterbury. The average annual incidence of PSC for this period was 0.77/100,000 (95% CI 0.10–1.45/100,000). Excluding patients who had moved away from the region and deceased, there were 82 prevalent cases in 2023. The point prevalence of PSC in Canterbury on 31st December 2023 was 12.6/100,000 (95% CI 9.87–15.32/100,000). Ethnicity-specific prevalence showed that PSC prevalence was significantly higher in ethnic European (14.35/100,000; 95% CI 11.11–17.60/100,000) compared to non-European (5.45/100,000; 95% CI 1.41–9.48/100,000). The majority (66%) had a concurrent diagnosis of inflammatory bowel disease. Most (91%) had large duct PSC; 56% of cases had both intra- and extra-hepatic bile duct involvement at diagnosis, 33% intrahepatic duct involvement only and 2% extrahepatic duct involvement only. The median age of diagnosis was 52 years, and 60% were male.
Conclusion: Our population-based study showed that the incidence and prevalence of PSC in Canterbury were comparable to our previous reports, suggesting that the frequency and burden of PSC in Canterbury remained high. This study also demonstrated a significant difference in the prevalence of PSC among different ethnic groups living within the same geographical region, with the population of European descent having a significantly higher prevalence. It showed that ethnicity influences susceptibility to PSC and suggests a genetic predisposition to the development of the disease.

THU-359

Atherosclerosis in primary biliary cholangitis – more common than previously thought

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Background and aims: Hyperlipidemia (HL) is present in up to 80% of patients with primary biliary cholangitis (PBC) but does not appear to increase the risk of atherosclerotic cardiovascular disease (ASCVD). Guidelines recommend the use of statins in only those patients with independent risk factors for ASCVD. Given rising obesity prevalence, many patients with PBC may benefit from cardiovascular risk reduction with statins. New tools, such as coronary artery calcium scoring (CACS), have emerged to help risk stratify patients with HL. Our hypothesis is that the prevalence of ASCVD in patients with PBC who undergo a CT chest or CACS is high, and as a result, HL may be undertreated in this patient population.
Method: We retrospectively reviewed charts of PBC patients, as diagnosed by EASL guidelines, and included adults with CACS or CT for non-cardiac indications. Patients were followed from time of PBC diagnosis to last available clinical follow-up or liver transplantation. Primary outcome was the presence of ASCVD as defined by the presence of coronary calcification on imaging. Secondary outcomes included the prevalence of statin use in patients with strong indications (ASCVD by imaging or personal history of ASCVD), new ASCVD and all-cause mortality. Outcomes were assessed by multivariable regression and included *a priori* covariates (age, sex and presence of advanced fibrosis).
Results: 94 patients with PBC were included. The median age was 60 years and majority were female (92%) and White (55%). 42% were active or former smokers, 44% had hypertension, 11% had diabetes, and 12% had ASCVD diagnosed prior to PBC diagnosis. Steatotic liver disease was present in 12% of patients diagnosed by either liver biopsy or imaging. 84 patients had CT scans for noncardiac reasons. CT scans (or CACS) were performed a median of 5.8 years after PBC diagnosis. 50% of patients had coronary calcification on CT. Of the 58 patients with strong indications for statins, only 28% and 59% were prescribed a statin at time of PBC diagnosis and end of the study, respectively. 23% of patients were on statins at the time of PBC diagnosis and 40% by last follow up. Patients on statins at PBC diagnosis were male, older, and more likely to have metabolic dysfunction associated steatotic liver disease (MASLD) (all $p < 0.05$). 11 patients had new ASCVD events after diagnosis of PBC – 4 myocardial infarctions, 7 strokes, 3 with peripheral arterial disease. Statin use was not associated with ASCVD, death, or fibrosis (all $p > 0.05$). On multivariable analysis, age (OR 1.04, 1.01–1.07) and prior ASCVD (OR 20.33, 1.34–309.52) were associated with new ASCVD. Only advanced fibrosis (HR 6.80, 1.37–33.62) was associated with increased mortality.
Conclusion: ASCVD prevalence is higher in PBC patients than previously thought and likely undertreated. Further studies are needed to better identify those with ASCVD and PBC.

THU-360

Optimization of corticosteroid treatment for acute severe autoimmune hepatitis: slow simmering shows better prognosis

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Background and aims: Uncertainties persist regarding the optimal management of acute severe autoimmune hepatitis (AS-AIH), including the use of corticosteroids. This study aimed to compare the effectiveness and safety of rapid versus slow corticosteroid tapering in AS-AIH.
Method: A multicenter study involving patients with acute AIH was conducted. We defined acute AIH as an acute presentation (<30 days) with AIH and exhibiting no evidence of pre-existing liver diseases. Initially, corticosteroid treatment and overall outcomes were reported. Subsequently, the role of corticosteroid tapering rate in modifying outcomes across subgroups was investigated. For patients with an initial corticosteroid dose of 20 mg/day or higher, we further classified patients into rapid tapering group (duration until dose of prednisone <20 mg/day <3 weeks) and slow tapering group (duration until dose of prednisone <20 mg/day ≥3 weeks). Adverse events were defined with any of the following events, progression (e.g., acute icteric AIH progression to AS-AIH or AIH-ALF, AS-AIH progression to AIH-ALF, non-cirrhotic progression to cirrhosis, compensated cirrhosis progression to decompensation), LT, and liver-related death.
Results: This retrospective cohort study enrolled 237 patients, with 109 presenting acute icteric AIH, 97 with AS-AIH, and 31 with AIH-acute liver failure (ALF). Among patients with acute icteric AIH, slow tapering significantly improved adverse outcome-free survival compared to rapid tapering (99% *vs.* 71%, $P < 0.0001$). Similarly, in

AS-AIH patients, slow tapering resulted in notably higher adverse outcome-free survival rates compared to rapid tapering (92% *vs.* 54%, $P < 0.001$). Slow tapering independently predicted fewer adverse events (OR 0.144; 95% CI 0.037–0.562; $P = 0.005$). However, in AIH-acute liver failure (ALF) patients, tapering rate did not significantly affect adverse outcome-free survival (38% *vs.* 50%, $P = 0.590$). Overall, there were no significant differences in osteoporosis or infection occurrence between tapering groups in the entire acute AIH cohort.
Conclusion: A slow corticosteroid tapering reduced adverse outcomes in acute AIH patients, particularly in acute icteric AIH and AS-AIH.

THU-365

Fibrosis stage is an independent predictor of liver-related complications in primary biliary cholangitis

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Background and aims: This study aimed to clarify the predictive ability of histological stage (HS) in comparison with biochemical response to ursodeoxycholic Acid (UDCA) (BR) for the development of complications in patients with primary biliary cholangitis (PBC).
Method: A total of 226 patients were diagnosed with serologically and histologically confirmed PBC. All the patients with asymptomatic PBC were treated with UDCA continuously for at least 1 year after the diagnosis were enrolled. Pathological staging was performed in accordance with the Scheuer and Nakanuma classifications (SC and NC). NC comprises grading for liver fibrosis (F) and bile duct loss (S). Nakanuma F and S scores were assessed on a four-point scale (F0–F3 and B0–B3). BR was evaluated according to three previously published definitions: the Nara criteria (NaC), Paris II criteria (PC), and Barcelona criteria (BC). This study investigated the relationship of the development of complications with HS and BR. PBC complications include pruritus, esophageal varices, ascites and jaundice.
Results: The distribution of patients in stage I, II, III, and IV based on the SC was 70/102/51/3. The distribution of patients in stage I, II, III, and IV based on the Nakanuma classification was 20/89/107/10. The cumulative complication rates (CCR) were significantly higher in the advanced stages (Scheuer III/IV and Nakanuma III/IV) than in the early stages (Scheuer I/II and Nakanuma I/II), respectively. CCR were significantly higher in the advanced Nakanuma F scores (Score 2/3) and Nakanuma B scores (Score 2/3) than the early Nakanuma F scores (Score 0/1) and Nakanuma B scores (Score 0/1), respectively. However, there was no differences in CCR between the favorite and poor response groups based on NaC, PC or BC. CCR for the four groups of early stages/favorable response (Group A: GA), advanced stages/favorable response (GB), early stages /poor response (GC) and advanced stages/poor response (GD) was estimated by combining histological stages based on HS and BR, defined as (1) SC/NaC, (2) SC/PC, (3) SC/BC, (4) NC/NaC, (5) NC/PC, (6) NC/BC, (7) F/NaC, (8) F/PC, (9) F/BC, (10) B/NaC, (11) B/PC, and (12) B/BC. CCR for (2) SC/PC, (3) SC/BC, (4) SC/NaC, (5) NC/PC, (6) NC/BC, (9) F/BC, and (11) B/PC were significantly higher in GB than in GA. CCR for (1) SC/NaC, (3) SC/BC, (4) NC/NaC, (6) NC/BC, (7) F/NaC, (8) F/PC, and (9) F/BC were significantly higher in GD than in GC. These findings suggest that CCR increase with progression of HS, regardless of BR. The multivariate COX regression analysis showed that the advanced Nakanuma stage was confirmed as independent factor associated with the development of complications in patients with PBC.
Conclusion: Both HS and BR play a pivotal role in the development of complications of PBC. HS is associated with a higher risk for the development of complications than BR in patients with PBC.

THU-366

Early assessment of treatment response in primary biliary cholangitis: key to timely management

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Background and aims: Primary biliary cholangitis (PBC) is an autoimmune liver disease that leads to destruction of the bile ducts and liver fibrosis. The goal of PBC treatment is to achieve a biochemical, histological and clinical remission. The drug of choice for PBC patients is UDCA. Second line PBC treatment for UDCA non-responders is available. The aim of our study was to explore predictive factors associated with compete biochemical response (CBR - both normal bilirubin and ALP levels) in primary biliary cholangitis (PBC) patients treated with ursodeoxycholic acid (UDCA) at month 12 and the end of follow-up. Overall aim of the research is to identify and refine early predictors of the treatment response to allow the inclusion of potential non-responders into second line treatment or clinical trials.
Method: We conducted a multicenter retrospective study of PBC patients. We enrolled patients with PBC treated with UDCA between 1999 and 2024 in 2 hepatology centers in Eastern Slovakia. At inclusion following variables were collected from the patient documentation: total bilirubin, AST, ALT, GGT, ALP, albumin, platelets, prothrombin time (INR) and CRP. Patients were followed every 6 months as is the standard of care for PBC both centers. At follow-up visits, further values of total bilirubine and ALP were collected. We determined the response to the treatment three times during follow-up. After 6 months of UDCA treatment, we assessed therapeutic response according to the modified Toronto criteria; defined as ALP $\leq 1.67 \times$ ULN and total bilirubin $\leq 2 \times$ ULN 13. After 12 months of UDCA treatment and at last check-up, we assessed CBR (ALP $\leq$ULN and total bilirubin $\leq$ULN). Primary outcome was defined as the proportion of patients that achieved CBR, defined as normal bilirubine and normal ALP levels, at last check-up. We had several secondary outcomes as well.
Results: A total 51 of 155 patients included in this study (32.9%) achieved complete biochemical response (CBR) at the end of follow-up. Among patients responding to treatment at month 6 according to Toronto criteria, 44.7% achieved CBR, while only 2.6% of non-responders did. Toronto response at month 6 was the strongest predictor of CBR at 12 months and overall survival. Patients achieving a Toronto response at month 6 had an 81% chance of achieving CBR and a significantly lower risk of decompensation and death compared to non-responders.
Conclusion: Patients with complete biochemical response last check-up had very low chance of hepatic decompensation or liver-related death during follow-up. None of the patients who did not achieve biochemical response at month 6 by Toronto criteria, had CBR at the end of follow-up. For non-responders by Toronto criteria at month 6, initiation of second line treatment should be considered after half a year of treatment.

THU-367

Prognosis of primary sclerosing cholangitis (PSC) in Hungary is independent of coexisting inflammatory bowel disease (IBD) and prognostic ability of the currently used PSC risk scores are limited

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Background and aims: Primary sclerosing cholangitis (PSC) is a rare, chronic disorder of the intra- and extrahepatic biliary tree characterized by cholestasis, periductal inflammation and fibrosis. Currently, there is very limited epidemiological data from the Central-Eastern European region. We assessed disease characteristics and natural history of PSC in a bicentre Hungarian cohort and compared its outcome with respect to co-existing inflammatory bowel disease (IBD).
Method: Imaging, laboratory and clinical data including presence of IBD, variant syndrome, disease course and outcome were prospectively collected in two large Hungarian Clinical Centre Patients were followed on a yearly basis. Median diseases follow-up (FUP) time was 8.82 (IQR: 5.2–13.5) years. A wide range of clinical scoring systems were applied. Poor disease outcome was defined as orthotopic liver transplantation (LT) and/or liver-related death during the FUP.
Results: Of 135 patients (57.8% males; median age at diagnosis: 31 [IQR: 20–47] yrs) with confirmed PSC, 73 (54.1%) had coexisting IBD. Nineteen patients already had cirrhosis at diagnosis and 31 more developed it during the FUP. A total of 21 (15.6%) patients died of which 85.7% were liver-related deaths. Twenty-five patients (18.5%) underwent liver transplantation (LT). Twenty-three (17%) patients developed malignancy (9 cholangiocarcinoma, 3 hepatocellular carcinoma, 6 colorectal carcinoma and 6 non-gastrointestinal malignancy) during the FUP. Patients with IBD were younger and had higher Mayo and Amsterdam-Oxford scores at diagnosis compared to those without, however there was no difference in disease outcomes in these groups ($p = 0.133$). Clinical scores at diagnosis had moderate prognostic ability for poor disease outcome (AUROC [95%CI], Mayo score: 0.637 [0.521–0.753]; $p = 0.018$; Amsterdam-Oxford: 0.687 [0.576–0.798]; $p = 0.002$; $p < 0.001$; UK-long: 0.695 [0.588–0.803]; $p < 0.001$), except UK-short PSC risk score (0.745 [0.643–0.847]). Persistent alkaline phosphatase (ALP) increase, despite ursodeoxycholic acid (UDCA) treatment, especially within the first two years of diagnosis had good prognostic ability (AUROC [95% CI], at diagnosis: 0.656 [0.556–0.757], $p = 0.006$; after one year: 0.724 [0.602–0.847], $p < 0.001$; after two years: 0.746 [0.617–0.875], $p < 0.001$).
Conclusion: Prognosis of PSC is independent of coexisting IBD in our large Hungarian prospective PSC cohort. Prognostic ability of the currently used PSC risk scores is limited. The UK-short PSC risk score and early ALP response to UDCA treatment showed to have the best accuracy.

THU-368
Unveiling the cholangiopathy of critical COVID-19: unique imaging patterns on magnetic resonance cholangiography

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Background and aims: COVID-19-related cholangiopathy, considered a variant of secondary sclerosing cholangitis in critically ill patients (SSC-CIP), represents a progressive cholestatic complication frequently associated with a high risk of progression to cirrhosis, the need for liver transplantation, or death. Diagnosis cannot rely solely on clinical and laboratory findings; therefore, imaging techniques such as magnetic resonance cholangiography (MRC) are essential. This study aimed to describe the imaging findings of COVID-19-related SSC on MRC.
Method: We studied a cohort of 42 adult patients who were mechanically ventilated and confirmed to have COVID-19 through molecular testing between June 2020 and September 2021. These patients had no history of liver disease and were observed until November 2024. A single radiologist reevaluated the MRC studies using a standardised protocol.
Results: Nineteen patients were included, with a median age of 60 [interquartile range (IQR) 51–63], of whom 11 were male (58%). A total of 27 MRCs were performed, with a median interval of 162 days [IQR 78–648.5] after the positive SARS-CoV-2 test. Of these, 24 (88.9%) were conducted prior to any biliary intervention via ERC (endoscopic retrograde cholangiography). In all 26 technically adequate studies, intrahepatic bile duct strictures were identified, with 65.4% presenting with upstream dilation, 81% displaying a "beaded" appearance, and 96% revealing periportal and peribiliary signal alterations without lobar predominance. Intrabiliary casts in the extrahepatic bile ducts were observed in five cases (19.2%). Hepatic morphological changes were detected in 58% of patients. In all follow-up examinations, there was either a worsening in the extent of strictures, an increase in the severity of narrowing, or a progression of upstream dilation. Over a median period of 934 days [IQR 551–1199], eight (42%) developed signs of advanced chronic liver disease, and six patients (32%) died. Significant associations were observed between the severity of MRC findings, age, and the duration of hospitalisation for ARDS (acute respiratory distress syndrome), $p < 0.05$.
Conclusion: COVID-19-related SSC demonstrates multiple intrahepatic bile duct strictures on MRC, with a characteristic "beaded" appearance and thickening of the bile duct walls, accompanied by enhancement and no lobar predominance. The extrahepatic biliary system is generally spared. These findings underscore the critical role of MRC in diagnosing and monitoring this condition.

THU-370
Direct visualization of fibroblast activation protein inhibitor expression in primary sclerosing cholangitis – a novel biomarker for disease activity and inflammation?

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Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease marked by fibrosis and strictures, with high cholangiocarcinoma (CCC) risk. Limited diagnostic tools hinder early tumor detection, worsening prognosis. Recently, ^{68}Ga-FAPI-PET/CT has emerged as a promising imaging modality for CCC detection. This study aimed to assess the diagnostic efficacy of the novel ^{68}Ga-FAPI-PET/CT in PSC, with a particular focus on early CCC detection.
Method: Eleven PSC patients, seven with histologically confirmed CCC, two with both PSC and CCC, and five controls without hepatic disease underwent ^{68}Ga-FAPI-PET/CT. For PET analysis, physiological liver uptake was defined as mean SUVpeak of all controls, plus 2 SD. FAP liver volume above physiologic uptake (FAP-livo) was calculated. Results were compared to endoscopic retrograde cholangiopancreatography (ERCP), laboratory parameters and Fibrosis-4 (FIB-4) score.
Results: Transaminase levels were highest in PSC patients (ALT median: PSC 87 U/L; AST median: PSC 86 U/L). CRP was highest in CCC (median: CCC 30.2 mg/L). Cholestasis markers were elevated across all groups with significant bilirubin elevation only in CCC (median:

CCC 92 µmol/L). Liver synthesis markers, CHE and INR, were mostly preserved, with slight CHE reduction in PSC/CCC and marked reduction in three CCC cases. FIB-4 predicted advanced fibrosis in three CCC cases. CA19.9 was elevated mainly in CCC patients, with high variability (median 171 kU/L; range 6–16,925 kU/L). Physiological liver FAP uptake in controls was homogeneous with a SUVpeak of 1.5 ± 0.2. FAP-livo was elevated in PSC, CCC and PSC/CCC patients (mean ± SD, 1267 ± 843 ml vs. 1362 ± 1302 ml vs. 1990 ± 1921 ml). Lesion SUVpeak did not differ between PSC and CCC (mean ± SD, 9.9 ± 3.9 vs.14.3 ± 5.8, p = 0.07). Due to the high level of diffuse FAP signal elevation in active PSC regions, additional detection of focal lesions typical for CCC was not feasible. However, PSC mainly exhibited diffuse regional uptake along bile ducts, while CCC showed mainly focal uptake. Furthermore, in PSC FAP expression corresponded with ERCP findings near dominant strictures, and FAP-livo correlated with FIB-4 and white blood cell count in PSC (p = 0.03 each), suggesting association to disease activity and fibrosis.

Conclusion: Our findings suggest that ^{68}Ga-FAPI-PET/CT effectively characterizes disease patterns and may aid in assessing fibrosis risk in PSC patients. Although FAP uptake was elevated in both PSC and CCC, limiting its utility for CCC detection in PSC patients, the correlation between FAP-livo, FIB-4 score, and white blood cell count in PSC suggests that ^{68}Ga-FAPI-PET/CT could still be a valuable tool for monitoring disease activity and inflammation in PSC.

Liver development and regeneration

TOP-074-YI

The reelin signaling pathway in lymphatic endothelial cells is a key driver of ductular reaction during liver injury

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Background and aims: Ductular reaction (DR) exhibiting histologically as proliferating ductal and hepatic progenitor cells (HPC) plays a crucial role in regeneration during liver injury. Mechanisms underlying DR during regeneration in injured liver remains poorly studied. We characterized vascular niche factors governing DR and HPC proliferation in liver injury models.

Method: To study liver regeneration in injury, 2-Acetyaminoflourene (2-AAF) followed by 70% PHx (AAF-PHx) models were developed along with AAF-sham. All analyses were performed from 12 h to D21 post AAF-PHx. Ov6+EpCAM+/CK19+ HPC and ductal cells, CD31+ liver sinusoidal endothelial cell (LSEC) and CD31+PDPN+ lymphatic endothelial cell (LyEC) were studied by Flow Cytometry and immunofluorescence. Proteomic analysis was performed on sorted LSEC and LyEC and differentially expressed proteins and pathways were identified. A single cell RNA seq (scRNA seq) atlas of fibrotic human livers was analysed to identify LyEC ligands expressed in human disease. LyEC:ductal cell co-cultures were employed to validate effect of identified protein and pathway on cell proliferation. Inhibition studies were done using CRISPR-Cas9 mediated transfection of ductal cells with DNA plasmids encoding guide RNA targeting specific genes.

Results: Ductular cells and HPC increased from D4 with maximum increase at D8 and D15 post AAF-PHx. Maximum increase in LSEC and LyEC were observed at D8 and D15. Confocal imaging of liver tissues revealed close association between LyEC and CK19+ ductal cells in portal areas. In-vivo inhibition via MAZ51, a vegfr3 lymphangiogenesis inhibitor led to decline in LVs number and LyEC (60%) along with ductal cells (50%) at D8 post AAF-PHx. Compared to sham, LSEC and LyEC from D8 showed an enrichment and activation of common cell proliferation pathways like Wnt/β-catenin, Ras/MAPK, PI3 K/Akt, actin etc. From rodent proteomics data, human liver scRNA seq and ELISA, we identified reelin (Reln) in LyEC as one of the significant upregulated secretory protein. A high gene expression of Reln and two of its receptors (ITGB1 and ITGA3) was seen on LyEC and ductal cells of AAF-PHx models respectively. Compared to control, treatment of ductal organoids with LyEC-conditioned media and recombinant Reln led to their increased diameter (12 ± 2 vs 21 ± 3 and 19 ± 2)µm. Compared to control cultures, inhibition of ITGB1 and ITGA3 on 2D ductal cell cultures significantly reduced subsequent organoid numbers in 3D cultures (27 ± 2 vs 17 ± 4 and 15 ± 3) and also decreased expression of downstream pathway proteins, pAkt (2fold) and pERK (1.5fold).

Conclusion: Our study suggest that LyEC contribute to ductular proliferation via Reelin-ITGB1/ITGA3 pathway during liver injury. Understanding of mechanisms involved in liver regeneration by HPCs holds promise for potential development of novel therapeutic approaches to life-threatening liver diseases.

SATURDAY 10 MAY

SAT-049

Harnessing antioxidant nano-chimeras for combining targeted transforming growth factor β receptor I degradation and transforming growth factor β reduction to attenuate liver fibrosis

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Background and aims: Polydopamine nanoparticles (PDA NPs) have manifested reactive oxygen species (ROS) scavenging capabilities to alleviate the progression of liver fibrosis. Targeting the transforming growth factor β (TGF-β) receptor I (ALK5) to disrupt the TGF-β -Smad2/3 signaling pathway emerges as a potent therapeutic strategy for liver fibrosis. Lysosomal targeting chimeras (LYTACs) technology particularly utilizes various cell membrane receptors to redirect both secretory and membrane-associated target proteins towards lysosomal degradation. Notably, CI-M6PR is a transmembrane receptor highly expressed on the surface of activated hepatic stellate cells (HSCs) that transports mannose-6-phosphate (M6P)-tagged cargos to lysosomes. The aim of the study was to ascertain whether LYTAC constructed with M6P, ALK5 small molecule inhibitor and PDA NPs, which called MAPs, could exert a good role in anti-liver fibrosis.

Method: MAPs' effects of reducing the expression of TGF-β and degrading ALK5 by lysosome to alleviate the activation of HSCs were respectively assessed in H_2O_2-treated mouse monocyte - macrophage leukemia cells (RAW264.7) and TGF-β-induced human hepatic stellate cells (LX-2) by western blot and qPCR. The therapeutic potential of MAPs against liver fibrosis was further evaluated in a CCl_4-induced murine liver fibrosis model, mice were intragastric administrated CCl_4 twice weekly for 1 month, and received treatment of MAPs via the caudal vein every other day from the third week of model construction.

Results: MAPs efficiently scavenged ROS within the macrophages, thereby reducing both the transcriptional and protein levels of TGF-β, and utilized the high affinity of M6P for the CI-M6PR to target activated HSCs for lysosomal degradation of ALK5, leading to

impairment of the TGF-β-Smad2/3 pathway and a decline in the secretion of the ECM in HSCs. In the CCl_4-induced murine liver fibrosis model, MAPs located in liver mostly, reduced fibrotic biomarkers and alleviated liver fibrosis. In addition, CCl_4 treatment robustly augmented phosphorylation levels of Smad2 and Smad3, while MAPs treatment led to significant decreases, thereby markedly dampening the TGF-β-Smad2/3 signaling pathway.
Conclusion: Our research developed an innovative LYTAC system, MAPs, using antioxidative PDA nanoparticle as the core, with R268712 as the ALK5 targeting ligand and M6P as the CI-M6PR targeting ligand, which effectively reduced TGF-β production by scavenging ROS and downregulated ALK5 expression through lysosomal degradation. These dual mechanisms synergistically inhibit the activation of the TGF-β-Smad2/3 signaling pathway in HSCs, effectively reducing ECM expression and alleviating the progression of liver fibrosis. Our work pioneers the use of LYTAC technology in the therapeutic landscape of liver fibrosis, expanding the potential treatment modalities.

SAT-050
Knockout of DDX3X promotes liver regeneration through CD36-mediated hepatic lipid accumulation
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Background and aims: The liver possesses a unique regenerative capacity, which is indispensable for the recovery process following liver resection and the management of various liver diseases. Accumulation of lipids in hepatocytes has been recognized as a pivotal factor during liver regeneration, yet the intricate mechanisms underlying this process remain elusive. This study endeavors to elucidate the mechanism through which DDX3X mediates lipid accumulation during liver regeneration.
Method: We collected serum samples from patients at various time points post-hepatectomy. A liver regeneration model in C57BL/6 mice was established by performing a two-thirds partial hepatectomy (PH). Hepatocyte-specific DDX3X knockout (DDX3XΔhep) mice were generated using CRISPR/Cas9/Cre-LoxP technology to investigate the pivotal role of DDX3X in liver regeneration. High-throughput RNA sequencing was conducted to dissect the downstream signaling pathways in DDX3XΔhep mice during liver regeneration. Oil Red O staining was utilized to visualize liver lipid accumulation. qPCR and Western blotting were employed to assess the expression levels of target genes and proteins, respectively.
Results: Patients undergoing PH exhibited a progressive decrease in serum DDX3X levels. In the mouse liver regeneration model, hepatic DDX3X expression initially surged (0–12 hours) and subsequently declined (24–96 hours). Following two-thirds PH, DDX3XΔhep mice demonstrated a significantly augmented regenerative capacity compared to controls, accompanied by a marked increase in liver lipid levels. RNA sequencing revealed enhanced fatty acid uptake in DDX3XΔhep mice during liver regeneration. Notably, knockdown of the key fatty acid receptor CD36 significantly reduced hepatocyte lipid accumulation and impeded liver regeneration in DDX3XΔhep mice.
Conclusion: During liver regeneration, hepatocyte DDX3X deficiency promotes hepatocyte proliferation by augmenting liver lipid accumulation through CD36 regulation. Our findings offer novel insights into the mechanisms underlying liver regeneration and identify potential targets for accelerating postsurgical recovery in patients.

SAT-055
Echinococcus multilocularis infection induces pathological angiogenesis in mouse liver via PDGFR/PI3 K/AKT/FAK signaling pathway
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Background and aims: Alveolar echinococcosis (AE) is a globally prevalent zoonotic disease caused by Echinococcus multilocularis (E. multilocularis) infection, characterized by the formation of tumor-like growths primarily in the liver, with the potential to spread to other organs. Similar to tumors, E. multilocularis infection is accompanied by pathological angiogenesis, suggesting that the implementation of anti-angiogenic therapeutic strategies may also have promising applications in the treatment of AE. However, the mechanism of angiogenesis in AE remains unclear and needs to be clarified.
Method: To investigate the mechanism of pathological angiogenesis induced by E. multilocularis infection, we established a mouse infection model by inoculating protoscoleces via the hepatic portal vein. Mice were sacrificed at different time points post-infection (2, 4, 10, and 12 weeks) for histopathological and gene expression analyses. Liver tissues were subjected to hematoxylin and eosin (H&E) staining, periodic acid-Schiff (PAS) staining, Sirius red staining, and immunohistochemistry (IHC) to assess pathological changes and angiogenesis. Quantitative real-time PCR (qRT-PCR) was performed to measure the expression levels of angiogenesis-related genes. In vitro experiments were conducted using human umbilical vein endothelial cells (HUVECs) to explore the angiogenic effects of E. multilocularis protoscoleces protein (EmP). Various signaling pathway inhibitors, including PDGFR-β inhibitor AG1296, PI3 K inhibitor LY294002, AKT inhibitor MK2206, and FAK inhibitor Y15, were utilized to elucidate the underlying signaling pathway. Cell viability, migration, and pseudocapillary formation assays were conducted to assess the functional effects of EmP on HUVECs.
Results: In this study, we discovered that angiogenesis related genes are significant up-regulated in the mouse model of E. multilocularis infection and pathological angiogenesis around the lesion was significantly increased at 10–12 weeks after infection compared to the control group. Interventions utilizing a range of inhibitors at the in vitro level, including the PDGFR-β inhibitor AG1296, the PI3 K inhibitor LY294002, the AKT inhibitor MK2206, and the FAK inhibitor Y15, demonstrated that E. multilocularis protoscoleces protein (EmP) induces angiogenesis through PDGFR/PI3 K/AKT/FAK signaling pathway.
Conclusion: Our findings provide new perspectives on how E. multilocularis infection triggers pathological angiogenesis in the host liver, and may provide a novel anti-angiogenic therapeutic strategy against E. multilocularis infection.

SAT-056
Regulation of interleukin-6- and epidermal growth factor receptor-dependent pathways by augmenter of liver regeneration is mediated by activation of ADAM17
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Background and aims: Liver regeneration is a process that is tightly regulated by several cytokines and growth factors. Augmenter of liver regeneration (ALR), a ubiquitously expressed anti-apoptotic, anti-oxidative and anti-inflammatory co-mitogen, is known for its hepatotrophic properties, especially during regenerative processes. Despite its established role in supporting liver regeneration, the molecular mechanisms by which ALR influences cell proliferation and inflammation remain poorly understood. This study seeks to

elucidate ALR's molecular effects on key signaling pathways involved in liver regeneration, providing deeper insights into its regulatory functions.
Method: Hepatoma cell lines and primary mouse hepatocytes were treated with recombinant human ALR (rALR) and/or various specific inhibitors, and the respective signaling pathways were analyzed by immunoprecipitation, Western Blot, qRT-PCR and ELISA techniques.
Results: Our findings reveal that rALR plays a multifaceted role in modulating molecular pathways. It phosphorylates EGFR at cytoplasmic sites independent of direct receptor binding, activating downstream mediators ERK1/2 and Akt. rALR also suppresses IL-6-induced JAK1 and STAT3 phosphorylation, reducing STAT3 target genes involved in inflammation (e.g. ICAM-1) and iron homeostasis (e.g. hepcidin, transferrin receptor, ZIP14). This occurs independently of EGFR activation and without the involvement of regulatory proteins such as SOCS1/3, PIAS, or SHP1/2. Additionally, rALR enhances membrane-bound ADAM17/TACE expression and activity, promoting the release of EGFR ligands and IL-6 receptor (IL-6R) subunit alpha. Mechanistically, rALR activates a GPCR, triggering src and PKC, which induces ADAM17. These findings underscore ALR's intricate role in regulating cell proliferation and inflammation.
Conclusion: In conclusion, rALR modulates key signaling processes by activating the sheddase ADAM17/TACE via GPCR, PKC, and src pathways. This activation promotes the release of EGFR ligands and IL-6R subunit alpha, with EGFR ligands triggering MAPK and PI3 K/Akt pathways to drive cell proliferation. By inducing IL-6R shedding, rALR reduces the functional IL-6 receptor complex, suppressing STAT3 target gene expression in hepatocytes and mitigating inflammation. These actions highlight ALR's broad regulatory impact, influencing EGFR transactivaiton, IL-6R shedding, and potentially other ADAM17-mediated pathways.

SAT-057

Time-restricted feeding modulates genes involved in liver regeneration and damage regression processes in a rat model treated with diethylnitrosamine

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Background and aims: Chronic liver damage can lead to various pathologies ranging from early, reversible conditions like fibrosis and steatosis to irreversible, life-threatening diseases such as cirrhosis and hepatocellular carcinoma. The relationship between inflammation, fibrosis, and regeneration processes is crucial in the progression of damage, and thus, clinical intervention at early stages is critical to prevent its progression. However, the mechanisms driving this progression remain poorly understood, as these stages are subclinical. Time-restricted feeding (T-RF) protocols have shown protective effects against liver damage in both animal models and human clinical studies. By promoting reversible and regenerative processes, T-RF serves as a potentially significant intervention for patients with early-stage liver disease. In this study, we investigated the protective mechanisms of T-RF against chronic inflammation and fibrosis while promoting hepatic regeneration using a rat model treated with the hepatotoxic diethylnitrosamine (DEN).
Method: Forty males Wistar rats were randomly divided into four groups: A) AL group: Untreated rats with 24 hours (h) of food access (Ad libitum). B) AL+DEN group: Rats treated with DEN and Ad Libitum food access. C) T-RF group: Untreated rats with only 2 h of food access per day. D) T-RF+DEN group: Rats treated with DEN and 2 h of food access per day. After 8 weeks of DEN treatment (50 mg/kg), followed by 2 weeks of hepatotoxic depuration, the regression effects induced by T-RF were assessed through blood markers of inflammation and hepatic damage, histopathology, immunohistochemistry technique, and bulk RNA-seq analysis.
Results: Signs of damage were shown in groups treated with DEN but with differential signs of regression pathways. Histopathological evaluation using the Ishak ratio determined, that the liver in both groups AL+DEN and T-RF+DEN underwent regression and regenerative processes, albeit through different mechanisms. In the T-RF+DEN group, chronic inflammation markers were significantly reduced; total leukocytes and lymphocytes count were 34% and 40% lower compared with the AL+DEN group, indicating a significant decrease in systemic chronic inflammation. Additionally, by immunohistochemistry the TNF-alpha levels were significantly lower in the T-RF +DEN group with 1.1 of arbitrary units (AU) compared to the AL+DEN group with 4.8 AU. Through RNA-seq, in AL+DEN group presented 7649 down regulated and 7176 up regulated genes, while T-RF induced 10% upper and 54% downer regulated genes compared with AL+DEN. Also, we identified 53 key genes involved in regeneration and regression processes. The top five of up regulated genes in the T-RF+DEN group compared to the AL+DEN group were STAT6, SP1, SMARCA4, IL6R, and NFkB1, which are associated with regeneration.
Conclusion: The T-RF protocol improved the liver regeneration process by avoiding the establishment of chronic inflammation and favouring regenerative processes.

SAT-058-YI

MAIT cells mediate liver tissue repair via VEGF and VIM secretion

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Background and aims: Mucosal-associated invariant T (MAIT) cells are highly abundant in the human liver, comprising 20–50% of intrahepatic T cells. MAIT cells express transcriptional signatures linked to tissue repair, but the specific factors driving this function in human tissues remain undefined. The aim of our study is to identify such factors and examine their in vivo relevance, especially in the liver.
Method: Peripheral MAIT cells were isolated from healthy donors and activated using TCR ligands and cytokines. The production of growth factors and vimentin (VIM) was assessed via flow cytometry or in cell culture supernatants using LEGENDplex and Western blot techniques. To evaluate the role of MAIT cells in tissue repair, supernatants were applied to hepatocyte (HHL12) and epithelial (Caco-2) monolayers in wound-healing assays. The role of VEGF/VIM signaling inhibition in repair-associated processes was investigated by blocking VEGFR2 and VIM. To corroborate the relevance of these findings in vivo, single-cell RNA-sequencing data from human liver injury models were analyzed.
Results: Activated MAIT cells were found to produced VEGF and PDGF-AA, with VEGF levels notably higher than those produced by conventional naïve, central memory, and effector memory T cells.

Further, we discovered that activated MAIT cells also secrete VIM, a structural protein that can function as an alternate ligand of VEGFR2. Functionally, supernatants from MAIT cells accelerated wound closure, an effect that was blocked by VEGFR2 and VIM inhibition. Analysis of liver injury models further revealed that MAIT cell-derived VEGF and VIM expression was prominently upregulated in regenerating liver tissue, underscoring their role in tissue repair in vivo.
Conclusion: Our findings demonstrate that MAIT cells play a critical role in tissue repair through the secretion of pro-proliferative factors like VEGF and VIM. For the first time, we provided evidence that by producing VEGF and VIM, MAIT cells drive tissue regeneration via VEGFR2. These results highlight MAIT cells as key mediators in tissue repair, particularly liver regeneration.

SAT-059-YI
A comprehensive study on acute and chronic liver injury response in Acomys (Spiny mice): insights into the role of p21 in liver regeneration
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Background and aims: Although mammalian livers possess remarkable regenerative abilities, sustained injury leads to fibrosis and eventual cirrhosis. The genus *Acomys* has emerged as a promising model for studying mammalian regeneration. They demonstrated regenerative capabilities across multiple organ systems, including the central nervous, renal, musculoskeletal, and cardiac systems. Based on these consistent outcomes, we hypothesize that *Acomys* livers exhibit accelerated, scarless regeneration. This project aims to investigate whether *Acomys* livers regenerate efficiently with minimal fibrosis following acute and chronic injury.
Method: We employed 1) surgical model of 2/3 partial hepatectomy (PHx), 2) acute injury model of acetaminophen (APAP) overdosing, and 3) chronic fibrosis-inducing model of carbon tetrachloride (CCl4). Liver samples were processed for histological analysis. Mass spectrometry-based proteomics was carried out in PHx model.
Results: In all models, irrespective of the mode of injury, *Acomys* consistently displayed an increase in p21+ hepatocytes at injury sites, a response that was absent in *Mus*. In PHx model, *Acomys* restored liver function within 48 hours and achieved complete liver mass regeneration within 7 days (n = 7). A significant increase in p21+ hepatocytes was observed in the PHx compared to the sham group (20.47% vs 0.57%; p = 0.002). Despite the upregulation of cell cycle inhibitor, the remnant livers remained proliferative (median BrdU+ hepatocyte: 2.94%). Proteomic analysis also confirmed an upregulation of cell cycle-associated proteins in regenerating liver tissues (Sham n = 2; PHx n = 3). In APAP model, *Acomys* demonstrated higher tolerance than *Mus* (median necrotic area: 6.05% vs 31.02%; p = 0.029). Time-course studies revealed a transient increase in p21 in *Acomys*, which then resolved as liver regenerated (median p21+ hepatocyte: 40.20% vs 0.30%). Interestingly, those cells predominantly localized around the portal vein, forming a distinct boundary from the central vein. In CCl4 model, *Acomys* exhibited no significant elevation in liver damage markers, despite pronounced histopathological changes (n = 7). While *Mus* displayed a significant increase in fibrotic tissue between control and injured groups (median fibrotic area: 1.58% vs. 3.29%; p = 0.027), *Acomys* exhibited minimal fibrotic tissue accumulation (2.93% vs. 3.13%; p = 0.81).
Conclusion: A key finding across all models was the consistent p21 overexpression coincided with injury and resolved during the regeneration process. This precise regulation of p21 appears to facilitate the initiation of the repair cascade while minimizing senescence-associated damage. Investigating the molecular mechanisms underlying *Acomys*' ability to resolve cell cycle arrest and re-enter proliferation holds potential for advancing tissue repair and regenerative medicine, particularly in the context of age-related diseases where cellular senescence plays a significant role.

SAT-060
Extending the lifespan of human chemically derived hepatic progenitors by treating with Drug A
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Background and aims: In clinical trials, mature hepatocyte transplantation has shown potential as an alternative to organ transplantation. However, this approach faces challenges, including limited cell engraftment efficiency, maintenance of function, and long-term *in vitro* culture. To address these issues, we developed human chemically derived hepatic progenitors (hCdHs) capable of differentiating into hepatocytes and cholangiocytes using small molecules to reprogram human primary hepatocytes (hPHs), as demonstrated in previous studies. Despite this progress, variability in cell characteristics among patients and the difficulty of maintaining stem cell properties during long-term culture remain significant obstacles. To overcome these limitations, we identified Drug A to enable prolonged culture while preserving stem cell properties.
Method: Drug A-treated hCdHs (Drug A-hCdHs) were generated by reprogramming hPHs isolated from liver tissue using a medium containing HGF, A83-01, CHIR99021 (referred to as HAC), and Drug A for 8–12 days. hCdHs generated from HAC-containing reprogramming medium without Drug A served as control. The generation of Drug A-hCdHs was confirmed through qPCR and immunofluorescence (IF). To induce cholangiocyte differentiation, Drug A-hCdHs were treated with HAC medium supplemented with EGF, HGF, and CHIR99021 (referred to as CDM). Additionally, Drug A-hCdHs were plated on Matrigel to generate organoids.The organoids generation was observed at day 3 of culture. Drug A-organoids were divided in the day 7 of culture or when the organoids reached the 100 um.
Results: We successfully generated Drug A-hCdHs, and we assessed the mRNA and protein expression of hepatic progenitor cell markers using qPCR and IF. We found that the expression of hepatic progenitor cell markers was maintained at higher levels in Drug A-hCdHs compared to hCdHs as passages increased. Additionally, we confirmed through qPCR analysis that the expression of hepatic stellate cell (HSC) markers increased in hCdHs with prolonged culture, while Drug A-hCdHs did not show them. Furthermore, the results from western blot using PCNA marker indicated that treatment with Drug A enhanced the cell proliferation capacity. Drug A-hCdHs were shown to be capable of differentiating into cholangiocytes. Finally, we successfully generated organoids using Drug A-hCdHs in 3D culture.
Conclusion: These results demonstrated that Drug A regulates the lifespan of cells while preventing HSC-like properties and maintaining hepatic progenitor cell characteristics. Additionally, we showed that Drug A-hCdHs can differentiate into cholangiocytes, and furthermore, can generate organoids.
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SAT-061-YI
Impact of NEDDylation on aging and liver senescence: key insights
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Background and aims: Liver aging involves a series of cellular and molecular changes that impair liver function and affect the ability to maintain metabolic homeostasis. This process is characterized by an increase in cellular senescence, where cells lose their ability to divide and proliferate, but remain metabolically active, secreting inflammatory and pro-fibrotic factors that contribute to a pro-inflammatory microenvironment. This environment promotes progressive deterioration of liver tissue. With aging, energy metabolism is altered, particularly in the pathways related to lipid and glucose processing. These changes not only reduce the energy efficiency of liver cells, but also predispose the liver to pathologies such as metabolic dysfunction-associated fatty liver disease, which is common in older individuals. NEDDylation, a post-translational modification that regulates the activity of various proteins, plays a key role in liver metabolic processes. Its dysregulation affects glucose and lipid metabolism and interferes with signaling pathways and protein stability. Consequently, NEDDylation may act as a "driver" of liver aging, contributing to the prosenescent and inflammatory state observed in the aging liver. This study aimed to identify the key changes in the NEDDylation process associated with aging.
Method: We conducted an in-depth analysis of NEDDylation in liver samples from murine aging models, including Progeria and SAMR1/SAMP8 models, as well as mice of different ages. Additionally, we performed experiments involving NEDP1 overexpression in the livers of mice of varying ages to further investigate its role in aging-related processes.
Results: Our findings revealed progressive dysregulation of key molecules involved in NEDDylation, which correlated with aging. This suggests that this post-translational modification is intrinsically linked to liver aging. Notably, we observed significant alterations in the level and activity of NEDP1, a critical regulator of NEDDylation, underscoring its potential role in driving age-related changes in the liver. Preliminary results from NEDP1 overexpression experiments indicated that this manipulation induces senescence markers and disrupts metabolism and mitochondrial function. These findings highlight the impact of NEDDylation dysregulation on liver aging and its contribution to the pro-senescent and inflammatory state in aged liver tissue.
Conclusion: Our study underscores the critical role of NEDDylation in liver aging, linking its dysregulation to the key metabolic and cellular changes associated with this process. The observed effects of NEDP1 overexpression on senescence markers and mitochondrial function further emphasized the importance of NEDDylation as a potential therapeutic target. Exploring strategies to modulate NEDDylation could pave the way for novel approaches to address chronic liver diseases and promote health at an advanced age.

SAT-062

Generation and functional profiling of injury-resistant ductal organoids with biliary tree networks optimized by genipin

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Background and aims: Cholangiocytes may suffer from oxidative stress injury and mitochondrial dysfunction during the construction of functional ductal organoids (FDOs) for liver regenerative medicine, which limits the functional performance and application potential of the organoids. We aimed to construct injury-resistant FDOs with biliary tree networks.
Method: We used genipin, a crosslinking agent with anti-inflammatory and antioxidant properties, to optimize rat decellularized liver scaffolds (DLSs) and reconstructed FDOs with primary cholangiocytes isolated from mouse bile ducts. The genipin-crosslinked FDOs (GNP-FDOs) were characterized through functional assays and transcriptomics. Hepatotoxic drug chlorpromazine was used to assess the injury-resistance ability of GNP-FDOs.
Results: We observed that genipin-crosslinked DLSs exhibited improved resistance to degradation, showing a degradation rate of about 60% after 120 hours of treatment with collagenase, while non-crosslinked DLSs were completely degraded. Calcein-AM/PI double staining revealed that GNP-FDOs formed a continuous and multi-branch biliary tree network at 7 days. JC-1 staining showed that cholangiocytes in GNP-FDOs had stable mitochondrial potential at day 7 compared with non-crosslinked FDOs. The primary cilia in biliary lumen of GNP-FDOs was observed at day 7 with scanning electron microscopy and immunostaining for acetylated α-tubulin. The rhodamine 123 transport assay exhibited the mature functions of bile secretion and transportation in GNP-FDOs by day 7. Transcriptomic analysis of GNP-FDOs cultured for 1, 7, and 14 days revealed that anti-apoptotic genes were significantly upregulated, while apoptosis-related genes were downregulated at days 7 and 14. Enrichment analysis of 1,014 differentially expressed genes between days 1 and 7 demonstrated that GNP-FDOs exhibited enrichment in gene sets related to primary cilia at 7 days. Pathways related to bile synthesis and secretion, drug metabolism, lipid metabolism, and retinol metabolism were significantly activated at day 7 and remained activated at day 14. The GNP-FDOs upregulated Muc5ac and Lcn2 expression by the IL-17 signaling pathway, exerting antibacterial effects and protecting cells from injury. After exposure to the hepatotoxic drug chlorpromazine for 24 hours, Calcein-AM/PI double staining and JC-1 staining revealed that the GNP-FDOs cultured for 7 days maintained high cell viability and preserved the stability of biliary trees. The expression of apoptosis- and inflammation-related genes in GNP-FDOs were significantly suppressed in response to chlorpromazine exposure.
Conclusion: Such GNP-FDOs with the specific functions of bile secretion and drug metabolism exhibit high resistance to injury, providing promising potential for future clinical therapeutic applications in biliary diseases.

SAT-065-YI

Engineered extracellular vesicles derived from mesenchymal stem cell carrying insulin-like growth factor I to promote liver regeneration after partial hepatectomy

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Background and aims: Liver transplantation is currently the only curative treatment for end-stage liver diseases. Impaired regeneration after liver resection may cause liver failure. Because extracellular vesicles (EV) derived from mesenchymal stem cells (MSC) largely reproduce their immunomodulatory, cytoprotective, and pro-regenerative effect, they are proposed as an alternative to cell therapy. Furthermore, EV are also emerging as a strategy to deliver therapeutic genes. We have recently demonstrated in experimental models that the anti-fibrotic effect of MSC from the umbilical cord (human umbilical cord perivascular cells, HUCPVC), genetically modified to express the hepatoprotective and pro-regenerative factor IGF-I (insulin-like growth factor I), is mediated by EV carrying IGF-I. The aim of this study was to evaluate the effect on liver regeneration of EV carrying IGF-I on partial hepatectomy (PH) model in mice.
Method: EV were isolated by ion exchange chromatography from supernatants of HUCPVC infected with adenoviruses codifying for green fluorescent protein (GFP-HUCPVC-EV) or IGF-I (IGF-I-HUCPVC-EV). EV phenotype was evaluated by flow cytometry for CD63, CD9, CD81 markers and nanoparticle tracking analysis was used to determine EV concentration and size distribution. EV´s biological function was assessed by anti-inflammatory assay on macrophages J774 cells. PH of 66% of liver mass were performed on adult C57BL6 mice by surgical removal of right and left lobes (2/3 of total liver mass). After 1 hour of PH, vehicle (saline solution); GFP-HUCPVC-EV; or IGF-I-HUCPVC-EV were administered by tail vein (1 dose, 50 microgram/mice) and 3 days later animals were euthanized to liver sample collect (n = 6/group). Liver index was calculated as ratio of liver/body weight and liver regeneration rate (LRR) as % of recovered liver mass. qPCR and histological analysis, including mitotic index and PCNA immunohistochemistry for cell proliferation were performed on liver sample.
Results: IGF-I-HUCPVC-EV were able to load and deliver IGF-I while keeping their phenotype, size and biological function. Also, in vivo treatment with IGF-I-HUCPVC-EV led to a higher LI and LRR compared to control groups. An increase in PCNA+ cells following IGF-I-HUCPVC-EV administration indicated enhanced liver regeneration. Moreover, IGF-I-HUCPVC-EV treatment upregulated markers associated with hepatocyte proliferation, such as PCNA, HGF, and cyclin D1, as well as IGF-I, a marker of hepatocyte function. In contrast, the treatment with IGF-I-HUCPVC-EV reduced the expression of pro-inflammatory genes such as IL-1beta, TNF-alpha and iNOS.
Conclusion: Our findings provide experimental evidence supporting IGF-I-HUCPVC-EV as a promising therapeutic agent for enhancing liver regeneration following surgical injury.

SAT-066
A 3D human liver organoid model to study the impact of ischemia-reperfusion injury on liver regeneration during transplantation

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Background and aims: End-stage liver disease (ESLD) is a major global health burden, with liver cirrhosis and hepatocellular carcinoma (HCC) as leading causes of mortality. Liver transplantation (LTx) is the only treatment for ESLD, offering the best chance for survival, but its success is often limited by ischemia-reperfusion injury (IRI), a key cause of graft failure. Stem/progenitor cell-derived organoids, including liver organoids, are 3D *in vitro* models replicating native organ functions. These systems are promising tools for studying liver function, disease modeling, and regenerative medicine. Here, we implemented a 3D human liver organoid (hLiO) model to investigate the impact of IRI on liver regeneration.
Method: We isolated EpCAM+ liver progenitor cells from healthy liver biopsies using enzyme digestion, and seeded them in basal membrane extract (BME) to expand undifferentiated hLiO in a tailored expansion medium. Organoids were characterized by assessing liver progenitor markers (LGR5, EpCAM) via RT-PCR and immunofluorescence. To evaluate the differentiation potential of hLiO, we used a specific medium to differentiate hLiO into hepatocytes. Differentiation was confirmed by mature hepatocyte marker expression (HNF4A, CYP3A4) and albumin secretion (ELISA). Finally, undifferentiated hLiO were used to model ischemic injury through cold storage at 4°C for varying durations (4 to 20 hours), with cell viability assessed at each time point.
Results: We first analyzed undifferentiated hLiO, which expressed higher levels of LGR5 and EpCAM but lower levels of albumin, HNF4A, and CYP3A4 compared to iPSC-derived hepatocytes and primary hepatocytes. Following the differentiation protocol, hLiO exhibited increased albumin secretion and higher expression of CYP3A4 and HNF4A compared to hLiO maintained in expansion medium. Our hLiO model effectively mimics the liver regeneration process through a straightforward *in vitro* differentiation protocol over 11 days. We then evaluated the impact of cold ischemia on undifferentiated hLiO. Our data showed mortality rates of 47 ± 15% at 13 hours, 75 ± 11% at 17 hours, and 84 ± 10% at 20 hours, while no significant effects were detected after 4 hours of cold ischemia.
Conclusion: We presented hLiO as a valid 3D model capable of recapitulating liver regeneration capacity. Consequently, hLiO can serve as a robust model to study the impact of IRI on liver regeneration. We preliminarily evaluated the effects of ischemia on undifferentiated hLiO, but further studies are required to investigate the mechanisms underlying ischemic liver injury, the effects of reperfusion following cold ischemia, and their implications for liver regeneration. This work reveals a promising approach to studying the impact of IRI on liver regeneration, with the ultimate goal of improving liver recovery and regeneration outcomes after transplantation.
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SAT-067
3D assembloid model as a useful in vitro tool to study acute and chronic liver diseases

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Background and aims: The study of acute and chronic liver diseases in vitro relied on 2D cell cultures, which often failed to capture the complexity of the in vivo liver environment. In contrast, 3D cultures more accurately replicate liver architecture, and cell-to-cell interactions, enabling a more physiologically relevant representation of liver functions. 3D assembloids, composed of multiple cell types in a spatially organized structure, more closely mimic in vivo conditions, providing a scalable and human-relevant platform for preclinical testing. 3D assembloids can derive from hiPSCs, offering greater reproducibility and consistency than primary cells. hiPSCs are ideal for creating functional liver assembloids due to their plasticity and ability to self-organize into 3D spheroids. As proof of concept, our preliminary study aims to generate a multicellular 3D liver assembloid composed of hiPSC-HEPs and HUVEC endothelial cells.
Method: Human dermal fibroblasts were reprogrammed into hiPSCs using the CytoTune-iPS 2.0 Sendai Reprogramming Kit, and their pluripotency was assessed through gene and protein expression

analysis (qRT-PCR and IF). 2D hiPSC-HEPs were generated using the STEMdiff™ Hepatocyte Kit. For 3D hepatocyte cultures, the differentiation protocol was adapted for non-adherent conditions. HEP differentiation was evaluated via marker expression and albumin release. 3D liver assembloids were created by combining 3D hiPSC-HEPs and HUVEC endothelial cells in a specific ratio, and the assembloids were analyzed for the expression of cell-specific markers.

Results: We generated functional 2D hiPSC-HEPs, characterized by the expression of specific markers and albumin production and secretion. We also optimized a protocol to create mature hepatocyte organoids that expressed the same markers. While differentiation protocols for hiPSC-derived liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs) are still in progress, we initiated a proof-of-concept approach to create a 3D multicellular system by combining 3D hiPSC-HEps and HUVEC endothelial cells. Over 14 days, we monitored assembloid formation and performed IFs for HEPs and HUVEC-specific proteins. Whole-mount staining revealed a multicellular system positive for CK18 (hepatocyte marker) and CD31 (endothelial marker), with HUVECs exhibiting a typical elongated, organized arrangement around the hepatocytes, a characteristic behavior of endothelial cells in 3D models.

Conclusion: Our preliminary data support the feasibility of generating hiPSC-HEP organoids that express cell-specific markers and exhibit hepatocyte functions in vitro. While differentiation protocols for LSECs and KCs are still under development, our findings suggest that 3D liver assembloids can be generated to recreate the liver lobule niche, highlighting important cellular crosstalk in physiological and pathophysiological contexts.

This work was supported by project PNRR-MAD-2022-12375707 CUP I73C22000670006, funded by the European Union - Next Generation EU - NRRP M6C2 Investment 2.1 Enhancement and strengthening of biomedical research in the NHS.

SAT-068-YI

Room for improvement in female authorships across leading medical journals

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Background and aims: The field of hepatology is undergoing a pivotal transformation with emerging medical treatments for steatotic liver disease (SLD). Randomized controlled trials (RCTs) remain the gold standard for evaluating clinical interventions, and prominent authorship positions—particularly first, second, and last authors—are key indicators of academic leadership and influence. However, gender equity in these positions remains a concern.

Method: The current analysis focused on RCTs across all specialties published on PubMed in four major journals: *The Lancet*, *The New England Journal of Medicine* (NEJM), *The British Medical Journal* (BMJ), and *The Journal of the American Medical Association* (JAMA), starting from January 1, 1965. Article metadata were retrieved from PubMed on October 30, 2024, and included variables such as title, authors, year of publication, and identifiers. Data were processed and analyzed in Python 3.10.9. Author first names were extracted from various web sources and used for binary gender classification using a pre-trained machine learning model. Starting in 2005, journals were required to disclose funding sources, which were categorized into two groups: pharmaceutical-sponsored and non-sponsored. The final dataset included 8,872 articles, representing 79% of the original dataset.

Results: A total of 8,872 RCTs were analyzed, comprising 1,261 (BMJ), 2,535 (The Lancet), 3,781 (NEJM), and 1,295 (JAMA). Since 1990, an average of 223 RCTs have been published annually, with the proportion of women across all authorship positions increasing steadily by approximately 5 percent per decade—from 25.6% (1990–1995) to 40.2% (2019–2024). Women as first authors increased from 20% (1990–1995) to 33.5% (2019–2024), while women as last authors increased from 21.5% to 29% respectively. In the past five years NEJM had the lowest representation, with 27.4% of first authors and 26.0% of last authors being women (BMJ with 49.3% and 32.3%). Over the decades, NEJM exhibited only a 5 percent point increase in women as last authors, rising from 20.3% (1990–1995) to 26.0% (2019–2024). Pharmaceutical-sponsored RCTs showed lower female representation compared to non-sponsored studies in the past five years. In pharmaceutical-sponsored publications, women comprised 25.6% of first authors and 26.3% of last authors, compared to 38.9% and 30.5%, respectively, in non-sponsored studies. Across all authorship positions, women accounted for 36.8% in pharmaceutical-sponsored RCTs versus 42.6% in non-sponsored RCTs.

Conclusion: There is still room for improvement in female representation in RCT authorship, despite significant progress over time across all journals. NEJM has shown a notably slower rate of advancement compared to its peers. Last authorship positions have not kept pace with the broader increases in female authorship. Additionally, pharmaceutical-sponsored RCTs continue to show low female representation in both first and last author roles compared to non-sponsored studies.

SAT-069

Cathepsin L inhibitor enhances liver regeneration in fibrotic liver

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Background and aims: Impaired liver regeneration in fibrotic liver is a well-documented clinical phenomenon. While collagenolytic cathepsins, including cathepsin L (CTSL), show enhanced activity in CCl4-induced fibrotic liver, lysosomal proteolysis and cathepsin biosynthesis are suppressed following partial hepatectomy (PH). Our previous studies demonstrated that CTSL deficiency enhances liver regeneration after PH. This study investigated whether CTSL inhibition could improve regenerative capacity in fibrotic liver.

Method: Male C57BL/6 mice were administered CTSL inhibitor (Z-FY-CHO, 10 mg/kg/day) or vehicle intraperitoneally for 3 days before undergoing 70% PH. Liver regeneration was assessed by measuring wet weight of the remaining liver at 2 and 5 days post-PH, expressed as a percentage of calculated pre-hepatectomy liver weight. To evaluate CTSL inhibition in fibrotic liver, mice were first treated with CCl4 (0.25 mg/g body weight in olive oil) intraperitoneally every 3 days for 2 weeks, followed by CTSL inhibitor or vehicle administration for 3 days. Hepatocyte proliferation was assessed by bromodeoxyuridine (BrdU) immunostaining, and cyclin D1 expression was evaluated by Western blot analysis.

Results: CTSL inhibitor treatment significantly enhanced liver mass restoration at 5 days post-PH compared to controls. BrdU-positive hepatocytes increased from 14.86 ± 0.9% in controls to 23.74 ± 0.8% in CTSL inhibitor-treated mice at 48 hours post-PH. Cyclin D1 expression showed approximately 2-fold elevation in the CTSL inhibitor group compared to controls. In CCl4-induced fibrotic liver, CTSL inhibition increased BrdU-positive hepatocytes from 2.16 ± 0.3% to 8.92 ± 2.3% and upregulated cyclin D1 expression, indicating enhanced regenerative response.

Conclusion: This study demonstrates that CTSL inhibition accelerates liver regeneration after PH, supporting our hypothesis that decreased CTSL activity plays a crucial role in liver regeneration. Furthermore, CTSL inhibition enhanced hepatocyte proliferation in fibrotic liver,

suggesting that the elevated CTSL activity observed in CCl4-induced fibrotic liver may contribute to impaired regeneration. These findings identify CTSL as a potential therapeutic target for addressing regenerative disorders in hepatic cirrhosis.

SAT-070

Extracellular matrix protein 1 (ECM1) as a dual regulator of liver regeneration via HGF/c-MET and TGF-β signaling pathways

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Background and aims: Extracellular matrix protein 1 (ECM1) is crucial for liver homeostasis and negatively correlates with chronic liver disease (CLD) progression. However, its role in acute liver injury and regeneration (LR) remains unclear. This study investigates ECM1's impact on LR and its underlying mechanisms.
Method: Ecm1-tdTomato mice were administered adeno-associated virus 8 (AAV8)-ECM1 seven days before 70% partial hepatectomy (PHx). Hepatic gene expression was analyzed with RNA sequencing. Functional assays were done with hepatocytes, mouse liver tissue and patient samples.
Results: ECM1 is downregulated during LR after PHx. Interference with ECM1 downregulation by AAV8-ECM1 delays proliferation and liver mass gain at days 2 and 4, but catches up by day 8, as indicated by the liver-to-body weight ratio and immunostaining of PCNA and Ki67. Mechanistically, in early-stages of LR (days 0–4), downregulation of ECM1 is required for efficient HGF/c-MET/ERK/MYC signaling to mediate cell cycle progression, including CyclinA2, B1, B2, and Birc5 expression. In the late stage (days 4–8), overexpression of ECM1 inhibits latent TGF-β activation, therefore interfering with TGF-β-induced cell cycle kinase inhibitors p15, p16, p18, and p19, required for regeneration termination, which finally restores the liver mass. Additionally, Myc overexpression in hepatocytes rescues ECM1 mediated proliferation inhibition. In liver tissue of patients, ECM1-positive hepatocytes display reduced nuclear Myc expression.
Conclusion: ECM1 regulates liver regeneration by modulating HGF/c-MET/ERK/MYC and TGF-β/SMAD pathways. We hypothesize that for patients requiring liver regeneration, ECM1 downregulation benefits hepatocyte proliferation and liver function restoration. However, its inhibitory effect on TGF-β signaling should also be considered.

Liver immunology

TOP-071

Integrated single-cell transcriptome and protein analysis unveils long-lasting liver NK cell dysfunction in NUC-treated chronic HBV

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Background and aims: Chronic hepatitis B virus (HBV) infection is a leading cause of cirrhosis and hepatocellular carcinoma. While nucleos(t)ide analogues (NUCs) suppress replication, they require lifelong therapy. The immune landscape in NUC-HBV is rarely biopsied and remains understudied, though it has potential to reveal therapeutic targets, as long-term NUC therapy reduces inflammation-related confounders, enabling identification of immune dysfunctions. Liver fine-needle aspiration (FNA) combined with single-cell RNA sequencing (scRNA-seq) has revolutionized access to NUC-HBV livers. CXCR6+ hepatic NK cells, key mediators of antiviral defense, emerge as a critical focus. This study aimed to define immune alterations and identify therapeutic targets in NUC-HBV livers.
Method: HBeAg-negative patients on long-term tenofovir or entecavir therapy with normal transaminases and no fibrosis (F0-F1) were included (n = 18). Blood and paired liver FNAs were sequenced using 10X Genomics scRNA-seq and integrated with healthy liver and blood datasets. Bioinformatic analyses included unsupervised clustering, differential gene expression (DEG), and cell-cell interaction mapping. Multiplex flow cytometry (n = 54) and multicolor immunofluorescent staining of liver biopsies (n = 19) validated findings.
Results: Unsupervised clustering of 221,383 immune cells identified 24,517 NK cells (11.1%) across four clusters. CXCR6+ NK cells, the dominant hepatic subset, were significantly reduced in NUC-HBV livers compared to controls (22% vs. 5% of immune cells, p = 0.002). These cells exhibited the highest IFN-γ gene expression, alongside hallmark genes *XCL1, GZMK, TNFSF10* (TRAIL), and *TIGIT*. Transcriptional profiling revealed 84 DEGs, with downregulated cytokines (e.g., *IFNG, XCL1, CCL3, CCL4*). Cytotoxicity pathways were intact, and exhaustion genes (e.g., *PDCD1* [PD1]) remained low. Immunofluorescence confirmed significant depletion of CXCR6+ NK cells (9% vs. 2% of hepatic cells) and severe loss of in situ IFN-γ production (24.2% vs. 0.2% of CXCR6+ NK cells). Hepatic IFN-γ production was not compensated by CD56dim or CD3+ T cells. Blood NK cells showed minimal changes, supported by extensive flow cytometry. Receptor-ligand analyses revealed a TGF-β-enriched liver microenvironment in NUC-HBV, alongside reduced Kupffer cell responsiveness to IFN-γ (e.g., downregulated *IFNGR1/2*).
Conclusion: Even after years of NUC therapy, CXCR6+ hepatic NK cells remain profoundly suppressed in their ability to produce IFN-γ and other key cytokines, while retaining cytotoxic capacity. The TGF-β-enriched hepatic milieu, rather than IL-10 or exhaustion, is associated with impaired NK immunity. Prolonged IFN-γ suppression by CXCR6+ NK cells may affect non-cytolytic viral control and cccDNA integrity. Restoring liver-resident NK cell functionality could represent a promising immune-based strategy to boost intrahepatic antiviral responses targeting infected hepatocytes.

TOP-072-YI

Human cirrhotic ascites contains myeloid reprogrammed T-cells capable of enhancing peritoneal immune surveillance

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Background and aims: Peritoneal leukocytes are essential for immunoregulation, tissue homeostasis and repair. When peritoneal homeostasis is disturbed leukocytes are recruited to help restore balance. Previously we described the reprogramming of liver-resident CD8$^+$T-cells upon interaction with neighbouring myeloid cells (Pallett et al. Nature 2023). Upon interaction, hepatic CD8$^+$T-cells can 'steal' fragments of the plasma membrane acquiring constitutive immunomodulatory features at rest and enhanced antiviral/anti-tumour functionality. We hypothesised that myeloid cells within the peritoneal cavity reprogramme CD8$^+$T-cells to help maintain peritoneal homeostasis, providing local antiviral/anti-tumour immunosurveillance.
Method: Using spectral flow cytometry and confocal imaging we assessed the phenotype and function of myeloid instructed T-cells, detected by co-staining for CD8 and CD14. For this, leukocytes were isolated from fluid accumulation (ascites) in the abdominal cavity of patients with chronic liver disease.
Results: Here we show myeloid-instructed CD8$^+$T-cells accumulate in ascites, correlating positively with acute-phase-protein (CRP) and negatively with disease severity (MELD). Using a short-term T-cell receptor (TCR; anti-CD3/CD28) stimulation protocol we demonstrate myeloid reprogramming substantially impacts effector function. Peritoneal CD14$^+$CD8$^+$T-cells become 'super-responders' to TCR stimulation with significantly increased production of anti-microbial cytokines and chemokines. We further show that CD14$^+$CD8$^+$T-cells respond to viral peptide stimulation (CMV/EBV/Flu), with increased numbers of polyfunctional dual-cytokine producing (IFNg$^+$TNF$^+$) CD8$^+$T-cells. Furthermore, these cells produce more autocrine IL-2, likely to support their own proliferation and can better mobilise cytotoxic granules (CD107a) upon antigenic encounter. Stealing of the LPS-receptor from the surface of myeloid cells also allows CD14$^+$CD8$^+$T-cells to respond directly to local bacteria. We confirmed LPS-receptor internalisation, indicating that some T-cells may be sensing LPS *in vivo*. Peritoneal CD14$^+$CD8$^+$T-cells take up significantly more LPS than their CD14-negative counterparts in an LBP-dependent manner, indicating a role for the physiological environment of the ascites which is rich in LBP.
Conclusion: As a result of their improved effector functionality, myeloid-instructed CD8$^+$T-cells likely contribute to the maintenance of peritoneal homeostasis, representing an important immune sentinel providing critical antiviral/antitumour and antibacterial immunosurveillance. Targeting myeloid reprogramming may provide an effective approach to controlling chronic inflammation while also addressing the immune dysregulation that contributes to the high mortality rates associated with ascites.

FRIDAY 09 MAY

FRI-033-YI

TIGIT blockade on CD8+T cells induces hepatocyte apoptosis

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Background and aims: TIGIT blockade has recently undergone a phase III trial for the treatment of small-cell lung cancer (SKCRAPER-02), however, the potential adverse effects of TIGIT blockade therapy on the liver is unknown. TIGIT has an inhibitory effect on cytotoxic effector T cells, and blocking TIGIT enhances CD8$^+$ T cell effector functions in tumour-bearing mice. To address this in humans, we investigated the phenotype and function of TIGIT$^+$effector T cells in the liver and their effect on hepatocytes with and without TIGIT blockade.
Method: Liver infiltrating and peripheral TIGIT$^+$effector T cells were phenotyped by flow cytometry, and their localisation was examined by immunohistochemistry. TIGIT$^+$effector T cell-induced primary hepatocyte apoptosis was investigated using co-culture experiments and blocking assays using a TIGIT neutralised antibody and imaged over a 24 h period.
Results: TIGIT$^+$effector T cells expressed CXCR3 and VLA-4 and localised around hepatocytes expressing TIGIT ligand CD155 and CXCL10, VCMA-1 on hepatic sinusoids. TIGIT-expressing CD8$^+$ T cells contain significantly higher granzyme B than non-TIGIT-expressing CD8$^+$ T cells. Additionally, perforin expression is significantly increased in TIGIT$^+$CD8$^+$ T cells compared to TIGIT$^-$CD8$^+$ T cells in controls. We then cocultured primary human hepatocytes (PHH) with TIGIT$^+$ or TIGIT$^-$ CD8$^+$ T cells with or without blocking TIGIT. Our results showed hepatocytes undergo apoptosis at a higher frequency when co-cultured with TIGIT$^-$CD8 T cells than when co-cultured with TIGIT$^+$CD8$^+$ T cells. TIGIT blockade restored PHH killing by TIGIT$^+$CD8$^+$ T cells.
Conclusion: TIGIT+ CD8 cells can recruit to liver via sinusoids and localise around hepatocytes. By blocking TIGIT, inhibition of TIGIT$^+$CD8 T cells is lost, leading to activation and hepatocyte apoptosis. Thus, we reason that anti-TIGIT therapies can potentially induce hepatitis by releasing inhibition of TIGIT$^+$CD8 T cells. These findings serve as a caution on the potential untoward side effects of using TIGIT-blocking therapies, which could lead to checkpoint-induced liver injury.

FRI-034

Crohn's associated invariant T (CAIT) cell subphenotype analysis for inflammatory bowel disease and primary sclerosing cholangitis

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Background and aims: Primary sclerosing cholangitis (PSC) is a rarer liver disease where chronic inflammation coupled with fibrosis leads to a narrowing of the bile duct, which impedes the flow of bile. A large subset of patients with PSC has concurrent inflammatory bowel disease (IBD)-like that is characterized by a right-sided predominance, rectal sparing, and backwash ileitis. While the complete etiological understanding of PSC or IBD is currently still lacking, we have previously identified a group of type II invariant natural killer T cells that were significantly expanded in a subset of Crohn's disease (CD) patients, hence, we named this subset CAIT cells. These cells recognize non-peptide antigens presented by CD1d. While CAIT cells were more expanded primarily in CD compared to healthy controls and other subsets of IBD, *e.g.,* ulcerative colitis (UC), their expansion and potential pathogenic role in individuals with PSC was not studied yet.
Method: We profiled the T cell receptor alpha (TRA) chain repertoire of 154 individuals with PSC and 64 healthy controls in addition to 855 individuals with IBD or suspension of IBD from the Norwegian inception cohort IBSEN-III. Specifically, 246 symptomatic controls, 228 treatment-naïve CD and 357 UC patients, and 176 and 329 treated CD and UC patients were analyzed.
Results: The expansion of CAIT cells was comparable in individuals with PSC relative to healthy controls, suggesting that these cells are not implicated in the pathogenesis of PSC. By analyzing the repertoire of individuals with IBD, we observed that CAIT cells are significantly expanded in CD (P-value = 5.4×10^{-4}) and that 10.9% of CD patients had a significantly increased CAIT level, particularly in patients with ileal and ileocolonic involvement. Furthermore, the expansion of these clonotypes was higher in individuals with stricturing or penetrating disease behavior.
Conclusion: Our findings indicate that CAIT cells are not implicated in PSC, however, we could replicate that these cells are specifically expanded in individuals with CD, predominantly with ileal and ileocolonic involvement. Although a large subset of PSC patients has a backwash ileitis, this ileal inflammation did not correlate with the expansion of CAIT cells. These findings strengthen the notions that distinct pathophysiological mechanisms, and potentially antigens, are causative for PSC and different IBD subtypes.

FRI-035
The role of FOXP3+ regulatory T (Treg) cells in mouse models of liver disease

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Background and aims: Chronic liver diseases such as viral hepatitis and metabolic associated steatotic liver disease (MASLD) are associated with inflammation and dysregulated immune responses. The contribution of Treg cells to these liver conditions is only partially understood. This study aims to elucidate the role of Treg in the regulation of immune responses in the liver and determine whether they can be targeted for therapeutic benefit. To address this, the phenotypes and kinetics of Treg cells in the liver during both chronic Hepatitis B virus (HBV) infection and MASLD required establishment, in order to elucidate the function of these cells in inflammation and immune dysregulation.
Method: A transgenic mouse model of replication competent Hepatitis B virus (HBV-Tg) was used to mimic the chronic infection setting with transfer of naïve $CD8^+$ HBV Antigen (Ag)-specific T cells not leading to viral clearance but a dysfunctional immune response. To model MASLD mice were fed a choline-deficient high fat diet, western diet, or normal chow from 8 weeks of age and monitored for disease progression up to 1 year. Plasma biochemistry (ALT, total cholesterol, and triglycerides) was used to assess the inflammation in each setting and Treg phenotypes were measured with spectral flow cytometry.
Results: In HBV-Tg mice, transfer of naïve viral Ag-specific $CD8^+$ T cells resulted in an increased percentage and number of liver Treg and specifically favored expansion of Treg expressing CD25 and the receptor for IL-33 (ST2). During MASLD progression, multiple phases of inflammation and resolution were observed with expansion of Treg cells corresponding to increases in effector T cells within the liver. This was distinct from the phenotype in the visceral adipose tissue in which Treg increased after four weeks of diet and proceeded to dramatically decline, highlighting the distinctive nature of the liver environment. Flow cytometry analysis revealed differences in the phenotype of Treg cells between diets and timepoints identifying PD-1^+ $CD25^-$ and $ST2^+$ $CD25^+$ activated and proliferative populations as increased within the liver.
Conclusion: Treg cells were increased in the liver both in the context of dysregulated viral antigen-specific T cell responses in HBV-Tg mice, and during MASLD progression. This study identifies significant changes in Treg populations corresponding to disease stage in each model and is positioned to identify how to manipulate these cells for therapeutic benefit. To further investigate the role of Treg cells, $FOXP3^{DTR\text{-}eGFP}$ mice will be used for depletion of Treg in both models. By depletion of Treg prior to Ag-specific T cell transfer in HBV-Tg mice, this stands to reveal the contribution of Treg cells to the development of dysfunctional $CD8^+$T cell responses in chronic HBV infection. In contrast, Treg depletion will be conducted at defined disease stages in MASLD to increase our understanding of their influence on disease progression.

FRI-036
Single nucleotide polymorphisms of the vitamin D receptor and their impact on vitamin D- and Interleukin-6 levels in liver cirrhosis and acute-on-chronic-liver failure

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Background and aims: Vitamin D ($25(OH)D_3$) is a regulator of both adaptive and innate immune system. It has anti-inflammatory, anti-fibrotic and immunomodulatory properties. Therefore, it is important in cirrhosis-associated systemic inflammation. Simultaneously, 25 $(OH)D_3$-deficiency is a frequent phenomenon in chronic liver disease. This study investigated what impact single nucleotide polymorphisms (SNPs) within the Vitamin D receptor (VDR) have on $25(OH)D_3$-status and $25(OH)D_3$-mediated immunological effects in liver cirrhosis and acute-on-chronic liver failure (ACLF).
Method: Clinical data were analysed of patients with compensated and decompensated liver cirrhosis with or without ACLF that were enrolled prospectively from a monocentric cohort study (n = 355). Pyrosequencing was performed to examine VDR for defined SNPs (rs7968585, rs731236, rs7975232, rs2239179, rs2228570). Interleukin-6 (IL-6) levels were quantified using Enzyme-Linked

Immunosorbent Assay (ELISA) and 25(OH)D_3 plasma-concentrations were assessed by ADVIA Centaur® Immunoassay.
Results: Severe 25(OH)D_3-deficiency was frequent in the overall cohort with mean 25(OH)D_3-concentrations at 15.3 ng/mL. As cirrhosis progressed, 25(OH)D_3-levels decreased significantly (compensated vs. ACLF: $p = 0.007$). Likewise, concentrations of inflammatory molecules, for example IL-6, increased with aggravation of liver cirrhosis (compensated vs. ACLF: $p < 0.0001$). In total, 25(OH)D_3- and IL-6-levels showed inverse correlation. 25(OH)D_3-supplementation could significantly increase 25(OH)D_3-status in compensated and decompensated cirrhosis, while in ACLF, 25(OH)D_3-levels were unaffected by supplementary therapies (ACLF supplemented vs. unsupplemented: $p > 0.9999$). Notably, a trend indicating an opposing association between the genotype of the VDR haplotype rs731236/rs7975232/rs7968585 as well as rs2239179 and IL-6-concentrations was observed in both compensated liver cirrhosis and ACLF. Finally, the GG-genotype of the rs2239179 variant showed significant lower expression in ACLF as compared to other patients ($p = 0.0003$) and was associated with 25(OH)D_3-levels in the overall cohort (AG vs. GG: $p = 0.002$).
Conclusion: These data prove the VDR-genotype to affect 25(OH)D_3-status, the efficacy of a supplementary therapy and inflammatory markers in liver cirrhosis. Taking these aspects into account, future analyses should study further immunological effects of 25(OH)D_3, patient outcomes and different supplementation strategies in subgroups of specific VDR-variants.

FRI-037-YI
miRNA/mRNA signature of mouse Kupffer cells during the progression of chronic liver disease from fibrosis to hepatocellular carcinoma

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Background and aims: Chronic liver disease (CLD) progression from fibrosis to hepatocellular carcinoma (HCC) involves profound immune dysregulation, with Kupffer cells (KCs) playing a pivotal role. KCs are liver resident macrophages that form the primary line of defence in liver. An imbalance in the hepatic macrophage population becomes evident during CLD progression from liver fibrosis to HCC. This study aims to explore the deregulated (DE) miRNA and mRNA profiles in mouse KCs to elucidate key molecular mechanisms driving liver fibrosis and HCC.
Method: C3H mice were given a single injection of diethylnitrosamine (DEN) at 4 weeks of age, followed by continuous injections of carbon tetrachloride (CCl4) for 6 and 21 weeks to induce liver fibrosis and HCC. KCs were isolated by fluorescence-activated cell sorting (FACS) from the non-parenchymal cell fraction of enzymatically digested liver (Collagenase P- Roche), and total RNA was extracted using miRNeasy micro kit (Qiagen), for sequencing. Differential expression and functional enrichment analyses were performed to identify key pathways and biological processes.
Results: For both miRNA and mRNA sequencing, the fold change and p value threshold were set at | logFC | > 1 and p value <0.05. In-depth miRNA sequencing identified 7 DE-miRNAs in fibrosis and 15 in HCC compared to naïve controls. Among the miRNAs analyzed, mmu-miR-210-3p, was uniquely expressed in fibrosis and mmu-miR-126a-5p, mmu-miR-3082-5p, mmu-miR-199a-5p, mmu-miR-125b-5p, mmu-miR-29c-3p, mmu-miR-5128, mmu-miR-714, mmu-miR-709, mmu-miR-362-3p expressed only in HCC, compared to the naïve liver. Notably, mmu-miR-199b-5p was upregulated 4-fold in both conditions. Transcriptomic analysis revealed 140 downregulated and 686 upregulated DEGs in fibrosis, and 243 downregulated and 1,068 upregulated DEGs in HCC compared to naïve controls, and 56 unique to HCC compared to fibrosis. Gene set enrichment analysis highlighted dysregulation of pathways related to immune response, cytokine-chemokine signalling, and inflammatory processes in both fibrosis and HCC groups. DE-genes of the cytokine pathways include Ccr2, Irf4, Il20rb in fibrosis and Cxcl13, ccl12 in HCC. Inflammatory genes include Ednrb, Il33, Il2ra in fibrosis and CCl5, Ilr12 in HCC.
Conclusion: Our study identified distinct DE-miRNAs and DE-genes in KCs during liver fibrosis and HCC, compared to naïve group. These findings highlight the critical role of KCs driving inflammation and immune modulations during CLD progression to tumorigenesis, offering potential therapeutic targets.

FRI-038
Unraveling the liver immune rheostat: How contact-dependent regulation causes dysfunction of antigen-specific CD8 T cells over the course of chronic hepatitis B

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Background and aims: While acute hepatitis B virus (HBV) infections are controlled by a robust, antiviral CD8 T cell response, CD8 T cells are scarce and dysfunctional in chronic HBV infections. Recently, we showed that the liver immune rheostat is the underlying mechanism that is responsible for the functional inhibition of CD8 T cells during persistent hepatic infections. Here we demonstrate the effect of the microenvironment of the liver on CD8 T cells over the course of infection.
Method: To analyze the liver immune rheostat, we utilized a preclinical model system based on hepatotropic, recombinant adenoviruses to transfer the HBV genome into hepatocytes, thereby inducing acute-resolving or persistent infections. Subsequently, we conducted analysis on these tissues by using confocal microscopy, flow cytometry using isolated CD8 T cells or hepatic cells and by RNA sequencing. Using *in vitro* co-cultures, we could further investigate interactions between hepatic cells and CD8 T cells.
Results: During persistent infection, antigen-specific $CXCR6^+$ CD8 T cells exhibit sustained loss of effector function and dysfunctionality imposed by the liver immune rheostat. Analysis of hepatic interaction partners revealed an extensive contact with $CXCL16^+$ LSECs over the course of persistent infections. Further, complementary *in vitro* studies phenocopied increased PKA phosphorylation and expression of CXCR6, and revealed molecule transfer between LSECs and CD8 T cells.
Conclusion: Our findings reveal that extensive interactions with LSECs induce dysfunction in antigen-specific CXCR6+ CD8 T cells. Further they suggest, that by molecule transfer and signaling changes LSECs could establish the liver immune rheostat and thus contribute to immune modulation during chronic infection.

FRI-039-YI
Single-cell profiling of hepatic dendritic cells in metabolic-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) is a prevalent chronic liver disease, with increasing incidence linked to rising obesity rates. MASLD can

progress to Metabolic dysfunction-associated Steatohepatitis (MASH), characterized by hepatic necroinflammation and fibrosis. Previous studies, including work from our group, have shown alterations in hepatic conventional dendritic cells (cDCs) in MASH, with a reduced cDC1-to-cDC2 ratio in both humans and mice. However, the role of cDC subtypes in MASH pathophysiology is still unclear. In this study, we aimed to characterize the spectrum of hepatic cDC phenotypes present in MASLD and determine the metabolic and immune signals that induce these signatures.

Method: Single-cell RNA sequencing (scRNA-seq) was performed on sorted cDCs from the livers of chow-fed and MASH-diet-fed mice, with regression after 24 weeks of diet. *In vitro*, bone marrow-derived progenitors (BMDCs) were differentiated into cDC1- or cDC2-like cells using FLT3L+GMCSF or GMCSF alone, respectively. BMDCs were cultured under various conditions and analyzed for gene expression by RT-qPCR and metabolic phenotype by single-cell energetic metabolism by profiling translation inhibition (SCENITH).

Results: Our scRNA-seq analysis identified 9 cDC clusters in the livers of chow- and MASH-fed mice. Cluster 4 was significantly enriched in MASH-fed mice (1.7% in chow vs. 10.7% in MASH) and showed high expression of migratory dendritic cell markers, including *Ccr7*. This cluster's gene expression profile resembled mregDC, a phenotype associated with the tumor microenvironment. In a MASH regression model, we observed a decrease in hepatic mregDC levels after 4 weeks, though levels did not return to those in chow-fed mice. Gene expression in BMDCs showed that mregDC markers were induced by TLR stimulation and further upregulated by free fatty acid treatment.

Conclusion: Our findings suggest that metabolic changes during MASLD drive the mregDC transcriptional program. Further research is needed to identify the signals regulating mregDC induction and their role in MASLD progression or regression.

FRI-040

Transcriptional and functional profiling of HBV-specific CD8 T cells in chronic HBV infection for the design of novel targeted T cell correction strategies for HBV cure

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Background and aims: In chronic HBV infection, HBV-specific CD8 T cells consist of a heterogeneous cell population composed of different subsets which display variable degrees of dysfunction or attenuation of their antiviral functions in relation to the stage of disease/infection and to the specificity for distinct HBV antigens. In particular, simultaneous staining with exhaustion (PD-1) and memory (CD127) markers identifies two main subsets of HBV-specific CD8 T cells ($PD1^{hi}CD127^{low/-}$ and $PD1^{+}CD127^{+}$) variably distributed in individual patients with HBeAg negative chronic hepatitis. Aim of the study was to characterize the transcriptional profiling and functional features of HBV-specific CD8 T cell subsets in patients with HBeAg negative untreated chronic active hepatitis (CH) and in CH patients who achieved HBsAg clearance either spontaneously or by NUC therapy (Re) to better understand their role in HBV pathogenesis and to identify intracellular pathways relevant for HBV functional cure.

Method: Gene expression profiles of individual HBV $core^{18-27}$-specific CD8 T cell subsets sorted by PD-1 and CD127 co-staining were analyzed by Nanostring, adapted for low-input samples (e.g. 1–10 cells) in 5 HBeAg negative CH patients and in 6 Re patients. The analysis of checkpoint/differentiation molecules (CD39, Bcl-2), transcription factors (TOX, TCF1) and cytokines (TNF-alpha and IFN-gamma) by flow cytometry was performed in an expanded cohort of 21 CH and 19 Re patients.

Results: Transcriptional analysis of HBV-specific CD8 T cell subsets shows an enrichment in exhaustion-related genes in the $PD1^{hi}CD127^{low/-}$ subset as compared to $PD1^{+}CD127^{+}$ memory like (ML) cells in CH patients, which is even more significant when the comparison focuses on $PD1^{+}CD127^{+}$ ML cells of Re patients. A signature of 13 genes identifies the progressive transition from the more exhaustion-oriented $PD1^{hi}CD127^{low/-}$ CD8 T cells of CH patients to the intermediate phenotype of $PD1^{+}CD127^{+}$ T cells of CH patients and the more memory-oriented $PD1^{+}CD127^{+}$ ML T cells of Re HBsAg negative patients.

Conclusion: Our study identifies distinct exhaustion signatures in the different HBV-specific CD8 T cell subsets that coexist at different ratios in the distinct phases of the disease and that may guide individualized transcriptional/functional correction therapies for CHB patients.

FRI-041

Enhancing restorative macrophage functions through genetic modification improves liver fibrosis in MASH models

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Background and aims: Liver fibrosis is a central pathway in multiple liver diseases, including metabolic dysfunction-associated steatohepatitis (MASH). Treatment options remain few for severe MASH patients, and current therapies have minimal direct impact on fibrosis. Macrophage-based therapies represent an opportunity to target fibrosis in liver diseases. Macrophages are innate immune cells that support fibrosis resolution by regulating tissue remodeling and inflammation. Here, we sought to augment macrophages' pro-restorative capabilities by engineering them to express fibrosis-modifying transgenes. We demonstrate that macrophages can be rationally engineered to express proteins that target distinct liver disease pathways by reducing inflammation, inhibiting fibrosis, and clearing apoptotic hepatocytes. We then assessed the therapeutic benefit of macrophage engineering in multiple murine MASH models.

Method: Human and murine macrophages were engineered to overexpress newly identified fibrosis-modifying transgenes including IL-10, relaxin, and TIM-4. *In vitro* assays demonstrated the ability of each transgene to promote pro-restorative macrophage functions, such as efferocytosis and fibroblast inactivation. The *in vivo* efficacy of engineered murine macrophages was evaluated using diet-induced models of liver fibrosis: a 26-week westernized diet (WD) with low-dose CCl_4 (WD-MASH; cells dosed IV at weeks 21, 23, 25) and a 6-week CDAHFD model (cells dosed IV at week 4). The CDAHFD model was additionally implemented in immunodeficient NSG mice, using human macrophages expressing human transgene sequences.

Results: Engineered macrophages successfully expressed newly identified anti-fibrotic transgenes both *in vitro* and *in vivo*. In one embodiment, macrophages were engineered to co-express IL-10 and relaxin. Systemically administered engineered cells reduced fibrotic

area in both the WD-MASH and CDAHFD models (45% and 69% vs. control, respectively). In an additional approach, macrophages were engineered to express the efferocytosis receptor TIM-4. In the context of both murine and human TIM-4, a single dose of engineered cells reduced fibrotic area in CDAHFD models (69% and 58% vs. control, respectively). Importantly, the anti-fibrotic efficacy of engineered cells was superior to that of non-engineered cells in all studies. Multiple fibrosis-modifying transgenes and macrophage engineering strategies were analyzed *in vitro* and *in vivo* to expand the utility of this approach.
Conclusion: Macrophages engineered to express fibrosis-modifying transgenes improved liver fibrosis in multiple MASH models. These results demonstrate preclinical proof-of-concept for using engineered macrophage therapies to treat liver fibrosis. The approach represents a platform technology that has the potential to address key underlying pathologies driving liver fibrosis as an off-the-shelf therapy.

FRI-042-YI
Defining the role of tissue-resident Kupffer cells in the pathogenesis of chronic liver disease
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Background and aims: Cells of the innate immune system are crucial mediators of fibrosis progression in chronic liver disease (CLD) and have gained attention as putative therapeutic targets. However, whilst the role of monocyte-derived macrophages, specifically $TREM2^+CD9^+SPP1^+GPNMB^+$ scar-associated (SAMac)/ lipid associated macrophages (LAM), in fibrosis pathogenesis are now well described, the functional role of embryologically-derived liver resident Kupffer cells (KCs) in disease progression remains largely unknown. To address this, we developed a new transgenic mouse model which is deficient in KCs and investigated the impact on CLD pathogenesis.
Method: Clec4f-Cre;$Csf1r^{flox/flox}$ mice were generated, exploiting the early expression of Clec4f during KC development and essential role of Csf1r signalling for macrophage survival. Clec4f-$Cre^{-/-}$;$Csf1r^{F/F}$ (Cre^{neg}), Clec4f-$Cre^{+/-}$;$Csf1r^{F/F}$ (Cre^{het}) and Clec4f-$Cre^{+/+}$;$Csf1r^{F/F}$ (Cre^{hom}) mice were bred and characterised in homeostasis and following induction of CLD by either twice-weekly carbon tetrachloride (CCl4) injections for six weeks or administration of the choline-deficient amino acid-defined high-fat diet (CDAHFD) for five weeks. Flow cytometry and multiplex immunofluorescence (IF) staining were used to quantify hepatic macrophage subpopulations in different genotypes and conditions. Fibrosis and steatosis levels were quantitated histologically by picrosirius red staining followed by machine learning analysis using QuPath.
Results: Using spectral flow cytometry and IF, significant depletion of $TIMD4^+$ KC was observed in Cre^{het} and Cre^{hom} animals in both healthy liver tissue and following the induction of CLD. However, overall macrophage number was not different between genotypes, indicating replenishment of the liver with $TIMD4^-$ macrophages in Cre^{het} and Cre^{hom} animals. Ly-$6C^{hi}$ monocytes and SAMac/LAMs expanded in CLD liver tissue compared to healthy but no significant difference was observed in hepatic Ly-$6C^{hi}$ monocyte or SAMac/LAM numbers between genotypes. Histological analysis showed that $TIMD4^+$ KC depletion had no effect on the degree of hepatic steatosis in CDAHFD model or on the levels of liver fibrosis in either CCl4 or CDAHFD-treated mice.
Conclusion: We present a new model which enables assessment of the functional consequences of chronic depletion of embryologically-derived $TIMD4^+$ KCs. Our data indicate a functionally redundant role for $TIMD4^+$ KCs in the development of liver fibrosis, with $TIMD4^-$ macrophages replenishing this population following depletion and maintaining similar tissue responses to chronic injury. Hence, therapeutic interventions aimed at targeting macrophages in CLD should be focussed on modulating monocyte-derived macrophages rather than embryologically-derived $TIMD4^+$ KCs.

FRI-043
Safety and efficacy of everolimus in autoimmune hepatitis – a single center retrospective analysis
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Background and aims: Autoimmune hepatitis (AIH) is a rare autoimmune liver disease that is typically managed with standard steroid- and immunosuppressive regimens including azathioprine, mycofenolate mofetil, tacrolimus or cyclosporine. However, some patients fail to respond to these therapies or develop treatment-related skin cancer and require alternative treatments. Mammalian target of rapamycin (mTOR) inhibitors have been reported as potential alternatives, but available data are sparse, with limited patient number and conflicting outcomes. This study aims to evaluate the safety and efficacy of the mTOR – inhibitor everolimus in AIH.
Method: We performed a retrospective analysis of patients with AIH treated at our center from January 2020 to October 2024. AIH was diagnosed by specific autoantibodies, increased IgG concentrations, histological demonstration of interface hepatitis and periportal necrosis as well as prompt response to corticosteroids. Patients who received everolimus either due to non-response to other immunosuppressive therapy or due to a *de novo* skin cancer under the therapy were included in the analysis. We documented side effects of everolimus and analysed its effects on liver status. Changes in liver function tests under the therapy with everolimus were analysed using paired student t-test of unequal variance.
Results: From our collective (about 500 patient contacts per year) a total of 18 patients (14 women, median age 60 years, age range 28–77 years, nine with cirrhosis) received everolimus due to non-response to immunosuppressive therapy (n = 12) and/or skin cancer (n = 11). Fourteen patients (78%) reported no side effects from everolimus, while four experienced mild side effects during the first month, leading to therapy discontinuation. Among 12 patients who received everolimus for lack of disease control, nine (75%) demonstrated significant ALT reduction at three (p = 0.01) and six months (p = 0.03). Everolimus was discontinued in two patients due to non-response and in one patient due to mild side effects. Among six patients with skin cancer, three discontinued the therapy due to side effects of everolimus, while the remaining three achieved sustained remission with persistent normalization of serum AST, ALT, AP, GGT and immunoglobulin G (IgG). Side effects reported in the entire cohort included pruritus and apthae in mouth (1/18 (5.5%)), mild pancytopenia (1/18 (5.5%)), mild depressive symptoms (1/18 (5.5%)) and mild face swelling (1/18 (5.5%)), completely resolving after treatment discontinuation. No severe side effects such as infection, pneumonitis, hepatitis B reinfection, Pneumocystis-jirovecii-pneumonia (PCP), kidney injury and amenorrhea were observed.
Conclusion: Everolimus appears to be a safe and effective therapy for AIH in most cases. Larger prospective studies are warranted to confirm these findings and further asses in role in the therapy of AIH.

FRI-044
Dynamic adaptations of CD8+γδ T cells in acute and chronic hepatitis E virus infection
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Background and aims: Hepatitis E virus (HEV) is the leading cause of viral hepatitis worldwide, typically resulting in an acute, self-limiting infection in immunocompetent individuals. However, in immunocompromised individuals, HEV can cause chronic hepatitis. γδ T cells, a unique population of T cells abundant in the liver, play a crucial role in bridging innate and adaptive immunity. Several subsets of γδ T cells have been identified as key regulators in chronic infections. This study aims to investigate the role of γδ T cells at different stages of HEV infection, focusing on their phenotypic and functional adaptations.
Method: We analysed 53 patients (23 immunocompetent, 30 immunocompromised) with acute, chronic or resolved HEV infections and 15 healthy controls. Peripheral blood mononuclear cells (PBMCs) were analysed by high-parameter flow cytometry to characterise the ex vivo phenotype of γδ T cells. Intracellular cytokine assays were performed following in vitro stimulation of PBMCs to assess functional responses.
Results: Using dimensionality reduction of high-parameter flow cytometry data, we identified a distinct subset of γδ T cells - specifically CD8-positive γδ T cells - that differed between acute and chronic HEV cases. In chronic HEV, $CD8^+$γδ T cells were skewed towards Vδ1 and non-Vδ1Vδ2 subsets compared to acute infections. These cells displayed a robust effector phenotype, characterised by increased activation markers (CD38, CD69) and antiviral mediators (perforin, granzyme B, T-bet) compared to CD8-negative γδ T cells. Effector memory $CD8^+$γδ T cells (CCR7-/CD45RA-) were positively correlated with liver inflammation (ALT) in chronic HEV infection ($r = 0.67$, $p < 0.05$). In addition, $CD8^+$γδ T cells expressed higher levels of CD16, suggesting enhanced antibody-dependent cellular cytotoxicity (ADCC). However, prolonged infection was associated with reduced CD16 expression in chronic cases. In chronic HEV, $CD8^+$γδ T cells produced less IFNγ after TCR stimulation and exhibited a weaker pro-inflammatory (IL-17A) and anti-inflammatory (IL-10) cytokine response after IL-12/IL-18 stimulation in vitro compared to acute HEV cases.
Conclusion: $CD8^+$γδ T cells represent a distinct effector immune cell subset that adapts dynamically during acute and chronic HEV infection. In chronic infection, their skewed effector phenotype and reduced regulatory functions may contribute to impaired antiviral responses and increased inflammation, thereby promoting disease progression, making them potential biomarkers or therapeutic targets for chronic HEV infection.

FRI-045-YI
Hepatic stellate cells orchestrate the retention and functional impairment of tissue-resident CD8+ T-cells in the fibrotic human liver

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Background and aims: Stromal cells regulate tissue homeostasis, orchestrating local immunity by imprinting cell fate, producing immunomodulatory mediators, promoting leukocyte tethering and altering immune cell function. Here we explored the capacity of primary hepatic stellate cells (HSCs) - resident non-parenchymal pericytes - to dictate the derivation and function of tissue-resident $CD8^+$T-cells (T_{RM}) in the human liver.
Results: Transdifferentiated HSCs (proliferative myofibroblasts secreting TGF-beta and retinoic acid) induce expression of prototypic tissue retention signals (CD69/CD103/CD49a) on peripheral $CD8^+$T-cells in 2D co-cultures and HSC-repopulated 3D decellularised liver scaffolds. Interestingly, HSC repopulating 3D scaffolds obtained from the healthy liver, compared to the fibrotic liver, exhibit a less activated, more quiescent phenotype. Associated with this, the frequency of 'induced T_{RM}' ($CD69^+CD103^+$) T-cells is significantly reduced. In support of our *in vitro* findings, the proportion of hepatic $CD8^+T_{RM}$ ($CD69^+CD103^+$) increase in individuals with fibrosis as a consequence of a range of chronic liver diseases, where HSC are highly activated *in vivo*. A previous study in mice has suggested that T_{RM} may play an anti-fibrotic role by eliminating activated HSCs. Therefore, we assessed the functionality of healthy and fibrotic T_{RM} by stimulating (anti-CD3/CD28) intrahepatic leukocytes for 4 hours. T_{RM} from both the healthy and fibrotic liver produced equivalently high levels of IL-2, characteristic of hepatic T_{RM}. In contrast, the amount of anti-fibrotic IFN-gamma and the ability to mobilise cytotoxic granules (CD107a) was significantly impaired in fibrotic T_{RM}. In line with their reduced functionality, fibrotic $CD8^+T_{RM}$ express higher levels of co-inhibitory receptors (PD-1/TIGIT) and less co-stimulatory molecules (CD28) *ex vivo*, despite comparable levels of activation (HLA-DR/CD38/CD44). Finally, we demonstrate that HSCs upregulate the corresponding co-inhibitory ligands (PD-L1/CD155) in fibrosis and directly suppress hepatic T_{RM} IFN-gamma production when co-cultured. Remarkably, pre-treatment of transdifferentiated HSCs with anti-PD-L1/L2 antibodies restored the ability of T_{RM} to secrete IFN-gamma.
Conclusion: We demonstrated that HSCs imprint a tissue-residency program on hepatic T-cells and directly limit effector function. Critically our data suggest treatment with checkpoint inhibitors such as PD1/PD-L1 may reduce the extent of fibrosis and subsequent disease sequalae by reinvigorating the anti-fibrotic potential of well positioned, long-lived T_{RM} effector cells.

FRI-046-YI
Fine needle aspiration reveals immunotherapy biomarkers and targets compartmentalised within hepatocellular carcinoma

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Background and aims: Harnessing tissue-resident immunity for tumour clearance requires approaches that rescue local effector CD8+ T cells from intrinsic dysfunction, while overcoming extrinsic suppression by regulatory immune counterparts within the tumour niche. Thus, sampling immune cells sequestered in tumours is critical to the discovery of targetable regulatory pathways and subsets. In hepatocellular carcinoma (HCC), diagnostic biopsies often contain a mixture of immune cells from HCC and surrounding non-tumoural liver, and their invasive nature and requirement for tissue processing has restricted their application. We hypothesized that fine needle aspiration (FNA) of liver tumours would offer a minimally invasive method to monitor local tissue-compartmentalised immune

responses to dissect primary and secondary immunotherapy resistance mechanisms.
Method: Patients with advanced HCC were consented to provide matched blood, FNA and biopsy. Peripheral blood mononuclear cells (PBMC) from blood (n = 25) and tumour infiltrating leukocytes (TIL) from FNA (n = 25) and biopsy (n = 15) were isolated for *ex-vivo* spectral multi-parameter flow cytometric and *in vitro* functional characterisation of effector and regulatory immune populations.
Results: FNA reproducibly sampled a broad range of viable immune subsets local to the tumour microenvironment (TME) and yielded significantly more leukocytes than biopsies (mean 73% v 27% of all live cells, $p < 0.001$). Crucially, FNA were able to extract tissue-resident $CD8^+$ T cells ($T_{RM,}$ $CD69^+CD103^+CD8$) that could not be sampled in blood (10% v 0.1% of total CD8+ cells, $p < 0.0001$). The majority of tumour $CD8^+T_{RM}$ sampled before immunotherapy expressed multiple immune checkpoints including PD-1, Tim-3 and 2B4, accounting for significantly higher expression of these therapeutic targets on the global $CD8^+$ T cells extracted from FNA or biopsies than from blood. Within the myeloid compartment, dendritic cells were reduced whereas functionally suppressive neutrophils with a granulocytic/polymorphonuclear myeloid derived suppressor cell phenotype (g-MDSC/PMN-MDSC) were markedly expanded in tumour FNA compared to blood, allowing characterisation of their dominant homing and immunoregulatory mechanisms to define novel therapeutic targets.
Conclusion: We show that minimally invasive FNAs are capable of comprehensively sampling the distinct immune landscape of HCC compartmentalised at the site of disease, including the presence of key immunotherapeutic targets (T-cell checkpoints and g-MDSC). The resulting data have allowed characterisation of immunotherapeutic targets paving the way for future personalised refinement of targeted immunotherapy to overcome tumour immune escape.

FRI-047

Low-dose lipopolysaccharide administration improves the survival rate of septic shock by enhancing the bactericidal activity of Kupffer cells and reducing hepatic infiltration of pro-inflammatory monocyte-derived macrophages in mice

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Background and aims: Lipopolysaccharide (LPS) administration induces a severe inflammatory response in experimental animals. However, repeated administration of low-dose LPS effectively stimulates innate immune cells and improves survival rates in the septic shock model, called LPS preconditioning (LPS precon, DOI: 10.1159/000475931). Kupffer cells, a special macrophage found in the liver, eliminate blood-borne bacteria and are essential to survive septic shock. In this study, we sought to elucidate the impact of LPS precon on Kupffer cells.
Method: Male C57BL/6 mice were preconditioned with LPS by daily intraperitoneal injection of various concentrations of sub-lethal LPS for three consecutive days. We isolated liver non-parenchymal cells 24 hours after the final injection for flow cytometry analysis. The bactericidal activity of Kupffer cells was assessed *in vitro* by pH-rodo labeled *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). The subset analysis of $F4/80^{low}$ monocyte-derived macrophages (MdMphs) was performed according to our previous study (DOI: 10.1002/cyto.a.24783).
Results: LPS precon upregulated the expression of CD11b on Kupffer cells, suggesting the activation of these cells. *In vitro*, bactericidal activity was up-regulated not only against *E. coli* but against *S. aureus* as well. Interestingly, only Kupffer cells showed a significant dose-dependence between bactericidal activity and LPS dosage, whereas MdMphs or neutrophils did not. Although the cell number of MdMphs increases after the treatment, the percentage of pro-inflammatory MdMphs decreased, which suggested that immune-suppressive monocytes are recruited to reduce the inflammatory reactions in subsequent sepsis induction.
Conclusion: LPS precon dramatically impacted Kupffer cells and augmented bactericidal activity against both gram-positive and negative bacteria. We propose that the enhanced bacterial clearance by Kupffer cells and recruitment of immunosuppressive monocytes are crucial mechanisms of the improved survival rate of sepsis in LPS precon mice.

FRI-048-YI

Establishing an optimised method for single-cell RNA-seq based immunophenotyping from cryopreserved human liver needle biopsies

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Background and aims: Single-cell RNA-seq (scRNAseq) has transformed our understanding of immune cell heterogeneity in chronic liver diseases (CLD). However, due to fresh human liver tissue availability, most scRNAseq studies focus on end-stage liver disease, a point at which pharmacological interventions are unlikely to be effective. In contrast, single-cell or single-nucleus (snRNAseq) profiling of liver needle biopsies have the capacity to define the immune landscape during CLD evolution, yielding more tractable therapeutic targets. To take advantage of these samples, better methods are required to comprehensively profile all immune and non-immune cell types from small archival liver needle biopsies. Consequently, we performed benchmarking of five single-cell approaches to define the optimal strategy for immune profiling in human liver needle biopsies.
Method: Human liver biopsy tissue was obtained from the University of Edinburgh or Indiana University with ethical approval. We compared single-cell data from five methods: (a) Fresh scRNAseq (10X Genomics) on FACS-enriched viable cells following enzymatic dissociation of fresh liver biopsies (n = 2). (b) Publicly available fresh snRNAseq data (10X Genomics) from cryopreserved liver biopsy tissue (n = 9). (c) Fixed snRNAseq (Parse Biosciences) on cryopreserved liver biopsies (n = 5). (d) Fixed snRNAseq (10X Genomics Flex) on cryopreserved liver biopsies (n = 4). (e) Fixed scRNAseq (10X Genomics Flex) on cryopreserved liver biopsies following fixation and enzymatic dissociation (n = 6). Comparative bioinformatic analysis was performed using R.
Results: Fresh scRNAseq (method a) yielded the fewest cells and failed to capture non-immune cells. Fixed snRNAseq sequenced using Parse Biosciences (method c) had the worst immune cell coverage, with low cell and transcript counts preventing full characterisation. The impact of ambient RNA was apparent in all snRNAseq methods (methods b-d), resulting in low confidence annotation of cell types. In contrast, fixed scRNAseq using the 10X Flex protocol (method e) captured the full repertoire of immune and non-immune cells from each cryopreserved biopsy sample, with lower ambient RNA contamination and mitochondrial gene detection, improving cluster separation and enabling high-confidence annotation of myeloid and lymphoid subtypes.
Conclusion: We describe a fixed scRNAseq approach which can be applied to cryopreserved human liver needle biopsies, capturing immune and non-immune cells from a single small sample and facilitating robust subclustering and annotation. Importantly, this approach generates high quality immune cell data at lower per sample cost, due to sample multiplexing and reduced sequencing depth. Application of this method to study early-stage liver biopsies

offers the opportunity to define new therapeutic targets for immune-mediated CLD.

FRI-049

Influence of T cell exhaustion versus senescence in the development of spontaneous operational tolerance following liver transplantation

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Background and aims: In the setting of transplantation the liver exerts unique immunoregulatory properties, which accounts for the feasibility of completely discontinuing maintenance immunosuppression in a small subset of patients (spontaneous operational tolerance). The gradual exhaustion of alloreactive T cell clones as a result of the high antigenic load provided by the liver allograft has been proposed as a potential mechanism to account for this phenomenon. However, to date this has only been investigated in recipients with chronic hepatitis C infection. In contrast to exhaustion, T cell senescence is associated with increased inflammatory markers and reduced immunological tolerance, but its role in clinical liver transplantation remains to be investigated. Here we report the results of immunophenotypig studies conducted on sequentially collected blood samples from liver transplant recipients enrolled in a multi-centre European immunosuppression withdrawal trial (LIFT trial, NCT02498977).
Method: Out of the 82 patients who initiated drug withdrawal, 13 (16.3%) met the primary end-point of spontaneous operational tolerance and 54 (67.5%) either rejected or developed sub-clinical histological changes. We analysed PBMC samples from 10 tolerant (TOL) and 10 rejecting (Non-TOL) recipients before the initiation of weaning (baseline), 6–9 months after, and 12 months after having completely stopped immunosuppression. We combined multi-parameter spectral cytometry (25 phenotypic parameters) and time-of-flight mass cytometry (CyTOF; 28 phenotypic/metabolic parameters) to assess the phenotype and metabolic state of circulating T-cells and their association with the development of tolerance.
Results: TOL and Non-TOL patients differed in the proportion of exhausted and senescent T-cells. TOL patients displayed increased exhausted CD8+ CD45RA+ effector memory T-cells (TEMRA), which positively correlated with recipient age (but not with time post-transplant). In contrast, in Non-TOL we observed increased senescent CD8+ TEMRA, which negatively correlated with circulating levels of telomerase. Metabolic profiling revealed that both CD4+ and CD8+ effector memory T-cells from TOL were metabolically quiescent, whereas CD8+ TEMRA from Non-TOL exhibited a highly metabolically active state.
Conclusion: Our findings suggest that immunological outcomes following liver transplantation (rejection versus tolerance) are orchestrated by a finely tuned balance between T-cell exhaustion and senescence.

FRI-050-YI

CD155 blockade modulates monocyte responses in acute-on-chronic liver failure

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Background and aims: Monocytes play a critical role as a first-line defence against bacterial infections. In acute-on-chronic liver failure (ACLF) however, monocytes adopt an immunosuppressive phenotype characterised by increased anti-inflammatory cytokine secretion and impaired phagocytosis. CD155, an immune checkpoint expressed on monocytes, binds to the inhibitory receptor CD96 on T cells. CD155 signalling has been shown to drive macrophages toward an M2-like, immunosuppressive state in tumours and reduce their ability to activate T cells during antigen presentation. This study investigates the role of CD155 in monocyte dysfunction in ACLF and its therapeutic potential as an immunomodulatory target.
Method: Participants included healthy controls (HC, n = 33), patients with compensated cirrhosis (n = 7), stable decompensated cirrhosis (n = 11), acute decompensated cirrhosis (n = 21), and ACLF (n = 20), recruited within 48 hours of hospital admission. Peripheral monocyte CD155 expression was assessed via flow cytometry. Peripheral blood mononuclear cells (PBMCs) from HCs were conditioned with patient-derived plasma for 48 hours, and CD155 or CD96 were blocked using monoclonal antibodies. Monocyte function was evaluated by analysing activation/exhaustion markers (CD86, HLA-DR, MERTK, CD206, PDL1), phagocytosis (pHrodo *E. coli* BioParticles), and cytokine production (IL-6, IL-10, TNF-alpha, IL-1beta) after lipopolysaccharide (LPS) stimulation.
Results: A higher proportion of CD14+CD16+ monocytes expressed CD155 in ACLF patients compared to HCs (61.1% vs. 28.9%, p = 0.003), with expression correlating positively with Child-Pugh (r = 0.28, p = 0.03) and MELD scores (r = 0.34, p = 0.01). Conditioning HC PBMCs with ACLF plasma upregulated CD155 expression on monocytes (54.3% to 83.0%, p = 0.001) and recapitulated the immunosuppressive phenotype observed in ACLF with increased MERTK and PDL1 expression, elevated IL-10 production, and reduced phagocytosis. Blocking CD155 completely reversed suppressive marker expression to HC levels (MERTK MFI 26300 to 7600, p < 0.001; PDL1 MFI 7400 to 4700, p = 0.001) and ameliorated the increase in IL-10 production (5.67% to 3.50% IL-10 positive, p = 0.02). However, blocking CD155 did not restore phagocytic capacity.
Conclusion: This study highlights CD155 as a mediator of monocyte dysregulation in ACLF. Targeting CD155 could modulate monocyte function, enhance antibacterial immunity, and reduce dependence on antibiotics in ACLF patients.

FRI-055-YI

Inhibition of the lysophatidylcholine-autotaxin-lysophosphatidic acid axis restores monocytic pro-inflammatory cytokine production in patients with acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome characterised by monocytic immunoparesis, leading to systemic bacterial infection and high rates of sepsis. Autotaxin (ATX) hydrolyses lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA) and is upregulated in liver failure and is associated with increased mortality. The mechanistic role of the individual lipids of the LPC-ATX-LPA axis in modulating monocyte capabilities are unclear. We hypothesise that ATX inhibition restores monocyte-specific cytokine production, surface phenotype, and phagocytic capacity.
Method: Fifteen ACLF patients and seventeen healthy controls (HC) were prospectively recruited. Whole blood was cultured with LPA

16:0 (30uM), LPC 16:0 (30uM), ATX inhibitor HA130 (100nM), or LPC in combination with HA130. Monocyte-specific cell surface immunophenotyping (CD163, HLA-DR, MerTK, PD-L1), and intracellular cytokine staining (IFNg, IL-1b, IL-6, TNFa, IL-10) following stimulation with lipopolysaccharide (LPS), was assessed by flow cytometry gating for CD14+ monocytes. Monocyte phagocytic capacity was measured by uptake of GFP-tagged *E. coli* with flow cytometry.

Results: Incubation with LPA downregulated monocytic MerTK and PD-L1 expression in ACLF (p = 0.0057; p = 0.0312 respectively) and impaired intracellular expression of pro-inflammatory cytokines IFNg and IL-1b in ACLF (p = 0.03; p = 0.06) and HC (p = 0.02; p = 0.005). In HCs, LPA also suppressed IL-6 production (p = 0.02). LPA-induced IFNg suppression was restored with ATX inhibition in both HC and ACLF (p = 0.005; p = 0.09). ATX inhibition also restored IL-6 expression in HC (p = 0.03). Interestingly, LPA and ATX inhibitor treatment yielded no differences in TNFa and IL-10 production in either cohort. LPC incubation significantly abrogated expression of CD163 in both ACLF and HC (p = 0.049; p = 0.064), and HLA-DR, and MerTK in HC (p = 0.031; p = 0.037). None of these phenomena were reversed with LPC and ATX inhibitor co-incubation, thus suggesting LPC-dependent suppression. In HC, LPA significantly impaired phagocytic capacity vs LPC and ATX inhibitor co-incubation (p = 0.0121) but not in ACLF, indicative of LPA driving monocytic function. LPC incubation did not alter intracellular cytokine production in either cohort.

Conclusion: ATX inhibition restores LPA-induced suppression of monocyte-derived pro-inflammatory cytokines in both ACLF and HC, and phagocytic capacity in HC. Pro-inflammatory cell surface proteins appear downregulated in an LPC-dependent fashion in both ACLF and HC. The LPC-ATX-LPA axis is a promising immunomodulatory target warranting further investigation in liver failure syndromes.

FRI-056

Investigating macrophage- phenotype and organ injury in acute-on-chronic liver failure

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Background and aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of liver cirrhosis, accompanied by multi-organ failure. Kidney failure is the most common extrahepatic complication. Changes in immune cell subsets including macrophages, neutrophils, and lymphocytes, may drive systemic inflammation and organ injury. However, the dynamics of immune cells, especially macrophages, in ACLF progression remain unclear. This study aims to investigate immune cell dynamics, focusing on macrophage patterns in ACLF models and their role in liver and kidney injury.

Method: We performed two ACLF mouse models, 1) 10 weeks of intraperitoneal (*i.p.*) CCl4 followed by LPS *i.p.* injection 2) 4 weeks of Western diet (WD)+EtOH (10%) in drinking water and followed by EtOH binge. Sirius red was used to quantify fibrosis, TUNEL staining to detect cell death, and spectral flow cytometry to characterize immune cell subsets.

Results: CCl4 treatment induced fibrosis in both the liver and kidney which remained unchanged after LPS injection. WD + EtOH feeding provoked a mild fibrosis in the liver and significantly enhanced kidney fibrosis. Both chronic liver injury models induced cell death in the liver and kidney which was further exacerbated by an additional acute insult. CCl4 treatment increased CD45+ cells in both liver and kidney. LPS triggered a decline in B cells and a surge in neutrophils infiltrating both organs, while T cells remained unchanged. In the liver, LPS exposure increased monocytes and monocyte-derived macrophages (MoMFs) ($CD11b^{high}$, $F4/80^{+}$) along with an upregulation of *Ccl2*, *Tnf-α* and *IL-10* mRNA. LPS triggered a significant recruitment of MoMFs to the kidneys. Kupffer cells (KCs) ($CD11b^{low}$, $F4/80^{high}$, $Tim4^{+}$) remained stable in the liver after LPS, while kidney-resident macrophages (KRMs) ($CD11b^{low}$, $F4/80^{high}$, $CD11c^{+}$, $CX3CR1^{+}$) were markedly decreased after LPS. LPS induced a reduced TLR4 expression in KC, and an increased TLR2 expression in KRM. Both populations demonstrated an enhanced PD-L1 and SIRPα expression while MHC II expression decreased, suggesting a shift towards an immunosuppressive phenotype. In the WD+EtOH model, EtOH binge reduced T cells and B cells in the liver, alongside an increase in neutrophils and monocytes. Unexpectedly, KCs expanded while MoMFs decreased in the liver after binge, alongside an increase in *Ccl2* and *Tnf-α* gene expression. In the kidney, WD+EtOH reduced KRMs. EtOH binge further increased neutrophils and to a lesser extent MoMFs. Both liver and kidney macrophages demonstrated increased SIRPα expression after EtOH binge, and MoMFs in the liver showed reduced MHC II expression.

Conclusion: Both ACLF models showed immune dysregulation, macrophage expansion, and a shift towards an immunosuppressive macrophage phenotype. Gene expression analysis further revealed elevated levels of *Ccl2* and *Tnf-α*. Altogether, these findings suggest a key role for macrophages in ACLF pathogenesis.

FRI-057-YI

Mucosal-associated invariant T (MAIT) cells possess direct cytotoxic potential against HCC, but are rendered dysfunctional within the tumour microenvironment

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Background and aims: Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide and only a minority of patients with advanced HCC respond to currently available immunotherapy. Innate-like mucosal-associated invariant T (MAIT) cells are protective against HCC in murine models but are often rendered dysfunctional in human HCC patients for reasons that are incompletely understood. Here, we aim to unravel the molecular mechanisms of MAIT cell cytotoxicity and dysfunction within the tumour microenvironment in HCC in human patients with the aim to identify novel therapeutic strategies against HCC.

Method: MAIT cells were isolated from human liver tissue and peripheral blood. Primary MAIT cells were co-cultured with various HCC cell lines and primary human hepatocytes in vitro. MAIT cell phenotype and function were analysed by multi-colour flow cytometry. MAIT cell cytotoxicity was tested by real-time viability assays using xCelligence.

Results: Here, we uncover a so far unrecognised, direct cytotoxic capacity of human MAIT cells against HCC cells employing an in vitro co-culture system. Importantly, activated MAIT cells selectively killed HCC cells but not primary hepatocytes. T-cell-receptor-mediated activation of MAIT cells was indispensable for MAIT cell cytotoxicity, which was, however, independent of MHC class I-related protein 1 (MR1) signalling. Mechanistically, MAIT cell cytotoxicity required signalling via death receptors of the tumor necrosis factor superfamily and effector cytokines secreted by MAIT cells. In human HCC patients, MAIT cells are systemically reduced in frequency and excluded from HCC tumour tissue. Moreover, tumour-educated MAIT cells express a dysfunctional phenotype, which was induced

by HCC cells in a cell contact-dependent manner. Importantly, MAIT anti-tumour capacity could be enhanced by targeting the death receptor – cytokine axis we have identified.
Conclusion: Our results demonstrate a novel, direct cytotoxic capacity of human MAIT cells against HCC cells, which is dependent on death receptor signalling and MAIT cell cytokines. These findings suggest that enhancing the anti-tumour potential of MAIT cells could be harnessed to improve current immunotherapeutic strategies against HCC.

FRI-058-YI
Time-resolved liver fibrosis regression at single-cell resolution in a murine CCl4-cessation model
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Background and aims: Liver fibrosis can regress after removal of the primary trigger for liver injury. The molecular switch from a pro-fibrotic to a restorative phenotype in hepatic stellate cells, macrophages, hepatocytes, and endothelial cells remains poorly understood.
Method: Advanced fibrosis in mice was induced with carbon tetrachloride (CCl_4 for 12 weeks). Animals were sacrificed at peak injury (Peak), during regression at 3 (3dR), 7 (7dR) or 14 days (14dR) after CCl_4 cessation or olive oil treatment as controls (Ctrl) (n = 7–13 animals/group). Portal pressure (PP), collagen proportionate area (CPA), serum AST, ALT, and bilirubin levels were measured in a time-resolved manner. Hepatic single-cell suspensions were isolated using a two-step perfusion method (n = 3 mice per group). Parenchymal and non-parenchymal cells (ratio-mix: 1:19) were fixed and sequenced. The obtained single-cell dataset was analyzed using Seurat, interactions were evaluated using Nichenet.
Results: At Peak, fibrosis (CPA: Peak: 3.83 ± 0.61%; Ctrl: 0.53 ± 0.12%,), PP (Peak: 7.32 ± 0.49 mmHg; Ctrl: 4.75 ± 0.46 mmHg), and liver injury (Peak: AST: 1666 ± 2485 U/L; ALT: 1406 ± 3117 U/L; bilirubin: 0.31 ± 0.09 mg/dL; Ctrl: AST: 51 ± 20 U/L; ALT: 30 ± 8 U/L; bilirubin: 0.14 ± 0.05 mg/dL) were significantly induced (all $p < 0.05$ vs. Ctrl), confirming successful model induction. Liver disease regressed significantly after 14 days for CPA (2.89 ± 0.29%), PP (6.18 ± 0.38 mmHg), and liver injury markers (AST: 61 ± 13 U/L; ALT: 44 ± 11 U/L; bilirubin: 0.18 ± 0.5 mg/dL). After quality control, single-cell transcripts of 115286 cells (total cell number from all animals) – clustered in major hepatic cell types – were analyzed. Subclustering macrophages revealed three major sub-populations: embryonically derived (*Timd4+*, *Vsig4+*), scar-associated (SAM, *Trem2+*, *Cd9+*), and a novel Kupffer-cell derived macrophage populations during regression (*Clec4f+, Il10ra+, Cd5l+*). The relative abundance of SAMs (main source of matrix-metalloproteinase 12; *Mmp12)* was highest in Peak and decreased significantly during early regression (3dR). The decrease of *Trem2*, *Cd9,* and *Mmp12* during fibrosis regression was confirmed on liver-bulk RNA-Seq from an independent study with similar study design. Interestingly the main producers of *Mmp8* and *Mmp9* in our dataset were neutrophils with for highest *Mmp8*/*Mmp9* expression at 3dR and 7dR.
Conclusion: The murine CCl_4-cessation model allows to study liver fibrosis regression at a single-cell resolution. SAMs are depleted in the initial phase of regression, during which they represent the main secreters of MMPs. Other cell populations, such as neutrophils further produce MMPs during the intermediate phase of regression. Different myeloid cells thus display multiple roles in collagen degradation during fibrosis regression and will be further evaluated based on the hereby represented dataset.

FRI-059
Identification and characterization of tumor-reactive CD8 and CD4 T cells in hepatocellular carcinoma
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Background and aims: Effective anti-tumor responses rely on the presence of tumor-reactive T cells in the tumor microenvironment (TME). Understanding the characteristics of these tumor-reactive T cells might reveal potential approaches for targeted immunotherapy. Most studies have been focusing on the identification of tumor-reactive CD8 T cells only, revealing CD39 as a potential marker for tumor reactivity in several tumor types. Recently, it has become clear that also a specific subset of CD4 T cells is capable of recognizing tumor antigens and may contribute to tumor clearance. In hepatocellular carcinoma (HCC) neither CD39 as a marker for tumor-reactive T cells nor the presence of tumor reactive CD4+ T cells has been studied. In this study we aimed to identify and phenotype CD39+ tumor reactive CD8 T cells in HCC and to study the presence and characteristics of tumor-reactive CD4 T cells.
Method: We used flow cytometry to phenotype tumor-infiltrating lymphocytes (TIL), peripheral blood mononuclear cells (PBMC) and tumor free lymphocytes (TFL) derived from HCC patients. Cancer germline antigen (CGA) and cytomegalovirus (CMV) peptide-loaded tetramers were used to identify tumor-reactive CD8 T cells and bystander T cells respectively. Using flow cytometry data Lineage tracing was performed to identify cell subsets with high phenotypic resemblance.
Results: Using flow cytometry we identified a population of CD8 T cells positive for CGA peptide-loaded tetramers. Analysis revealed that these specific CD8 T cells, in contrast to CMV peptide-loaded bystander T cells, have an enhanced activation status defined by increased 4-1BB expression as well as upregulation of CD39 and CD103. This specific population of tumor-reactive T cells was unique to the TME as it was absent in PBMC and tumor adjacent tissue. Using lineage tracing we were able to identify a possible tumor-reactive CD4 subset that phenotypically resembled the tumor-reactive CD8 T cell population.
Conclusion: To conclude, (I) we identified a unique HCC CD8 T cell population specific for tumor antigens characterized by CD39 and CD103 expression. (II) we identified a specific HCC CD4 T cell population with phenotypic resemblance to tumor-reactive CD8 T cells. Future functional analysis should determine the tumor-clearing capacity of these CD4 T cells.

FRI-060

Lnk/Sh2b3 regulates the development of hepatic memory CD8+ T cells via IL-15 signaling and suppresses the pathogenesis of MASLD

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely linked to obesity, insulin resistance and can progress to cirrhosis and hepatocarcinoma under conditions of lipid stress and inflammation. A GWAS analysis of MASLD patients identified missense mutations in the Lnk/Sh2b3 (Lnk) gene associated with metabolic and inflammatory traits. We have previously shown that the intracellular adaptor protein Lnk suppresses $CD8^+$ T cell activation by regulating IL-15 signaling. However, the role of Lnk in MASLD pathogenesis remains unclear. This study aimed to investigate the functional role of Lnk in the development of MASLD and its underlying regulatory mechanisms.
Method: Lnk expression was analyzed in liver tissues from MASLD patients and mice models. MASLD was induced in Lnk-deficient ($Lnk^{-/-}$) and wild-type (WT) mice via a high-fat/high-cholesterol diet. The impact of Lnk deficiency on hepatic $CD8^+$ T cells was assessed using single-cell RNA sequencing and flow cytometry. IL-15 responsiveness in $Lnk^{-/-}$ $CD8^+$ T cells was evaluated in vitro. Additionally, $CD8^+$ T cell inhibition and IL-15 deficiency in $Lnk^{-/-}$ mice were analyzed for their effects on MASLD.
Results: Lnk expression was significantly reduced in the livers of both MASLD patients and animal models. $Lnk^{-/-}$ mice in the MASLD model exhibited markedly increased liver steatosis as well as more severe liver injury and fibrosis compared to WT mice. Bone marrow transplantation studies confirmed that $Lnk^{-/-}$ immune cells exacerbate MASLD progression. Lnk deficiency activated cytotoxicity-related pathways in T cells, promoting differentiation into effector/resident memory $CD8^+$ T cells. IL-15 stimulation of $Lnk^{-/-}$ $CD8^+$ T cells in vitro induced their differentiation into effector memory T cells, leading to increased production of inflammatory cytokines (IFN-γ, TNF-α) and cytotoxic factors (Gzmb, Perforin) with enhanced STAT5 phosphorylation, resulting in aggravated hepatocyte injury. Inhibition of $CD8^+$ T cells or genetic deficiency of IL-15 in $Lnk^{-/-}$ mice alleviated hepatic steatosis, injury, and fibrosis.
Conclusion: Hepatic steatosis induces IL-15 expression while downregulating Lnk, thereby exacerbating MASLD/MASH pathology. Lnk regulates IL-15 signaling in $CD8^+$ T cells, and this regulation plays a pivotal role in suppressing MASLD progression. Targeting Lnk-mediated IL-15 signaling may offer a potential therapeutic strategy for MASLD.

FRI-061

Glucocorticoid receptor inhibits Th2 immune responses by downregulating Pparg and Gata3 in schistosomiasis

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Background and aims: The Th2 immune response is pivotal in the pathogenesis of schistosomiasis, contributing to hepatic granuloma formation and fibrosis. Although the glucocorticoid receptor (GR) is a ubiquitously expressed nuclear receptor that mediates anti-inflammatory effects, its influence on Th2 responses in schistosomiasis remains underexplored. Therefore, this study aimed to investigate the potential effects of GR activation on the hepatic Th2 immune response in schistosomiasis using the synthetic glucocorticoid dexamethasone (DEX).
Method: Dexamethasone was administered to activate glucocorticoid receptors in Schistosoma japonicum-infected mice to investigate the potential effects of GR activation on the hepatic Th2 response. RNA sequencing (RNA-seq) was employed to analyze the transcription factors influenced by GR activation in Th2 cells. Single-cell sequencing analysis was conducted to identify the transcription factors that promote Th2 cell polarization in schistosomiasis.
Results: In vivo, GR activation significantly reduced the size of Schistosoma egg granulomas and substantially inhibited the transcription of key Th2-related cytokines, including IL-4, IL-5, and IL-13. In vitro, GR activation inhibited the transcription of IL-4, IL-5, and IL-13, as well as the secretion of IL-4 from Th2 cells. An integrated analysis of RNA sequencing and single-cell sequencing, complemented by gene expression validation, was performed to explore key transcription factors affected by GR activation during Th2 cell differentiation. The expression levels of two major transcription factors, namely Gata3 and Pparg, were significantly elevated in the livers of Schistosoma japonicum-infected mice but significantly decreased following dexamethasone treatment in both infected mouse livers and Th2 cells.
Conclusion: GR activation may suppress the Th2 immune response triggered by egg antigens by downregulating the expression of key transcription factors Gata3 and Pparg. Overall, these findings offer a novel therapeutic strategy for the treatment of schistosomiasis.

FRI-062

Trained human bone marrow mesenchymal stem cells enhance immunoregulatory responses and alleviate ConA-induced acute liver failure

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Background and aims: The immunoregulation of human bone marrow mesenchymal stem cells (hBMSC) plays an important role in treating liver failure. However, the complex in vivo disease microenvironment, including inflammatory cytokine storms, poses challenges to the survival and homing of hBMSC, thereby affecting their therapeutic efficacy. Trained immunity has been proven to exist in immune cells and non-immune cells such as epidermal stem cells. The immune memory enables trained cells to either activate or tolerate upon re-encountering inflammation. This study aims to enhance the immunoregulation of hBMSC by trained immunity to improve the therapeutic effect on liver failure, and to optimize stem cell therapy strategies.
Method: Trained hBMSC (T-hBMSC) were induced with pro-inflammatory cytokines IFN-gamma and TNF-alpha as "trainers" for 24 hours, and untrained-hBMSC (control group) were cultured with standard medium. Then same dosage "trainers" were used to restimulate hBMSC after a 48-hour washout period. Cell samples were collected to perform qRT-PCR and transcriptome analysis. Serum derived from patients with acute-on-chronic liver failure was used to simulate the pathological microenvironment and assess the immune response of T-hBMSC. Murine liver failure models were established in Balb/c mice via tail vein injection of concanavalin A (ConA). Mice were treated with either T-hBMSC or hBMSC via intrasplenic injection, with normal saline (NS) as control. Survival rates, liver function, and inflammatory factors were assessed. Liver tissues were harvested for histological staining, flow cytometry, and bulk RNA-seq to evaluate treatment efficacy.
Results: The stem cell markers and trilineage differentiation potential of hBMSC were preserved after training. The results showed that pro-inflammatory (IL1β, IL6, IL8) and immunoregulatory

genes (PDL-1, IDO) were significantly upregulated in T-hBMSC compared to hBMSC. Time trajectory analysis revealed different responses to restimulation, with T-hBMSC exhibiting distinct expression profiles, especially lower expression of pro-inflammatory genes (IL8, CXCL9) compared to hBMSC. Murine liver failure models were established via tail vein injection of ConA. The 14-day survival of T-hBMSC group was significantly higher than NS group, with improved ALT and AST post-transplantation. Histology showed reduced necrosis area and TUNEL-positive cells in T-hBMSC group. Gene set enrichment analysis revealed significant enrichment of pro-inflammatory TNF and IL17 pathways in hBMSC group compared to T-hBMSC, suggesting milder liver damage in T-hBMSC group.
Conclusion: T-hBMSC can alleviate liver failure by regulating the inflammatory response of immune cells, providing a novel approach to optimizing stem cell therapy strategies.

FRI-063
Understanding the impact of the liver microenvironment on regulatory T cells
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Background and aims: To maintain tissue homeostasis, it is vital that the liver can mount inflammatory immune responses, necessary for pathogen clearance, whilst preventing chronic inflammation which could lead to hepatic injury and fibrosis. Unperturbed damage to the liver contributes to the progression of end-stage liver disease, for which there are limited treatment options. Given their key role in the suppression and resolution of immune responses, T regulatory cells (Tregs) are an attractive target for use in liver targeting immunotherapies. Despite classically being perceived as a tolerogenic organ, recent studies have shown that fewer Tregs persist within healthy liver tissue in contrast to other organs. Inversely, Treg numbers are increased within the hepatocellular carcinoma (HCC) tumour microenvironment. Why the healthy liver microenvironment is less favourable to Tregs is unknown. Identifying the factors influencing Treg survival is crucial to designing mechanisms to promote intrahepatic Treg persistence in cellular therapies. Therefore, our aim was to investigate the impact of the liver microenvironment on Tregs and isolate potential pathways that dictate intrahepatic Treg adaptation.
Method: Utilising single cell RNA (scRNA) data, it is possible to compare molecular differences between intrahepatic, circulatory and intratumoural Tregs. The scRNA dataset was comprised of Tregs and conventional $CD4^+$ T cells (Tconvs) isolated from histologically intact liver tissue, blood as well as background liver and tumour tissue from patients with HCC. Significant differentially expressed genes (DEGs) were classified as those with an adjusted p value of <0.05 and a log2 (fold change) >0.58.
Results: Intrahepatic Tregs differ on a transcriptomic level when compared to circulatory Tregs, with analysis showing 346 upregulated DEGs and 284 downregulated DEGs. Additionally, gene set enrichment analysis (GSEA) showed an upregulation of signaling pathways associated with IL-2/STAT5, mTORC1 and TNF-alpha. Apoptotic pathways were also enriched in intrahepatic Tregs. Annexin V staining and subsequent analysis by flow cytometry further supported that Tregs isolated from liver specimens were more apoptotic than those from blood. When compared to tumour derived Tregs, 292 DEGs were upregulated whilst 1040 DEGs were downregulated in intrahepatic Tregs. These DEGs were associated with cytokine signaling, mTOR regulation and metabolic pathways, suggesting that environmental stimuli drive genotypical differences between Tregs.
Conclusion: Exposure to the intrahepatic microenvironment leads to transcriptomic, signaling and metabolic changes that distinguishes liver-resident Tregs from their circulatory and tumour derived counterparts. These changes may contribute to the survival and function of intrahepatic Tregs.

FRI-064
MicroRNA-122 functions as a rheostat regulating liver tolerance, inflammation and fibrosis
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Background and aims: Chronic liver inflammation and fibrosis are hallmark features of liver diseases such as metabolic-dysfunction-associated steatohepatitis (MASH), chronic autoimmune liver diseases, and liver cancer. However, the interplay between these pathologies remains unclear. This study investigates the role of the liver-specific microRNA, miR-122, in regulating liver inflammation, fibrosis, and immune tolerance. Given its high abundance in hepatocytes, we hypothesized miR-122 is a key regulator of liver immune homeostasis, influencing both innate and adaptive immunity.
Method: A multi-faceted approach was employed, including mouse models with genetic deletion of miR-122, administration of miR-122 mimics and inhibitors (antagomirs), and comprehensive transcriptomic analyses such as RNA sequencing (RNAseq). We examined the effects of miR-122 modulation on immune and inflammatory pathways, including its direct regulation of targets like TLR3 and IRF2. To assess clinical relevance, we compared transcriptomic profiles from autoimmune hepatitis (AIH) patients to those of miR-122 knockout (KO) mice. Additionally, in vivo infection models for bacterial and malaria were utilized to evaluate immune activation in the absence of miR-122.
Results: MiR-122 expression was inversely correlated with liver inflammation and fibrosis in both mouse models and human AIH patients. Loss of miR-122 resulted in early-onset liver inflammation and fibrosis, accompanied by macrophage and lymphocyte infiltration and activation of pro-inflammatory cytokines such as TNFα, IL1β, and IL6. RNAseq revealed over 5,000 differentially expressed genes in miR-122 KO mice, highlighting an upregulation of chemokines, immune checkpoints, and pro-fibrotic pathways. Direct regulation of TLR3 by miR-122 via IRF2 was confirmed through luciferase assays

and in vivo antagomir experiments. miR-122 KO mice demonstrated enhanced resilience to bacterial (MRSA) and parasitic (malaria) infections, possibly due to increased activation of innate immune pathways and elevated erythropoietin levels.
Conclusion: MiR-122 serves as a critical regulator of liver immune tolerance, balancing inflammation and fibrosis through independent pathways. Its absence enhances innate immune activation and accelerates liver fibrosis, implicating miR-122 as a dual mediator of immune and fibrotic responses. These findings suggest that miR-122 is a promising therapeutic target, where its upregulation may suppress inflammation and fibrosis in autoimmune and chronic liver diseases, while its downregulation could bolster immune responses in infectious contexts.

FRI-065-YI
Non-neuronal role of immune cells in liver regeneration
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Background and aims: Humans recover from hepatic injury largely by liver regeneration. This complicated process requires hepatocyte proliferation driven by collaboration amongst multiple hepatic cell types. Immune cells also contribute, with some producing mitogenic cytokines such as IL-6 but others damaging hepatocytes by secreting IFNγ. A better understanding of immune cell functions in liver regeneration is necessary to improve clinical interventions.
Method: ChAT+ B Cell deficient mice ($Chat^{flox;Mb1\text{-}Cre}$), α7 Knockout Mice ($Chrna7^{-/-}$) were used. To induce acute liver damage, we used 70% partial hepatectomy (70%PHX).
Results: Here, we demonstrate that B cells expressing choline acetyltransferase (ChAT), the enzyme synthesizing acetylcholine (ACh), are specifically required for liver regeneration. Mice lacking ChAT+ B cells subjected to partial hepatectomy (PHX) display greater mortality due to failed liver regeneration. We show that both Kupffer cells and hepatic CD8+ T cells express the α7 nicotinic ACh receptor (nAChR; encoded by *Chrna7*), and that liver regeneration is also disrupted in mice lacking α7 nAChR. Thus, two regulatory axes promoting hepatocyte proliferation operate following PHX:one where hepatic ChAT+ B cells and α7 nAChR+ Kupffer cells interact to drive IL-6 production by Kupffer cells, and another where ChAT+ B cells and α7 nAChR+ hepatic CD8+ T cells interact to reduce IFNγ production by CD8+ T cells. Our work offers novel insights into liver regeneration mechanisms that may point to new therapies for liver damage.
Conclusion: In summary, our results suggest the following scenario within hours after PHX, a population of ChAT+ B cells expands and begins to secrete ACh. This ACh signals directly to α7 nAChR-expressing CD8+ T cells and Kupffer cells to inhibit IFNγ production and induce IL-6 secretion, respectively. This modulation of these cytokines in turn limits cytotoxicity towards hepatocytes and promotes their proliferation, achieving the numbers needed to secure proper liver regeneration.

FRI-066
The tumor suppressor miR-122 regulates liver cancer stem cells immune evasion and proliferation through CD24
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Background and aims: We have previously shown that liver cancer stem cells are a source of primary liver cancer. New factors, in particular immunological, are essential for converting liver cancer cells to immune targets. CD24 characterizes tumor stem cell and is a driver of liver cancer and as a "don't-eat-me-signal," repelling an immune affect against the cells. However, it is not known what increases CD24 expression and how this increase affects hepatic tissue and enhances hepatocarcinogenesis.
Method: To unfold the mechanism of how hepatic cancer stem cells proliferation is regulated and escapes the anti-cancer immune response, we performed *in vitro* and *in vivo* experiments, including therapeutics *in vivo* and performed analysis of human liver cancer samples and samples from chronic disease patients.
Results: We found that in chronic liver inflammation, both autoimmune and MASH, ductular reaction (DR) develops and is dependent on CD24 expression and signalling. We show that liver tumor cell propagation is dependent on CD24 expression and that CD24 expression is increased in livers of both human and mouse pre-malignant conditions and CCA and mixed HCC-CCA samples. To determine how CD24 is regulated, we found that microRNA miR-122, also known to act as a tumor suppressor, regulates CD24 by repressing its expression by targeting the miR seed in its 3′-UTR. We found that increasing miR-122 expression with compounds that we developed, that act to increase the activity of RORà, a known activator of the miR-122 promoter, leads to suppression of CD24 and DR. In addition, miR-122 regulates the do-not-eat-me signal of CD24. Furthermore, treating Mdr2-KO mice with anti-CD24, exhibited a therapeutic effect against DR and liver fibrosis. In addition, we investigated what causes miR-122 levels to decrease and enable CD24 expression and the development of DR. We found that upon liver inflammation, pSTAT3 activates miR-24, which targets HNF4à, which is a transcription factor for miR-122 expression. Thus, upon inflammation, miR-122 can be decreased due to pSTAT3 signalling. Consequently, suppressing pSTAT3, leads to increased miR-122 expression level. We hypothesize that a small molecule that increases miR-122 activity, could be assessed as a therapeutic agent against pre-malignant and malignant liver conditions.
Conclusion: CD24, a cancer stem cell marker, is a direct target of miR-122. Thus, reducing CD24 levels with miR-122 will enable an immune attack on the hepatic cancer stem cells, and suppress cancer stem cell proliferation in the liver. We show a therapeutic benefit using anti-CD24 and pSTAT3 inhibitors.

FRI-067
Intrahepatic TCF-1+ T cells reside with myeloid cells in peribiliary lymphoid follicles, respond to the autoantigen pyruvate dehydrogenase complex E2 and T cell receptor stimulation
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Background and aims: Chronic hepatitis, mediated by $CD4^+$ and $CD8^+$ T cells, drives ongoing liver inflammation and disease progression towards liver cirrhosis and failure. T cell factor 1 (TCF-1) is a hallmark transcription factor denoting a T cell subset with stem-like properties which contribute to chronic inflammation. Their presence and functional role have been reported in various extra-hepatic autoimmune conditions. To our knowledge, there are no data on the presence, regulation or function of TCF-1^+ T cells in human liver. We explored the contribution of TCF-1^+ T cells to chronic hepatitis, and the role of peri-biliary lymphoid follicles in supporting their survival, activation and proliferation.
Method: By combining flow cytometric and microscopic analyses, we studied TCF-1 expression by T cell populations in peripheral blood and liver tissue of patients with inflammatory liver diseases and control individuals. Confocal microscopy allowed us to further investigate the exact localization of TCF-1^+ cells within liver tissue. In addition, we FACS-isolated and cultured T cells *in vitro* and stimulated them with anti-CD3/anti-CD28, or co-cultured them with antigen-loaded monocytes, and investigated their functional response, proliferation and degree of exhaustion.
Results: We identified intrahepatic (n = 11) and circulating (n = 8) TCF-1^+ T cells, predominantly in the CD127-expressing population. They expressed biliary homing chemokine receptors, integrin (n = 7) and effector molecules (n = 5). In PBC livers, they resided in peri-biliary lymphoid follicles with the PDC-E2 autoantigen and antigen-presenting cells. Stem-like TCF-1^+ T cells produced effector molecules and acquired an exhausted phenotype upon T cell receptor stimulation in the presence of IL-7 (n = 3). Furthermore, monocytes primed with the PBC pathognomonic self antigen PDC-E2 induced the proliferation of TCF-1^+ $CD4^+$ T cells which acquired effector properties (n = 2).
Conclusion: The novel identification of intrahepatic stem-like TCF-1^+ T cells provides a better understanding of the etiology of biliary diseases, and more generally of immune-induced chronic liver diseases. We propose that these cells represent a local source of antigen-specific T cells, which can proliferate and repopulate the pool of proinflammatory exhausted effector T cells, hence supporting persistent inflammation and sustaining biliary autoimmune diseases. Their functional characterization and the study of their interactions with other cell populations in their niche will help to elucidate how TCF-1^+ T cells can be modulated, and will open new avenues for targeted treatments of chronic inflammatory liver diseases.

FRI-068-YI
The role of T-cell immunoglobulin and mucin domain 3 (TIM-3) in immune dysregulation and infection in patients with decompensated cirrhosis and liver failure syndromes

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Background and aims: Decompensated cirrhosis (DC) and acute-on-chronic liver failure (ACLF) are life threatening syndromes with infection and sepsis are key drivers for mortality. Immune checkpoints have been implicated in immunoparesis and lipids may act as endogenous checkpoint activators. We hypothesise T-cell immunoglobulin and mucin domain 3 (TIM3) acts as a co-inhibitory immune checkpoint and together with active lipids leads to monocyte and macrophage dysfunction and increased risk of sepsis.
Method: Patients with DC, ACLF, acute liver failure (ALF), as a proinflammatory control, and healthy control (HC) were included. Plasma TIM3 expression was measured by ELISA. Monocyte immunophenotype was assessed by flow cytometry. Whole blood was cultured with TIM3 antibody or control and, following stimulation with lipopolysaccharide (LPS), intracellular monocyte-specific cytokines were assessed. Targeted lipidomics in HC, DC and ACLF were assessed by mass spectrometry and correlated with plasma TIM3 expression.
Results: The predominant aetiology of cirrhosis (30 ACLF, 17 DC) was alcohol related liver disease (70%, n = 33); 72% of these patients developed infections during the first 10 days of the admission. In ALF (n = 31), the main aetiology was drug-induced liver injury (73%, n = 22), 57% (n = 17) developed infections. Compared to HC (n = 13; 240.6 +/− 75.0 pg/ml), plasma TIM3 concentration was increased in DC (1101 +/− 390.4 pg/ml; p = 0.002), ACLF (1907 +/− 781.9 pg/ml; p < 0.0001) and ALF (2717 +/− 1270 pg/ml; p < 0.0001). In DC, patients with infection had increased plasma concentrations of TIM3 (unpaired t-test p = 0.03, AUROC = 0.739). Immunophenotyping monocoytes on whole blood demonstrated increased membrane bound TIM3 expression in DC vs HC (% of positive cells and MFI, p < 0.05), reduced HLA-DR (% of positive cells and MFI, p < 0.05) and increased PD-L1 (MFI p < 0.05). In DC, but not in HC or ALF, LPS stimulated monocytes treated with TIM3 antibodies produced more interferon-gamma compared to untreated cells (% of positive cells p < 0.05). The treatment did not affect IL-1b, IL-6, TNF-a or IL-10 production. Lysophosphatidylcholine and lysophosphoethanolamine lipid species were highly discriminant between DC and HC orthogonal partial least squares discriminant analysis (OPLS-DA; R2Y = 0.96, Q2 = 0.82). There was significant negative correlation in DC between plasma TIM-3 expression and LPC 16:0, LPC 18:0, LPC 18:1, LPE 16:0, LPE 18:0 and LPE 18:1 (Spearman-R p < 0.001 respectively).
Conclusion: Membrane-bound and plasma TIM3 expression is increased in patients with DC and ACLF and is associated with positive microbiology and infection. The pathway significantly correlates to bioactive lipid markers associated with immunoparesis in liver failure syndromes. Blockade of TIM3 increases interferon-gamma production and further investigation is warranted to explore if the TIM3 pathway can restore monocyte function in patients with cirrhosis.

FRI-069-YI
Scar-associated macrophages demonstrate phenotypic plasticity during the progression and regression of liver fibrosis

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Background and aims: Single-cell RNA-sequencing studies have identified monocyte-derived TREM2+ CD9+ scar-associated macrophages (SAMacs) (also known as lipid-associated macrophages, LAMs) as an attractive therapeutic target for liver fibrosis. However, SAMacs potentially have both pro-fibrotic and pro-resolution functions. It remains unknown whether the same SAMac subpopulation transitions between these functionally distinct states and how contrasting SAMac properties might be therapeutically manipulated. To address this, we aimed to dissect the temporal kinetics, plasticity and fate of SAMacs during the progression and regression of murine chronic liver disease (CLD), using novel fate mapping approaches.
Method: SAMac kinetics were assessed in murine CLD models including the choline-deficient, L-amino acid defined high fat diet (CDAHFD) model of liver fibrosis. Following a 5 week CLD induction, mice were analysed at serial timepoints (0, 1, 2 and 5 weeks) during ongoing injury (progression) or following the cessation of injury (regression). Monocyte fate mapping during progression and regression was performed by a single gavage of 5 mg tamoxifen in our newly developed transgenic system (Serpinb10-CreERT2 × Ai14 mice). SAMac kinetics were assessed by flow cytometry and

immunofluorescence. SAMac plasticity was characterised by transcriptional profiling (Nanostring nCounter) of FACS-sorted Ai14+ SAMacs during progression and regression.
Results: SAMac numbers increased significantly in CLD models, remained persistently expanded during progression but contracted during regression. Fate mapping enabled Ai14+ labelling of monocytes and SAMacs, with minimal labelling of resident TIMD4+ Kupffer cells using Serpinb10-CreERT2 mice. Labelled SAMacs accumulated in the liver fibrotic niche 2 days following tamoxifen. However, labelled SAMacs did not persist in the liver during CLD progression or regression over a 2 week period, indicating a rapid turnover of SAMacs. Transcriptomics of Ai14+ SAMacs confirmed significant plasticity over time, initially adopting a pro-inflammatory profibrogenic phenotype and then progressively switching into a pro-resolution matrix-degrading phenotype, even in the presence of ongoing liver injury. Ongoing work is focussed on identifying the signals which promote this SAMac reprogramming so it can be harnessed therapeutically.
Conclusion: SAMacs are a highly dynamic and plastic population in the fibrotic liver, being constantly replenished and switching from a pro-inflammatory to pro-resolution phenotype even in the presence of ongoing liver injury. These data suggest that the balance of SAMac subtypes is a crucial driver of disease pathogenesis and indicates that therapeutic manipulation should focus on enhancing SAMac reprogramming *in vivo* to limit fibrogenesis and promote scar degradation.

FRI-070-YI
p120 catenin expression by CD8+ T cells correlates with their frequency of invasion into cholangiocytes in autoimmune liver disease

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Background and aims: Primary biliary cholangitis (PBC) is an autoimmune cholestatic disease with unmet clinical need. In relation, the mechanism which drives PBC pathogenesis is not fully understood. We recently demonstrated an enrichment of $CD8^+$ T cells in PBC patients that express E-cadherin$^+$, which drives their invasion into cholangiocytes through avesicular entosis (AVentosis). However, it is unclear how E-cadherin expression by $CD8^+$ T cells is regulated. Additionally, it is difficult to identify E-cadherin expression on T cells in association with cholangiocytes by tissue staining due to their own expression of E-cadherin. In epithelial cells, surface expression of E-cadherin is stabilized by p120 catenin (catenin delta-1; p120ctn). Is unclear if $CD8^+$ T cells employ the same mechanism.
Method: Fluorescence immunohistochemistry (IHC-F) was used to identify p120ctn-expressing $CD8^+$ T cells in formalin fixed paraffin embedded (FFPE) human liver tissue sections. This strategy was used to stain sections of explant livers from patients with PBC, autoimmune hepatitis (AIH) and non-cirrhotic donor livers. Semi-quantitative analysis was performed on these tissues to assess the frequency of cells in different localizations within the liver. Expression of p120ctn in primary human $CD8^+$ T cells that internalize into human cholangiocytes was assessed using immunocytochemistry (ICC).
Results: Expression of p120ctn was identified within $CD8^+$ T cells in all tissues stained. p120ct$^+$ $CD8^+$ T cells were observed both attached to the biliary epithelial surface and within cholangiocytes. Attached cells were more frequent in diseased liver tissues compared to non-cirrhotic controls. As previously observed, PBC cases exhibited the highest frequency of internalized $CD8^+$ T cells. This was mirrored with p120ct$^+$ $CD8^+$ T cells, as the majority of internalized T cells expressed p120ctn (85% minimum). p120ctn expression was documented within E-cadherin$^+$ $CD8^+$ T cells that were actively invading cholangiocytes *in vitro*.
Conclusion: $CD8^+$ T cell expression of p120ctn coincides with expression of E-cadherin and their ability to internalize into cholangiocytes. This marks a first step in understanding how E-cadherin expression by $CD8^+$ T cell is regulated. It also provides a method of identifying these cells in PBC liver tissues and provides new avenues for understanding PBC pathology that can be manipulated for therapy.

FRI-075-YI
Differential granzyme-mediated immune responses in CXCR6 +PD-1+ CD8 T cells in acute versus chronic ALT flares

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Background and aims: Previously, we showed that circulating CXCR6$^+$PD-1$^+$ CD8 T cells correlate with liver injury and are regulated by a T cell-stimulating cytokine milieu in patients with ALT flares (EASL 2024). A better understanding of the phenotypic and transcriptional characteristics of (CXCR6$^+$PD-1$^+$) CD8 T cells may clarify their role in liver inflammation pathogenesis.
Method: We analyzed blood CD8 T cells in 63 patients with ALT levels ≥5× ULN, including 24 with acute viral hepatitis (16 HBV), 16 with chronic viral hepatitis (15 HBV), and 23 non-viral cases (mainly autoimmune hepatitis) using high-resolution spectral flow cytometry. Public single-cell RNA sequencing data (blood and liver CD8+ T cells, Zhang et al., Gut 2023) from HBV-infected patients were reanalyzed to investigate transcriptional patterns.
Results: Circulating CXCR6$^+$PD-1$^+$ CD8 T cells are characterized by different granzyme expression patterns. In acute hepatitis, the expression of GZMB is predominant, whereas resolving acute and chronic hepatitis is characterized by higher levels of GZMK. UMAP analysis of transcriptome data shows that intrahepatic CD8 T cells mainly express GZMK, whereas circulating CD8 T cells mainly express GZMB. A subset of circulating cells characterized by high CXCR6, HLA-DRA and PDCD1 transcription shares the same transcriptional properties as intrahepatic cells. This subgroup also shows high expression of immunomodulatory and checkpoint genes, activation markers, CREM, and GZMK. Trajectory analysis suggests that CXCR6$^+$ CD8 T cells transition between liver and blood, characterized by a shift in granzyme expression from GZMB to GZMK.
Conclusion: During ALT flares in acute and chronic hepatitis, shifts in granzyme profiles of CXCR6$^+$PD-1$^+$ CD8 T cells are evident. The initial inflammatory response appears to be dominated by GZMB expression, followed by a shift towards GZMK, potentially reflecting evolving intrahepatic immune dynamics and adaption processes. Therefore, GZMK patterns may serve as potential biomarkers to differentiate ALT flares.

FRI-076

Exploiting the ChIP-Seq to validate the role of histone modifiers KDM and HDAC in seroconversion of hepatitis B reactivation patients

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Background and aims: Hepatitis B virus (HBV) infection remains a global health challenge, with functional cure being rare. Epigenetic modifications play a crucial role in driving seroconversion and achieving a functional cure. We aimed to investigate the histone modifiers in hepatitis B reactivation patients leading to seroconversion.
Method: Sixteen HBV reactivation (rHBV) patients were followed up till 24 weeks for seroconversion (HBsAg loss and anti-HBs > 10 IU/ml). Peripheral blood mononuclear cells (PBMCs) from seroconverters (SC) and non-seroconverters (NSC) were analysed for global methylation patterns and validated through chromatin immunoprecipitation sequencing (ChIP-seq) for H3K9 acetylation (H3K9ac) and methylation (H3K9me).
Results: At baseline, seroconverters showed hypomethylation of histone modifiers and transcription factors including *KDM4C, KDM2B*, *HDAC4*, *JMJD1C*, *GATA6*, *RAD51B* and *NCOR2* which was consistent through 24 weeks. Additional hypomethylation was observed in immune-related genes such as *IL17RA*, *IFNGR2*, *TLR5*, *IRF8*, *STAT5B*, and *TGF-beta*. ChIP sequencing with H3K9ac revealed increased acetylation of *KDM4C*, *KDM5B*, *JMJD1C*, *HDAC2*, *HDAC4*, *GATA6*, *NCOR2*, *RAD51B*, and *IL17RA*, as well as *IFNGR2*, *IL27*, *IL1RA*, *IL7R*, *IL15* and *IL15RA* in seroconverters at baseline and at 24 weeks. Similarly, decreased H3K9Me also leads to the activation of *G6PD, IGFR2, IL15RA, IL17B, IL2RA, DNMT3A, ATP6VOA1, ATP11C, ATP13A2* in seroconverters at baseline and 24 weeks. This enhanced acetylation and decreased methylation is associated with genes related to rapid immune metabolic activation, potentially facilitating HBsAg seroconversion. Conversely, ChIP sequencing revealed increased H3K9 acetylation of exhaustion genes including *LAG3, CTLA4*, *FOXP1*, *PDCD2L*, *PDCD10*, *TGFBR2*, *TGFBR3*, and *HIF1-alpha* in non-seroconverters. This upregulation of exhaustion related genes was observed both at baseline and 24 weeks. Similarly, increased H3K9 methylation was observed in non-seroconverters with upregulation of PDCD11 and TOX2 at baseline and 24 weeks.
Conclusion: Increased H3K9 acetylation and decreased methylation in rHBV patients at baseline and 24 weeks was associated with immune metabolic activation driving HBsAg seroconversion. However, non-seroconverters showed increased acetylation of *LAG3, CTLA4*, *FOXP1*, *PDCD2L*, *PDCD10*, *TGFBR2*, *TGFBR3*, and *HIF1-alpha* which causes immune exhaustion and viral persistence.

FRI-077-YI

T-cell receptor analysis of circulating T cells reveals non-epitope-driven clonal expansion in metabolic-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatic steatosis, frequently resulting in inflammatory associated steatohepatitis (MASH), which in turn often leads to liver fibrosis or even cirrhosis. The immune system is crucial for these severe MASH alterations. In our study, we aimed to investigate the clonal expansion of circulating T cells during the progression of MASLD.
Method: From a total of 210 obese patients who underwent bariatric surgery, liver biopsies were obtained intraoperatively and the MASLD progression was classified using the Kleiner score. Immune cells were studied by quantitative immunohistology. Buffy-coats were prepared from blood taken at the time-point of bariatric surgery. Simultaneous, multiplexed library preparation on 96 buffy-coats was performed using the AccuraCode® technology, followed by ultra-deep sequencing. For T-cell receptor (TCR) analysis (identification of clonotypes, clones, gene usage, TCR-repertoires, diversity, motif, sequence studies) a bioinformatic pipeline was established.
Results: By targeting the TCR heterogeneity, clonal expansion was analyzed in 96 buffy-coats, selected according to patient´s MASLD progression: MASLD score 0–1 (n = 22), MASH score 2–4 (n = 41) and 5–7 (n = 33). Interestingly, there was no association of the number of circulating T-cell clonotypes with hepatic infiltration of various immune cell-types. However, we observed a significantly enhanced number of TCR-clonotypes along with development of severe MASH (MASH 5–7). Moreover, clonotype/clone ratios indicated a tendency towards a higher clonal expansion in patients with severe MASH. Most notably, TCR motif and sequence studies revealed that the expanded clonotypes were directed against epitopes of opportunistic or frequently common viral infections (CMC, EBV), but not to liver-specific antigens.
Conclusion: These results provide primary evidence that a general, but not epitope-directed clonal T-cell expansion occurs during MASLD progression. Further insights into clonal T-cell activation will be gained by ongoing studies on expanded cohorts, healthy non-obese controls, and patients with MASH regression.

FRI-078

Inflammation-educated macrophages drive exacerbated re-injury patterns via innate immune memory

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Background and aims: Chronic liver injury leads to pronounced immune alterations, but the persistence of these changes and the impact of the immunological reprogramming on the liver's response to re-injury remains uncertain. Patients with chronic liver diseases suffer from phases of high disease activity followed by months of injury regression.
Method: Here we used a mouse model of chronic toxicity (CCl4) and regression of liver injury and simulated re-injury by administering a single dose of CCl4 after regression. Through the utilization of fate-mapping tools, intravital imaging, and multiplex flow cytometry, we tracked macrophages from different origins and analyzed the alternations in their phenotype and function.
Results: We found that while liver architecture and damage returned to normal levels during regression, rechallenge injury resulted in significantly more severe liver damage compared to long-term chronic injury and acute injury on an otherwise healthy liver. Moreover, we showed that chronic injury resulted in a significant influx of monocytes into the liver, with infiltration of monocyte-derived macrophages, which persisted into the regression phase. These monocyte-derived macrophages displayed a proinflammatory profile and engaged in frequent and prolonged interactions with circulating neutrophils. Furthermore, they were able to rapidly

secrete cytokines such as TNF-α and IL-1β upon re-stimulation, indicating an increased pro-inflammatory potential.
Conclusion: Our study reveals reprogramming of liver macrophages during the regression of chronic liver injury, resulting in a hyperirritable immune state of the liver and a heightened inflammatory response upon re-injury.

Liver transplantation and hepatobiliary surgery – Basic

TOP-521
Integrated spatial transcriptomics and multi-omics analysis of sequential extrahepatic bile duct biopsies reveal key mechanisms of ischemic biliary injury during liver transplantation
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Background and aims: Ischemic cholangiopathy (IC), a severe complication of liver transplantation caused by ischemia-reperfusion injury, primarily affects the extrahepatic and intrahepatic large bile ducts. Despite its clinical significance, the molecular mechanisms of IC remain poorly understood. Sequential EHBD sampling during transplantation offers a unique opportunity to reduce the variability of sampling and explore the spatiotemporal dynamics of IC. This study employs sequential biopsies, advanced spatial transcriptomics, and multi-omics strategies to uncover the critical mechanisms underlying IC.
Method: Sequential EHBD biopsies were obtained from donor livers during liver transplantation at three defined time points: T0 (non-ischemic control, during procurement), T1 (post-cold ischemia, during the back-table stage), and T2 (post-reperfusion injury, ~1 hour after reperfusion). Biopsies were immediately fixed, embedded, and subjected to hematoxylin and eosin staining for systematic histological assessment. Bulk RNA sequencing, proteomics, and untargeted metabolomics were performed on fresh frozen liver tissues from donors (n = 10), while spatial transcriptomics were conducted on snap-frozen samples from donors (n = 2) using Stereo-seq capture chips. Sequencing data were processed, normalized, and analyzed with the Stereo-Seq Analysis Workflow.
Results: T1 and T2 biopsies showed significant morphological damage compared to T0, including epithelial loss, periluminal and deep peribiliary gland (PBG) injury, etc. Histological scores were significantly higher for T1 and T2, with statistical differences ($p < 0.05$). Multi-omics analysis revealed that T2, compared to T1, showed significant upregulation of PPAR, Glucagon, cGMP–PKG, and cAMP signaling pathways ($p < 0.05$), and downregulation of PI3K–Akt, HIF–1, and Thyroid hormone synthesis pathways ($p < 0.05$). Spatial transcriptomics revealed region-specific injury patterns in the EHBD, with distinct programmed cell death modes (necroptosis, ferroptosis, apoptosis) observed in PBG-like progenitor cells and mature cholangiocytes at T1 and T2. Notably, PBG-like cells exhibited a higher proportion of cellular senescence at T1 compared to T2 ($p < 0.05$).
Conclusion: This study highlights the region- and phase-specific injury patterns in the EHBD during liver transplantation, characterized by distinct programmed cell death modes and cellular senescence dynamics in PBG-like progenitor cells and mature cholangiocytes. The integration of spatial transcriptomics and multi-omics approaches provides valuable insights into the molecular mechanisms underlying ischemic biliary injury, paving the way for targeted therapeutic strategies against IC.

SATURDAY 10 MAY

SAT-509-YI
Affinity-tuning chimeric antigen receptors could improve the therapeutic efficacy of regulatory t cells in liver transplantation
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Background and aims: Regulatory T-cells (Tregs), known for their potent immunomodulatory properties, can be genetically engineered to target donor liver antigens using chimeric antigen receptor (CAR) technology. Autologous anti-HLA-A2 CAR-Tregs are currently being evaluated in the clinic to induce allograft tolerance in HLA-A2-negative liver transplant recipients who have received an HLA-A2-positive liver. As compared to T cell receptors, CARs confer supraphysiological affinity to the target cognate antigen. Whether modifying the binding affinity of the single-chain variable fragment (scFv) of the CAR impacts the functionality of CAR-Tregs has not been investigated. In this study, we aimed to evaluate both in vitro and in vivo the functional properties of affinity-tuned anti-HLA-A2 CAR-Tregs, as a means to optimize CAR design for future applications in liver transplantation.
Method: Three second-generation anti-HLA-A2 CAR constructs expressing low-affinity (LA), moderate-affinity (MA) and high-affinity (HA) scFv antigen-binding domains were designed. Human HLA-A2 negative $CD4^+CD25^+CD127^-$ Tregs were FACS sorted and transduced using lentiviruses. The antigen-specificity and suppressive function of the affinity-tuned LA and HA CAR-Tregs in response to their cognate antigen were evaluated by performing activation and suppression assays in vitro and precision-cut human liver slices (PCLS) ex vivo. Therapeutic efficacy was evaluated in vivo by assessing their persistence within the graft and their ability to prevent $HLA\text{-}A2^+$ PBMC-mediated graft-versus-host disease (GvHD) in irradiated NSG mice. To further investigate the mechanistic basis of functional changes, the concepts of CAR target avidity, internalization and recycling were explored by tracking dextramer expression following cognate antigen engagement.
Results: Following stimulation with the HLA-A2 cognate antigen, LA CAR-Tregs exhibited a higher proportion of activated alloantigen-specific cells compared to HA CAR-Tregs. This resulted in a more suppressive cell product which demonstrated enhanced activation and infiltration in PCLS ex vivo. In vivo, infusion of LA CAR-Tregs together with $HLA\text{-}A2^+$ PBMCs resulted in delayed GvHD onset and improved CAR-Treg persistence, correlating with lower human PBMC reconstitution and prolonged recipient survival. Moreover, HA CAR-Tregs exhibited higher avidity for their target antigen. This prolonged antigen engagement resulted in reduced $dextramer^+$ expression on the cell surface when stimulated at physiological levels of HLA-A2 antigen, indicating rapid CAR internalization and surface downregulation.
Conclusion: Affinity-tuning the CAR of anti-HLA-A2 CAR-Tregs can drastically modify their function and should be considered when designing engineered Treg products for clinical applications.

SAT-510-YI

Reconstruction of native biliary networks in decellularized rat liver scaffolds with human intrahepatic cholangiocyte organoids

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Background and aims: The development of functional bioengineered livers is essential to address the current critical shortage of donor organs for transplantation. One major challenge in liver bioengineering is establishing a cell source that can proliferate and differentiate into a functional biliary tree capable of bile transport and seamless integration with hepatic tissue. This study addresses this challenge by using human intrahepatic cholangiocyte organoids (ICOs), which can be expanded at scale and differentiated within a decellularized liver scaffold to form a mature, functional biliary network.
Method: Human ICOs were derived from fresh or cryopreserved human hepatocytes and expanded in large-scale cultures using spinner flasks over a 14-day period. Organoids were then dissociated into single cells and injected into decellularized rat liver scaffolds via the bile duct (BD) using a syringe pump. To ensure cover across both large and small intrahepatic bile ducts, cells were introduced at alternating and specific high and low pressures. The scaffolds were maintained in a perfusion bioreactor for 7 days with continuous perfusion provided by a peristaltic pump and media changes every 2–3 days. Pressure levels were continuously monitored, and glucose and lactate levels were measured daily to assess metabolic activity. Following this maturation period in vitro, the recellularized scaffold was analyzed for hepatic markers and gene expression to evaluate the establishment of a functional biliary network.
Results: ICOs expanded in spinner flasks successfully attached to the decellularized adult rat liver scaffold. The scaffold's microenvironment promoted the differentiation of ICOs into cholangiocyte-like cells, as shown by the loss of Ki67 expression, indicating reduced proliferation. Organoids injected at high pressure formed biliary-like structures across both large and small intrahepatic bile ducts while maintaining compartmental specificity, with no parenchymal invasion. This was confirmed by immunofluorescence of cholangiocyte-specific markers and upregulation of mature cholangiocyte genes, including CK19 and CK7.
Conclusion: This study demonstrates that ICOs can effectively repopulate the biliary network of decellularized adult rat liver scaffolds, forming structured large and small intrahepatic bile ducts via a two-step injection process using alternating high and low pressures. These findings represent a significant advancement towards creating a functional biliary tree within bioengineered livers, paving the way for using decellularized scaffolds from larger animals in liver transplantation.

SAT-511-YI

Extracellular nicotinamide adenine dinucleotide as an independent prognostic marker for long-term survival after liver transplantation

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Background and aims: Liver transplantation remains the definitive treatment for both acute and chronic end-stage liver diseases. The success of this life-saving intervention heavily relies on reliable prognostic markers, which are essential for predicting post-transplant survival rates, guiding patient selection, and optimizing postoperative care. This study explores the relationship between pre- and postoperative plasma levels of extracellular nicotinamide adenine dinucleotide (eNAD$^+$) and patient outcomes.
Method: We monitored patients undergoing liver transplantation from December 2016 to May 2023. Fasting peripheral venous blood samples were collected pre-transplantation and on postoperative days (POD) 1, 3, 7, 14, and 30, along with routine clinical parameters. eNAD$^+$ levels were quantified using a novel enzymatic two-step cycling assay developed by our group.
Results: Fifty-three patients aged 28 to 72 (mean age 53) were enrolled from December 2016 to December 2017 and monitored until May 2023. The 5-year post-transplant survival rate was 61.5%. eNAD$^+$ levels peaked significantly on the first POD (0.40 ± 0.08 μM), compared to preoperative levels ($p = 0.002$) and subsequent days (POD 7: $p = 0.0277$, POD 14: $p = 0.0397$, and POD 30: $p = 0.0085$). There was a significant difference in eNAD$^+$ levels between survivors ($n = 29$, 0.38 ± 0.07 μM) and non-survivors ($n = 18$, 0.45 ± 0.07 μM) on POD1. The threshold eNAD$^+$ level of 0.3750 μM on POD1, identified using the Youden-J statistic, showed the highest sensitivity (83.33%) and specificity (58.62%), with an area under the receiver-operator curve (AUROC) of 0.773. Kaplan-Meier analysis revealed that patients with low eNAD$^+$ (*NAD_low:* ≤0.3750 μM) had a significantly higher 5-year survival rate (85%) compared to those with high eNAD$^+$ (*NAD_high:* > 0.3750 μM) (44.4%, $p = 0.0057$). Finally, no statistically significant correlations were found between eNAD$^+$ levels and conventional parameters—including age, transaminase, bilirubin, INR, creatinine, and CRP levels—of organ donors and recipients, nor with cold and warm ischemia times or MELD scores.
Conclusion: Our research identifies significant fluctuations in eNAD$^+$ levels after liver transplantation, providing new prognostic insights. Through a longitudinal analysis of clinical data spanning seven years, we demonstrated that eNAD$^+$ concentrations could serve as a valuable *independent prognostic* marker. Crucially, measuring eNAD$^+$ levels may allow for the early identification of high-risk patients, facilitating early and targeted interventions that improve patient outcomes.

SAT-512

HepatoPredict has a good prognostic value in patients with hepatocellular carcinoma independently of biopsied nodule

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Background and aims: Liver transplantation (LT) is the most effective early-stage hepatocellular carcinoma (HCC) treatment. However, current patient selection criteria poorly predict recurrence and may hinder equitable access to care. The HepatoPredict tool (HP), a machine learning-based model, was developed to address this need by combining molecular and clinical data to forecast LT outcomes and categorise patients based on the likely benefit of a LT. HP has previously outperformed existing clinical criteria. However, its reliance on needle biopsy raised concerns about the impact of sampling bias on its effectiveness. This study aimed to assess the

influence of sampling heterogeneity on HP's performance by sampling beyond the largest nodule.
Method: Tumor samples from HCC patients who underwent LT at two Portuguese centres were analysed. At least two independent tumour samples from different regions of one or more nodules per patient were collected and processed using the HP assay. Samples were classified as likely to benefit from LT or no predicted benefit. Predictions were evaluated based on clinical outcomes (relapse). Metrics included concordance (whether the algorithm produces the same HP classification in different samples from the same nodule) and prognostic accuracy in concordant cases.
Results: A total of 158 independent tumour samples from 77 nodules were collected from 46 patients. The HP tool achieved 84% accuracy overall. Among nodules, 83% were concordant, with HP correctly predicting prognosis in 91% of cases. At the patient level, 80% showed concordant classifications, with 89% correct predictions. Thus, sampling a nodule twice yielded an 80% likelihood of consistent HP classification. Focusing on the largest nodule did not reveal any significant difference in concordance (83% for the largest vs. 84% for others) or accuracy of prediction (92% for the largest vs. 89% for others).
Conclusion: HP's performance is largely unaffected by sampling heterogeneity, with single-region biopsies sufficient for reliable classification, even when taken from nodules other than the largest. These findings confirm that HP effectively captures tumour biology, supporting its role in optimising LT candidate selection, promoting equitable organ allocation, and improving outcomes through integrated molecular and clinical analyses.

SAT-515

"The feasibility of cell-free DNA for monitoring liver graft rejection: a pilot study perspective"

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Background and aims: Circulating cell-free DNA (cfDNA) is a promising biomarker in oncology and prenatal diagnostics. In transplant medicine, donor-derived cfDNA (dd-cfDNA) has been proposed as an early marker of graft rejection, but its reliance on sequencing or genotyping increases cost and limits accessibility. Total cfDNA, potentially elevated during graft rejection due to increased cellular turnover, could offer a simpler, cost-effective alternative. This pilot study aimed to determine if total cfDNA levels shortly after liver transplantation (LT) correlate with markers like AST, ALT, or ALP and predict rejection. A secondary objective was to explore whether total cfDNA levels vary across different etiologies of liver disease.
Method: The study included 70 LT recipients (46% male, median age 53 years, MELD 17) with liver failure from alcohol (n = 13), autoimmune diseases (n = 20), viruses (n = 9), HCC (n = 10), or other etiologies (n = 18). Patients were monitored for 18 months with bi-monthly lab tests. Peripheral blood (5 ml) collected 10 days post-LT was analyzed for total cfDNA using the Cobas® cfDNA Sample Preparation Kit (Roche) and quantified via Quantus fluorometer (Promega). Kendall's Tau tested correlations between cfDNA and AST, ALT, ALP, or tacrolimus dose. The Kruskal-Wallis test evaluated cfDNA differences among etiologies.
Results: cfDNA was successfully extracted from all samples, with a median concentration of 11 ng/ml. The highest levels (up to 70 ng/ml) were observed in HCC and autoimmune disease patients, reflecting higher cellular turnover, while the lowest (<3 ng/ml) appeared across other etiologies except HCC. A weak correlation was noted between cfDNA and ALT (Kendall's Tau = 0.46, p = 0.0105), but cfDNA did not correlate significantly with AST, ALP, or tacrolimus dose. No significant differences in cfDNA were found between etiologies. Neither cfDNA levels nor trends predicted graft rejection.
Conclusion: This study suggests total cfDNA levels are not reliable predictors of LT outcomes or graft rejection. However, elevated levels in HCC patients highlight the potential of cfDNA as a biomarker for tumor-related cellular turnover. Larger studies are needed to explore cfDNA's role in HCC and as an adjunct tool in transplant monitoring.

SAT-516

3D engineered endothelial cell implants protect liver explant viability ex vivo and reduce liver inflammation

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Background and aims: Endothelial cells play critical protective roles that contribute to tissue homeostasis. Indeed, retention or restoration of ECs healthy phenotype is important to reverse chronic liver disease and enhance liver graft viability during transplantation. Embedding healthy ECs in a 3D collagen-based matrix scaffold (MEECs) shields their immunogenicity and maximizes their protective roles. Here, we explore the beneficial effects of MEECs on tissue preservation and liver inflammation *ex vivo*.
Method: Precision-cut liver slices (PCLS) from fibrotic or healthy mice were cultured in direct contact with acellular matrices (AM) or MEECs for 24 hours. Liver fibrosis was induced in Balb/c mice by i.p. injection of CCl_4 for 8 weeks. To assess tissue viability, the ATP levels and the expression of CYP2B9 and HGF were analyzed in PCLS, and the amount of AST released into the medium was measured. The expression of a panel of genes related to liver inflammation (NOS2, TNF-α, ARG1, MRC1, ICAM-1, VCAM-1) was quantified using Real-time PCR. To investigate the protective role of MEECs secretome, healthy mouse PCLS were stimulated with LPS and treated with MEECs.
Results: PCLS from fibrotic (FB) and healthy (CT) mice treated with MEECs exhibited greater viability than slices exposed to AM as evidenced by an increase in ATP levels (FB: 5.3 vs 7.1 pmol/μg, $p < 0.05$; CT: 9.9 vs 12.9 pmol/μg, $p < 0.01$), and the hepatic expression of CYP2B9 (FB: 1.5 vs 3.1 fold change (fc), $p < 0.05$; CT: 1.2 vs 2.2 fc, $p < 0.05$) and HGF (FB: 1.0 vs 1.3 fc, $p < 0.05$; CT: 1.0 vs 1.5 fc, $p < 0.05$). This increase was accompanied by a decrease in the release of AST into the culture medium (FB: 139.5 vs 127.8 U/L, $p < 0.05$; CT: 143.6 vs 123 U/L, $p < 0.05$). Treatment with MEECs promoted the mitigation of liver inflammation, evidenced by a reduction in the expression of pro-inflammatory genes (NOS2 and TNF-α) and an increase in the expression of anti-inflammatory genes (ARG1 and MRC1) in both fibrotic and healthy mice PCLS. Treatment with MEECs also led to a reduction in the gene expression of the adhesion molecules ICAM-1 and VCAM-1 in fibrotic mice PCLS, indicating an improvement in the

endothelial inflammatory phenotype. These changes were not observed in healthy mice PCLS. MEECs expressed higher amounts of HGF compared to ECs grown in 2D. MEECs improved cell viability of healthy PCLS stimulated with LPS. Healthy PCLS stimulated with LPS and treated with MEECs showed higher ATP levels than those treated with AM. This beneficial effect was blocked when antibodies against HGF were added to the culture medium.
Conclusion: MEECs improve hepatic viability and exhibit anti-inflammatory properties in mouse liver explants. The protective role of MEECs on explant viability may be partly attributed to the secretion of HGF. This study demonstrates the potential of MEECs for the treatment of chronic liver disease and the *ex situ* preservation of healthy liver grafts.

SAT-517
Three-dimensional cell cultures for biliary disease therapies
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Background and aims: Cholangiocytes exhibit cellular plasticity and can repair various regions of the biliary tree in ex vivo models. Cholangiocyte cultures, particularly those in the form of three-dimensional (3D) organoids, therefore hold great potential for advancing bile duct repair and reconstruction in various clinical settings. Even more promising are multi-cellular biliary organoids, where cholangiocytes are combined with other cell types typically found in the native duct. Despite their potential, however, to our knowledge, such complex cultures have not yet been described. On the other hand, injectable hydrogels are increasingly used in regenerative medicine as they facilitate cell delivery to the target sites and may also recruit resident cells, contributing to the regenerative response. Thus, our long-term goal is to develop injectable therapeutic organoids for biliary regeneration by combining bile duct cells with a biocompatible biomaterial. Here, we present preliminary efforts toward this goal, including the generation of multi-cellular biliary organoids from cholangiocyte stem cells (CSCs) and mesenchymal stromal cells (MSCs), their in vitro characterization and behavior in type I collagen.
Method: 3D mono- and co-cultures of CSCs and MSCs were generated by seeding 500,000 cells/mL in ultra-low attachment plates and culturing them under agitation (80 rpm) for 14 days. The organoids were characterized by flow cytometry (assessing cell cycle, apoptosis, and phenotype) and immunofluorescence. Organoid function was assessed by investigating the ability of cells to export the bile salt derivative Cholyl-Lys-Fluorescein (CLF). Both dissociated single cells and whole organoids were embedded in type I collagen, and cell viability, as well as rearrangement within the gel, were analyzed through histology and immunofluorescence up to Day 14.
Results: CSCs in monoculture formed aggregates by Day 5 and grew significantly between Day 7 and Day 14, doubling their diameter. Day 7 CSC organoids exhibited increased expression of mature cholangiocyte markers, such as CFTR and AQP1, compared to both Day 14 organoids and 2D cultures. They also demonstrated CLF export activity. When CSCs and MSCs were co-cultured, CSCs predominated, comprising approximately 95% of the total cell population. Interestingly, 26% of the MSCs differentiated into endothelial-like cells, as indicated by the expression of VEGFR2, while the remaining MSCs retained their original phenotype. When embedded in type I collagen, both dissociated single cells and whole organoids reorganized into a tissue structure closely resembling the native duct.
Conclusion: We have successfully obtained organoids comprising three cell types. When embedded in a natural hydrogel, these organoids may support biliary epithelium regeneration, vascular integration and immunomodulation in vivo.

SAT-518
The recovery failure of fecal microbiota diversity in patients after liver transplant is associated with a complicated postoperative course
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Background and aims: The fecal microbiome plays a critical role in the development and progression of chronic liver diseases. Liver transplantation (LT) serves as a curative treatment for advanced liver diseases and significantly impacts the complex interplay between the gut and the liver, referred to as the gut-liver axis. This study aimed to investigate alterations in the fecal microbiota in patients before and after LT and to assess their relevance for the postoperative outcome.
Method: Between 2020 and 2023, a total of 241 fecal samples were obtained from 53 patients before and at various time points up to two years after liver transplant. Samples from 25 healthy individuals served as controls. 16S rRNA gene amplicon sequencing was conducted to examine the prognostic relevance of alpha diversity (measured as the effective species count) and relative bacterial abundance regarding post-transplant complications and mortality.
Results: During the postoperative course, the effective species count increased but did not reach the level observed in healthy controls (28.4 vs. 42.8; $p = 0.003$). The effective species count before transplantation did not correlate with length of hospital stay, occurrence of complications, or post-transplant mortality. However, patients who experienced a decrease in the effective species count (defined as the difference from pre-transplant to 2–4 weeks post-transplant) had significantly longer intensive care unit ($p = 0.02$) and overall hospital stays ($p = 0.002$). Additionally, these patients exhibited a higher incidence of post-transplant biliary complications. Taxonomic analysis revealed that patients with a reduction in *Lachnospiraceae* (30.9–0.2%) or *Ruminococcaceae* (13–0.5%) or an increase in *Enterococcaceae* (0.1–45.1%) 2–4 weeks postoperatively had increased lengths of hospital stay and more biliary complications.
Conclusion: In summary, we demonstrate that microbiota diversity in liver transplant recipients remains reduced for several weeks during the postoperative period. Reduced diversity and an increase in specific taxa are associated with a complicated postoperative course.

SAT-519
Kallikrein-Kinin system activation in hepatic ischemia/Reperfusion injury: a key driver of Edema and thrombosis
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Background and aims: Ischemia/Reperfusion (I/R) injury is a critical pathological condition affects liver, leading to tissue damage, vascular dysfunction and edema. The kinetics of Liver Sinusoidal Endothelial (LSECs) is less known. We investigated LSECs mediated underlying mechanism involved in pathogenesis of I/R injury.
Method: Hepatic I/R injury was developed by clamping left lateral & median lobes for 1H, followed by 24H reperfusion. *Invivo-exvivo* hemodynamic were monitored followed by biochemical,

haematological and coagulation investigations and ELISA. I/R lobe and hyperperfused (HP) lobe (Right lateral, caudate, quadrant) of same liver. bile duct (BD), hepatic artery (HA) and portal vein (PV) were collected. Liver Wet/dry weight ratio was estimated. Primary LSECs isolated and acquired, Gene and protein was estimated. Histological analysis of both I/R and HP lobes. Sham animals as controls.

Results: Hemodynamic analysis revealed increase portal flow (+30% $p < 0.001$) and decrease MAP (−39%, $p < 0.001$) in I/R rats vs sham. elevated HA flow was positively correlated with PP ($r = 0.851$, $p > 0.001$) indicates hepatic arterial buffer response (HABR), histologically, increased number and dilated HA (>2-fold vs sham, $p < 0.01$) in portal triad, suggesting increased angiogenesis. HIF-α (+2.9X), eNOS (+4.8X), adenosine A2A receptor (+38X), ET1 (+1.3X) and VEGFR2/3 were upregulated in HA validate these findings. Microsteatosis in PV and central vein (CV) zone in I/R and HP was observed, though more pronounced macrosteatosis in CV area in HP was seen. Elevated ALT, ALP, GGT levels indicates hepatic and biliary damage. Enhanced Portal and biliary fibrosis (2-fold vs sham) accompanied by increased α-SMA + (2-fold) and PDGFR-β+ portal fibroblasts (1.5-fold vs sham) were observed. Prolonged PT, elevated INR, D-dimer and Factor-XII, vWF, ADAMTS13 levels, suggests coagulation abnormalities, endothelium damage and PV thrombosis. CD31+ LSECs peaked in I/R (45%) and HP (39%) vs sham (5.4%) confirms its activated phenotype. Mechanistically, serum Kininogen-1/2 levels and its receptors B1/B2 were increased I/R: 47%, HP: 23%, sham: 2.7% in CD31+ LSECs, further confirmed by elevated calcium levels and increased expression of calcium-binding protein calpain (2-fold), indicating activation of kallikrein-kinin system (KKS). Interestingly, low expression of junctional (Claudin, VE-Cadherin) and cytoskeleton proteins (F-Actin, MLC, RhoA, ROCK, lamin A/C, B) in both I/R and HP suggested loss of cytoskeletal and nucleoskeletal stability, this promotes loss of vascular permeability and edema as confirmed by wet/dry weight ratio (sham = 4, I/R = 6.9).

Conclusion: I/R injury induced kallikrein-kinin system activation leading to hepatic microvascular dysfunction, coagulation, loss of vascular permeability and edema. Complement and coagulation system activation and vascular damage further develops pro-thrombotic microenvironment might contribute to portal hypertension.

SAT-520

Effective in vivo transplantation of revascularized porcine liver scaffolds in pigs for extended function over one month

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Background and aims: The clinical application of bioengineered livers offers a promising solution to the shortage of transplantable organs, yet challenges such as replicating organ-scale vascularization and sourcing suitable vascular cells persist. While microvasculature and large vessel networks have been achieved in small-scale in vitro models, establishing functional and patent vascular networks capable of sustaining organ perfusion and functionality post-transplantation remains a significant bottleneck in this approach. To tackle these issues in this study, we developed a revascularization strategy that mimics native vascular physiology, employing decellularized porcine liver scaffolds (pDLS) to assess in vitro and in vivo functionality over a 30-day post-transplantation period.

Method: Essential cell types critical to vascular reconstruction and physiology — porcine endothelial (pUVEC), endothelial progenitors (pOECs), smooth muscle (pA-SMCs), and mesenchymal stromal cells (pBM-MSCs) — were isolated, characterized and prepared for injection into pDLS. This was followed by a 3-day protocol, using alternating tailored injection pressures and specific cell ratios according to vessel diameter and target vessel - portal vein (PV), superior vena cava (SVC), or hepatic artery (HA). Vascular development was promoted through strategic growth factor exposure and gradual mechanical stimulation within a perfusion bioreactor. After a 14-day, the bioengineered scaffolds were transplanted in a porcine auxiliary heterotopic model, allowing for continuous blood perfusion. Perfusion were monitored in vivo via flow probes and CT angiography, with subsequent histological analysis after sacrifice to assess vascular tree reconstruction, integration, cell viability and function.

Results: Microscopic analyses post-revascularization assessed the spatial organization and cellular integration within the bioengineered vascular network. Key markers of vascular function — including nitric oxide (NO) and prostacyclin (PGI2) secretion, glucose and lactate metabolism, vessel contractility, and expression of genes linked to fluid shear stress — validated the functional viability of the bioengineered vessels. Histological examination at 32 days post-transplantation revealed well-organized perfused vascular structures within the hepatic parenchyma, facilitating comprehensive tissue-level histopathology.

Conclusion: This study represents a significant advance in liver bioengineering, particularly in overcoming the challenges of revascularization. By integrating specific cell types under tailored and calibrated seeding pressures within a controlled bioreactor environment with optimized maturation conditions. These engineered vascular networks exhibited robust functionality in vitro and sustained effective blood flow in vivo, highlighting their potential for future clinical applications in bioengineered organ transplantation and regenerative medicine.

Liver transplantation and hepatobiliary surgery – Clinical

TOP-506

Outcomes for patients listed for liver transplantation with low MELD-Na scores: high frequency of MELD-Na score increases, liver transplantation, death and removal from waitlist

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Background and aims: The MELD-Na score, is one of the most widely and consistently validated predictors of mortality for patients with cirrhosis. It is widely perceived that there is a threshold for MELD-Na score, e.g. 15, above which it is believed liver transplantation (LTx) confers a survival benefit at one year and referral to LTx centers is frequently deferred for patients with lower MELD-Na scores. No minimum MELD-Na score required for LTx evaluation or listing, though the threshold for referral for LTx evaluation varies widely between centers. Outcomes according to MELD-Na score at time of listing, e.g. are, however, not well described. The Scientific Registry

for Transplant Recipients (SRTR), which requires MELD-Na score updates and captures key major liver outcomes, including death, removals from LTx list, and transplantation, offers a unique resource to assess the outcomes of patients across the spectrum of MELD-Na scores at listing.
Method: We analyzed data from all adult patients listed for LTx in the United States in a five year period between Jan 2016, to Dec 2022. A total of 1,191,163 records from 88,512 patients who had at least were examined. Changes in MELD-Na score, LTx, death, removed (too sick) and removed (too well) were assessed at 1, 3, 6 and 12 months after listing.
Results: The proportion of patients with MELD-Na scores at listing 6–10, 11–15, 16–20, 21–25, 26–30, 31–35 and 36–40 was: 19.6%, 17.9%, 19.0%, 15.2%, 10.6%, 8.1% and 9.5% respectively. Overall, MELD-Na increases of ≥4 occurred in 62.6% of waitlisted patients at any point in follow up. Among patients with low MELD-Na scores at listing (6–10 and 11–15), ~10.0% had an increase in MELD-Na of ≥4 within 12 mos of waitlisting. Proportions were similar for those MELD-Na scores 6–10 and 11–15. A further 50.2% underwent LTx, were removed (too sick), or died. An increase in MELD-Na of ≥4 was strongly predictive of mortality regardless or transplantation ($p < 0.001$). Patients with MASH had significantly greater probability of waitlist mortality than patients with other indications (>50% more likely c.f. acute alcohol related liver disease).
Conclusion: In this prospective analysis of over 34,000 patients placed on LTx waitlist, with MELD-Na scores ≤15, a substantial majority either had MELD-Na increases of ≥4, died, were removed as too sick or underwent liver transplantation. Increases in MELD-Na are highly predictive of mortality, with or without LTx. This demonstrates that low-MELD patients are still at high risk of adverse outcomes and should be considered, if appropriate, for LTx evaluation and listing.

TOP-507
Quantifying liver function by cholate clearance in extracorporeal circuits with a genetically modified porcine liver and brain-dead human decedent

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Background and aims: One potential application of liver xenografts is augmentation of a patient's liver function via an extracorporeal liver cross-circulation (ELC) until the native liver recovers or until a human liver transplant becomes possible. To define the augmentation and stability of liver function during ELC, we measured the hepatic filtration rate (HFR) of intravenously administered 13C-cholate isotope in brain dead research donors (BDRD) during ELC in a circuit with genetically modified porcine livers.
Method: Three brain-dead research donors (BDRD) were studied during ELC via the METRA device (OrganOx, Oxford, UK). The genetically modified porcine livers (EGEN-5784) were from cloned ESUS-1784 Yucatan minipigs. ELCs were maintained for 72–96 hours via normothermic continuous perfusion. Cholate clearances were determined pre-ELC and at 24, 48, and 72 hours during ELC; and after ELC disconnection, in BDRD3. HFR was calculated using HepQuant SHUNT V2.0 methods. For each test, 20 mg of 13C-cholate premixed with human serum albumin was injected into a peripheral vein of the BDRD and blood samples for measurement of 13C-cholate concentrations were collected at 0, 5, 20, and 60 min post. Systemic hepatic filtration rates (HFR), which are the cholate clearances adjusted for body weight, were calculated for the ELC system comprised of the BDRD and porcine livers.
Results: BDRDs included a 79-year-old male (BDRD 1), a 74-year-old female (BDRD 2), and a 57-year-old male (BDRD 3). During ELC, there was a significant increase in HFR relative to baseline, and HFR levels of the combined native human and porcine livers were substantially higher than the mean of healthy controls (n = 50, data not shown), 5.4 ± 1.0 mL/min/kg. HFR for BDRD 1 was 5.6 (pre), 9.9 (24 h), 10.0 (48 h), and 8.43 (72 h) mL/min/kg; for BDRD 2 was 3.5 (pre), 6.9 (24 h), 6.7 (48 h), and 6.7 (72 h) mL/min/kg; and for BDRD 3 was 4.4 (pre), 6.6 (24 h), 6.9 (48 h), 7.4 (72 h), and 5.4 (post) mL/min/kg. Interestingly, BDRD 3 had cirrhosis by pre-trial surgical exploration and HFR showed a 1.0 mL/min/kg improvement from baseline post-ELC.
Conclusion: HFR using 13C-cholate and the HepQuant SHUNT V2.0 method may be useful for assessing the impact of ELC on hepatic function in BDRDs, and, by extension, both allografts and patients being maintained on extracorporeal circuits.

TOP-508
Derivation and validation of a new donor risk score incorporating graft steatosis and donor diabetes mellitus

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Background and aims: Pre-transplant assessment of donor liver graft quality is an important challenge for transplant physicians. Graft steatosis is an important risk factor for adverse outcomes after transplantation, and the concomitant presence of diabetes mellitus (DM) further increases risk. Incorporation of these factors in donor risk scores is of major importance, as the prevalence of metabolic dysfunction is increasing in the donor population. We aimed to derive and validate a simple donor risk score (DRS) based on presence of DM and graft steatosis and other readily available donor factors.
Method: We analysed data from all consecutive first adult full-graft DBD liver transplantations performed in the Eurotransplant region between 2010 and 2020. Presence of steatosis was assessed based on donor imaging reports. Cases were allocated to the derivation and validation groups based on year of transplant. We used backward selection cox-regression analysis to identify donor and graft factors (available at the time of graft offering) associated with retransplantation-free survival of the recipient. Identified risk factors were used to create a point-based risk stratification tool, the performance of which was assessed in the validation dataset and across clinically relevant subgroups.
Results: A total of 12174 transplants were available for analysis, 7650 of which were allocated to the derivation dataset. In the derivation dataset, median donor age was 57 (IQR 45–68), 54% was male, 484 (10.7%) had DM and 1050 (23.2%) had signs of steatosis. In the derivation dataset, donor age >50 ($p < 0.001$), GGT > ULN ($p < 0.001$), donor DM ($p = 0.002$), presence of graft steatosis based on imaging ($p = 0.007$) and non-local graft procurement ($p < 0.001$) were independently associated with impaired re-transplantation-free survival. A point-based model was built, allocating a point for each risk factor, yielding a DRS ranging from 0–5 points. In the validation dataset (n = 4524), a higher risk score was associated with worse retransplantation-free survival. Retransplantation-free survival at 5 years was 71.6% for recipients of a low risk graft (0–1 risk factor, 22% of cohort), 62.7% for recipients of an intermediate risk graft (2–3 risk factors, 67% of cohort) and 51.1% in recipient of a high risk graft (>3 risk factors, 11% of cohort; $p < 0.001$ by log-rank test). Sensitivity

analysis showed that higher risk grafts were associated with poorer outcomes regardless of recipient age and recipient MELD score.
Conclusion: This validated risk score based on donor age, GGT, presence of donor DM, graft steatosis and non-local procurement predicts retransplantation-free survival in adult DBD liver transplantation and can be used for rapid pre-transplant assessment of graft quality in clinical practice.

FRIDAY 09 MAY

FRI-455-YI
The impact of donor and recipient HSD17B13, PNPLA3 and TM6SF2 genotype on post-transplant fibrosis, steatosis and survival in liver transplant recipients

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Background and aims: The link between certain genetic variants and severity of metabolic dysfunction associated steatotic liver disease (MASLD) is well established. The G-allele in position rs738409 of PNPLA3 and the T-allele in position rs58542926 of TM6SF2 are known to contribute to the development of steatosis, steatohepatitis and fibrosis. The A-allele in position rs72613567 of HSD17B13 is protective. The aim of our study was to evaluate the impact of those genetic variants of recipients and their respective donors on the development of steatosis, fibrosis and survival after liver transplantation (LT).
Method: In this single-center retrospective study, adults who received a liver transplant between 2000 and 2019 and their respective donors were genotyped for PNPLA3, HSD17B13 and TM6SF2 risk variants. Steatosis after transplantation was assessed using MRI (PDFF ≥5%), Fibroscan (CAP ≥248 dB/m) and/or unenhanced computed tomography (CTLP score <42). FIB4-score was used as longitudinal surrogate marker for fibrosis risk.
Results: In our cohort of 435 liver transplant recipients, 34% developed steatosis after transplantation (median follow-up 8 years). The risk alleles of PNPLA3 and TM6SF2 were more common in liver transplant recipients compared to their respective donors (62% vs 43% for PNPLA3, $p < 0.001$; 19% vs. 10% for TM6SF2, $p < 0.001$). In contrast, the protective G-allele in position rs6834314 of HSD17B13 was more frequent in donors than in recipients (47% vs 37%, $p = 0.006$). A subgroup of 392 individuals was also genotyped for rs72613567 in HSD17B13 and we could show a strong linkage disequilibrium of both HSD17B13 variants ($D' = 0.94$, $r^2 = 0.87$, $p < 0.001$). A combined risk score composed of PNPLA3, TM6SF2 and HSD17B13 showed higher rates of post-transplant steatosis with higher scores without reaching statistical significance (27.5% with a score of 0 or 1 points, 31.7% with 2 points, 36.8% with 3 points and 39.2% with 4 to 6 points, $p = 0.470$). During long-time follow-up, FIB4-scores were sig. lower in patients homozygous for the protective variant in HSD17B13. Higher pre-transplant recipient BMI or history of ALD was sig. associated with higher rates of post-transplant steatosis. The presence of a TM6SF2 risk-allele in LT recipients was associated with a sig. shorter median survival (16 years vs 9 years, $p < 0.001$), independent of age, sex and donor TM6SF2 genotype. PNPLA3 and HSD17B13 risk genotypes were not associated with differences in post-transplant survival.
Conclusion: PNPLA3, TM6SF2 and HSD17B13 variants present specific risk alterations after liver transplantation.

FRI-456
Liver resection versus systemic therapy in patients with hepatocellular carcinoma and vascular invasion in the "Immunotherapy Era." On behalf of HE.RC.O.LE.S. and ITA.LI.CA study groups

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Background and aims: Solid evidence indicates that liver resection (LR) achieves better results than Sorafenib (SOR) in selected patients with hepatocellular carcinoma (HCC) and macroscopic vascular invasion (MVI). However, no studies have compared LR with Atezo-Beva (AB) in this setting. In the present study, we sought to compare the effectiveness of LR over ST (SOR and AB) in HCC non-metastatic patients with MVI.
Method: Only non-metastatic HCC patients with MVI treated consecutively in 2015–2024 were considered. Hence, 211 patients undergoing LR were selected from the HE.RC.O.LE.S. register (n = 5441) as the study group, whereas 342 patients were selected from the ITA.LI.CA register (n = 8166) as the control group (244 undergoing SOR and 98 AB). Since this study aimed to compare three potential treatments in advanced HCC patients, we used inverse probability weights (IPW) calculated using a machine learning technique (generalised boosted models) to decrease the selection bias among groups. To estimate the effectiveness of LR over systemic, overall survival (OS) and progression-free survival (PFS) curves were calculated using the Kaplan-Meier method and compared with the log-rank test pre- and after IPW. A LASSO Cox model was used to identify OS and PFS predictors through multivariable analyses.
Results: IPW created two well-balanced SOR and AB pseudo-populations with the LR group regarding the patient, liver function, and HCC characteristics. After IPW, the median survival times were 40 months (IQR 13–54), 12 months (IQR 7–24), and 21 months (IQR 8–43) for LR, SOR, and AB, respectively ($p < 0.001$). Systemic therapy significantly increased the risk of patient death over LR (SOR vs LR: HR 2.20, 95% CI 1.56–3.12, $p < 0.001$) and AB (AB vs LR: HR 1.66, 95% CI 1.02–2.72, $p = 0.042$). A Cox IPW-weighted multivariable regression identified the following independent survival predictors: systemic therapy, platelet count, comorbidity index, and non-VP1-2 MVI. Conversely, LR did not improve PFS over SOR and AB at multivariable analysis in weighted and unweighted populations.
Conclusion: This is the first study directly comparing LR with AB in patients with HCC and MVI without extra-hepatic metastases. Although AB has decreased the gap between surgery and ST in resectable tumours with MVI, LR should still be considered the first therapeutic option in these patients.

FRI-461
Impact of pre-transplant infection and multi-drug resistant organisms colonization on in-hospital post-transplant survival in subjects with pre-transplant liver failure

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Background and aims: Limited data are available on the impact of infections and colonization occurring before liver transplant (LT) on post-LT in-hospital mortality. We investigated the post-LT outcome in patients with pre-LT liver failure with and without pre-LT infections.

Method: A monocentric retrospective study was conducted from 01/01/2018 to 01/08/2024 including all LT recipients. Consecutive candidates with Mayo End-stage Liver Disease (MELD) score >30 and/or Acute on Chronic Liver Failure or Acute Liver Failure were enrolled. Clinical, biochemical, and microbiological data were collected in all enrolled subjects. Patients who did and did not experienced any bacterial, viral or fungal infections and/or colonization within 30 days before LT were compared.
Results: Among 751 LT recipients 99 patients were included. Median age was 57 (IQR 14) years, 73.7% were male (n = 73). Median Charlson Comorbidity Index and MELD score were 5 (IQR 5) and 32 (IQR 5) respectively. Multi-Drug-Resistant Organisms (MDROs) colonization was reported in 30.3% of patients (n = 30), while *Candida* spp. colonization in 62.6% (n = 62). Pre-LT infections were reported in 52 (52.5%) patients, with 68 infectious episodes. Bloodstream infections (n = 18; 26.5%), spontaneous bacterial peritonitis (n = 13; 19.1%) and urinary tract infections (n = 7; 10.3%) were the most common syndromes. Septic shock was reported in 10.3% of cases (n = 7). Fungal infections accounted for 5.8% of cases (n = 3). MDROs sustained 19.2% of the infections (n = 10): Extended-Spectrum Beta-Lactamase producing bacteria (n = 5; 50%), Vancomycin-Resistant Enterococci (n = 3; 30%), Carbapenem-Resistant *Enterobacterales* (CRE) (n = 2; 20%), Difficult-to-Treat Resistance *A. baumannii* (n = 2; 20%). At univariate analysis in-hospital mortality did not result significantly different between patients with and without pre-LT infection (p = 0.95). Post-LT complications were significantly more frequent in the pre-LT infection group: Acute Kidney Injury (p = 0.02), need of Continuous Renal Replacement Therapy (p = 0.03), length of hospitalization (p = 0.01), post-LT infections (p = 0.01), including infection sustained by MDROs (p = 0.03) and septic shock (p = 0.05). Kaplan-Maier analysis showed that overall in-hospital survival was similar among the two groups, while infection-free survival was lower in pre-LT infection patients (p = 0.017). At multivariate analysis higher MELD score (p = 0.006), pre-LT colonization by CRE (p = 0.025), pre-LT infections sustained by MDROs (p = 0.035), and re-transplantation (p = 0.024) predicted in-hospital mortality.
Conclusion: In our analysis pre-LT infections were associated with increased post-LT complications but not with reduced survival. Nevertheless, CRE colonization, and pre-LT infection sustained by MDROs significantly impacted post-LT mortality.

FRI-462

Benefits of calcineurin inhibitor sparing regimen in a biopsy-guided personalized immunosuppression program after liver transplantation

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Background and aims: Chronic immunosuppression (IS) including calcineurin inhibitors (CNI) although required is a source of morbimortality, including infections, malignancy risk and chronic kidney disease after liver transplantation (LT). Our personalized IS program, based on surveillance biopsies (svLbx) (Adult Liver Allograft Dysfunction Initiative (ALADIN)) demonstrated the safety of reducing CNI dose, with a short-term renal benefit. Here, we report an update on the long-term outcomes of our prospective ALADIN cohort.
Method: Single center retrospective study between (Oct/2018 – Oct/2024), of the prospective ALADIN study. All included LT recipients (LTR) had a basal svLBx. Rejection rates, graft- and kidney-function, and survival were monitored longitudinally.
Results: A total of 249 LTR were included, 171 (69%) were followed for up to three visits after the initial svLbx with median FU time of 14 months, 33 months, and 47 months (FU1, FU2, FU3). LTR with complete FU were grouped into those in whom CNI reduction was possible (n = 89) and those without CNI reduction (n = 82). At baseline svLbx, LTR who underwent CNI reduction had lower kidney function (eGFR: 63 ml/min vs 77 ml/min; p = 0.02), higher CNI IS score (p < 0.01), and a shorter time since LT (54 vs 120 months; p < 0.01) compared to those without CNI reduction. For a fair comparison of the two groups in terms of outcomes, a propensity score match was conducted, with the three afore mentioned variables included as covariates, ultimately resulting in a satisfactory balance between the groups. In those LTR with CNI reduction (n = 53), there was a 33% delta dose reduction between first and last visit, for no CNI reduction (n = 53) there was an increase delta dose of 16% (CNI IS dosis at last FU: CNI reduction vs. no CNI reduction: 0.75 vs. 1.5 p < 0.01). Kidney function was stable in LTR with reduced CNI regimen (eGFR basal-Last visit delta, 0 ml/min), whereas a decline was observed in those without CNI reduction (eGFR basal-last visit delta, –8 ml/min; p < 0.01). Including all LTR, a linear mixed model for kidney function (eGFR) adjusted for age, time after LT, diabetes, hypertension, and age, showed an independent negative influence of CNI dose (β estimate: –2.7; p = 0.01) in the eGFR. Regarding survival, an overall survival (OS) analysis was performed between patients with and without CNI reduction, matched for time after LT. We identified a survival benefit (no CNI reduction: 88% OS, CNI reduction: 95% OS, over 60 months of FU; log rank 0.05); causes of mortality included malignancy and infection. No differences were observed in fibrosis progression (median Delta Ishak F basal FU: 0 vs. 0, p = 0.5) in LTR (n = 69) who underwent FU biopsies, or in the rate of rejection (2% vs. 1.9%).
Conclusion: Whitin a personalized IS svLbx based program, CNI reduction stabilizes kidney function and improves OS without increasing graft injury.

FRI-463-YI

Effect of donor and recipient CYP3A5 genotypes on the pharmacokinetics of tacrolimus after liver transplantation

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Background and aims: Tacrolimus, the main immunosuppressant in liver transplantation (LT), is primarily metabolized in the intestine and liver through cytochrome P450 3A5 (CYP3A5). Carrying an *1 allele variant is associated with higher expression and activity of CYP3A5, which leads to more efficient metabolism (EM) of tacrolimus and requires higher doses to achieve therapeutic levels compared to allele variants without *1 (inefficient metabolism, IM). The aim of this study was to evaluate, in real-world practice, the influence of CYP3A5 *1 allele variants in both the donor and recipient on tacrolimus doses and the concentration/dose ratio (C/D) in a cohort of LT patients. In the available literature, there is insufficient evidence to make strong recommendations on dose adjustments specifically in LT, given the particularities of donor-recipient genotype discordances.
Method: CYP3A5 genotyping was performed to identify *1 allele carriers in liver donor-recipient pairs (1/2023–9/24). Clinical and analytical variables post-LT, tacrolimus doses, trough levels, and C/D ratios were collected at the first trough level, day 7 post-initiation, day 40, 3 months, and 6 months post-LT.
Results: Data from 48 donor-recipient LT pairs were analyzed. Both groups were predominantly male (75%) with a median age of 58 years

(IQR 54–65). Fourteen (29%) recipients had the EM genotype and 34 (71%) had the IM genotype. Seven (15%) donors were carriers of the EM genotype, and the rest had the IM genotype. In total, 30 (63%) pairs were donor-recipient IM, and 18 (37%) were EM. The starting tacrolimus doses were similar between the EM and IM genotypes (0.06 mg/kg). Tacrolimus doses/kg at day 7, 3 months, and 6 months were higher in LT recipients with the EM genotype in either donor or recipient compared to those with the IM genotype (0.11 mg/kg/day vs. 0.08 mg/kg/day, p = 0.07). The C/D ratio at the first trough level and day 7 was lower in recipients with the EM genotype compared to those with IM (0.55 ± 0.27 vs. 1.19 ± 0.92 and 0.87 ± 0.35 vs. 1.15 ± 0.58; p = 0.02 and p = 0.11, respectively). The donor EM genotypes were associated with a lower C/D ratio at 3 and 6 months compared to IM (0.95 ± 0.50 vs 1.3 ± 1.04 and 1.05 ± 0.46 vs 1.9 ± 1.28; p = 0.31 and p = 0.039, respectively). The 30 donor-recipient pairs with IM maintained a C/D ratio >1 at all time points (mean 1.29), while pairs with any EM genotype maintained a C/D ratio <1 (mean 0.63, p = 0.018).

Conclusion: The presence of CYP3A5 *1 allele variants in liver transplant donors and/or recipients is associated with different tacrolimus pharmacokinetic profiles. The CYP3A5 *1 genotype of the recipient is associated with the need for higher doses and lower C/D ratios of tacrolimus during the first month post-LT, whereas the CYP3A5 *1 genotype of the donor is associated with the need for higher doses and lower C/D ratios of tacrolimus from the third month post-transplant. These findings support the use of pharmacogenomics as a tool for individualizing immunosuppression in LT, though further studies are needed.

FRI-464

How immunosuppression influences cancer survival in liver transplant recipients: insights from a tertiary care center

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Background and aims: Cancer survival in liver transplant recipients is influenced by various factors, including the immunosuppressive therapies essential for preventing graft rejection. However, these therapies may increase the risk of malignancy and adversely affect long-term survival. This study aims to evaluate the survival rates of liver transplant recipients diagnosed with post-transplant malignancies, comparing them with general population benchmarks, and emphasizing the role of immunosuppression in modulating outcomes.

Method: This retrospective study analyzed 692 liver transplant recipients from a Spanish tertiary care hospital between January 2002 and December 2022, of whom 108 developed malignancies. Data were collected for dermatological, digestive, gynecological, hematological, and otorhinolaryngological (ORL) tumors. Immunosuppressive regimens were recorded to assess their correlation with survival outcomes. Survival times were calculated as the interval between diagnosis and death or last follow-up. Comparative analysis incorporated published general population benchmarks for each tumor type. Statistical analyses included mean, median, and survival distributions.

Results: Dermatological tumors: Mean survival was 2660 days, below the general benchmark of 3650 days. mTOR inhibitors appeared to reduce associated risks. Digestive tumors (Recurrence of HCC was excluded): Mean survival surpassed benchmarks (3110 days vs. 1825 days), suggesting better management or earlier detection despite immunosuppression. Gynecological/ Prostate tumors: Mean survival was lower than expected (1728 days vs. 2190 days/3000 days vs. 3650 days). Calcineurin inhibitors at high doses were linked to reduced survival. Hematological tumors: Median survival was 1825 days, compared to the benchmark of 3377 days. Mixed effects were observed with mycophenolate mofetil. ORL tumors: Patients showed significantly lower survival (median: 1460 days vs. 3211 days), with stronger associations observed in patients receiving prolonged high-dose corticosteroids. For most tumor types, survival in transplant recipients was inferior to population benchmarks, with the exception of digestive malignancies, which exhibited superior outcomes, potentially reflecting optimized immunosuppressive management and early detection strategies.

Conclusion: The findings highlight the intricate interplay between immunosuppressive therapy and post-transplant oncology outcomes. While indispensable for graft survival, immunosuppressive regimens may elevate cancer risk and influence survival trajectories. Enhanced screening protocols, personalized immunosuppressive strategies, and early interventions are essential to mitigate risks, particularly in hematological and ORL malignancies. Conversely, the superior outcomes observed in digestive tumors underscore the importance of tailored immunosuppressive approaches, which could serve as a model for other tumor types.

FRI-465

Sexual health after liver transplantation is significantly impacted and varies by gender

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Background and aims: Liver disease affects sexual health (SH) through factors such as hormone metabolism, autonomic or neurologic dysfunction, medication effects, and relationship dynamics. However, little is known about the impact of liver transplantation (LT) on SH and health-related quality of life (HRQoL), especially among different genders.

Method: We performed a cross-sectional study of adult LT recipients at least 1-year post-LT being followed at a large US transplant center. An electronic survey assessed: 1) sexual satisfaction and interest, 2) symptoms, and 3) HRQoL (physical and mental) using questions from Patient-Reported Outcomes Measurement Information System (PROMIS) reported as T scores (50 reflects a mean score among patients with cancer and chronic diseases with a standard deviation (SD) of 10). Additionally, we investigated patient preferences for sharing concerns about SH with LT providers, importance of sexuality on a Likert scale from 1 to 10 (low to high importance), and relationship dynamics.

Results: A total of 113 patients completed the survey; 68 (60.2%) were male with median age of 57 years and a median time of 4 (IQR 1.95–6.57) years post-LT. Median score for importance of sexuality was 6.5 (IQR 5.0–8.0). Among all-comers, 83.6% of males and 73.2% of females reported being sexually active since LT; the median time to resuming sexual activity was 4–6 months post-LT. The primary reason for sexual inactivity in the last 30 days was lack of interest for females (60.0%) and difficulty having an erection among males (64.0%). Females reported lower interest in sex compared to males with mean (SD) scores of 39.9 (11.6) and 49.2 (10.5) respectively (p-value <0.01). Mean sexual satisfaction scores were comparable at 47.9 (SD 8.1) for females and 48.1 (SD 7.8) for males (p = 0.90). Mean (SD) physical HRQoL scores were also similar: 45.3 (10.3) for females and 47.8 (8.3) for males (p = 0.16); whereas mental HRQoL T-scores were 47.7 (11.4) in females and 49.7 (10.7) in males (p = 0.36). Factors affecting sexual satisfaction included fatigue (56.9%), medication side effects (40.9%) and surgical scar (16.4%). Regarding relationships with partners,

36.4% reported no change in their physical relationship while 44.4% noted a positive impact on their emotional relationship. Although 82.1% of respondents considered SH as important, only 20.8% were asked about it during clinic visits in the past six months. While 78.2% expressed comfort discussing their SH with a LT provider,41.3% of female and 21.3% of male respondents preferred same-gender providers for these discussions.
Conclusion: SH and relationships are greatly impacted after LT and differentially affect women and men. Further research is needed to identify factors associated with better or worse SH by gender so that patients can receive better support and education while navigating this life-changing recovery.

FRI-466
Effects of sodium-linked glucose transporter 2 inhibitors in liver transplant recipients with impaired renal function
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Background and aims: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have gained significant attention in clinical research due to its diverse therapeutic effects. The aim of the following retrospective study was to analyze the nephroprotective effects of SGLT2i in patients experiencing renal insufficiency following liver transplantation.
Method: Patients with renal insufficiency following liver transplantation with and without being treated with SLGT2i inhibitors between 2021 and 2024 at the LMU University Hospital Munich were included in the study. We analyzed changes in eGFR, creatinine levels, liver parameters and the safety profile.
Results: A total of 42 patients with SGLT2i treatment and 42 controls without treatment were included. Main characteristics such as age ($p = 0.08$), gender ($p = 0.34$), baseline kidney and liver parameters were observed to be similar in both study cohorts. Median observation period was 12 (range; 1–24) and 18 months (range, 2–32) in patients with and without treatment of SGLT2i. A significant improvement in creatinine ($p = 0.02$) and eGFR ($p = 0.04$) levels was observed during treatment with SGLT2i, while renal function (creatinine, $p = 0.01$; eGFR, $p = 0.009$) significantly deteriorated in the relating control cohort. Improvement in renal function under treatment with SGLT2i was also observed to be significant in a subcohort of patients with a baseline GFR < 30 ml/min ($n = 10$; creatinine, $p = 0.02$). In contrast, no change in liver parameters could be detected over time in both cohorts. Regarding the safety profile of SGLT2i in this specific population, no adverse events could be detected.
Conclusion: SGLT2i seem to be safe and effective in patients with renal insufficiency following liver transplantation.

FRI-467
Incidence and risk factors for incisional hernias following liver transplantation: a retrospective single-centre european study
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Background and aims: Patients who develop incisional hernias after liver transplantation (LT) experience reduced quality of life. Retrospective studies from outside of the UK show varying incidences (between 4.6% and 43%) and risk factors for these hernias. This study aims to report the experience of post-LT incisional hernias in a large volume LT centre, identifying risk factors and time to development.
Method: A retrospective analysis of LTs from the Birmingham LT Unit (January 2013–May 2023) with at least 6 months of follow-up was conducted. Risk factors, including age, sex, BMI, refractory ascites, hypertension, diabetes, UKELD and MELD scores were recorded at time of listing. Data were analysed using the Mann-Whitney U test for continuous variables and Chi-squared test for binary variables. A multivariable analysis was also conducted.
Results: 1026 patients (63% male, mean age 52.80 (SD ± 13.5) years) were identified, with 129 (12.6%) developing post-LT incisional hernias (median follow up was 1326 (IQR 574.75–1930.30) days). The median dry BMI pre-listing was 27.47 (23.70–31.00) kg/m^2. At listing, 367 (35.8%) of patients had ascites, 199 (19.4%) hypertension, 244 (23.8%) diabetes, and 44 (4.3%) had a transplant during the follow-up period. Median UKELD score was 56 (52–59), and MELD 16 (12–20). Univariable analysis identified BMI > 25 kg/m^2 ($p = 0.0047$), refractory ascites ($p < 0.0001$), and re-transplantation during follow up ($p = 0.038$) as risk factors. None were significant in multivariable analysis. Any combination of one, two or three of the risk factors identified on univariable analysis increased the risk of incisional hernia formation. Median time to hernia development after LT was 454 (249–977) days.
Conclusion: This study of post-LT incisional hernias shows an incidence of 12.6% for incisional hernias post LT. Having a BMI > 25 kg/m^2 at listing, refractory ascites pre-LT, along with having a re-graft are risk factors for incisional hernia development on univariable analysis.

FRI-468
Chronic rejection outcomes in pediatric post liver transplantation-single center experience-King Faisal specialist hospital & research center,Riyadh, Saudi Arabia
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Background and aims: Chronic rejection (CR) of the donor organ after liver transplantation is an ongoing immunological injury that commonly leads to permanent dysfunction and ultimately to graft loss. The incidence of chronic rejection in pediatrics has decreased from 12% to 5.3% in previous reported rates (1, 2).
Method: We retrospectively studied 837 children who undergone liver transplantation between October 2010 to November 2024 in our center. We determined the incidence of CR, risk factors and its outcomes (remission, progression to a chronic allograft failure) In this cohort study, the children were divided into two groups those with (a remission, successful outcome) and those with (progressive, unfortunate outcome). We compared patient and graft characteristics that were associated with CR, remission and progression to chronic allograft failure.
Results: We identified 30 patients with CR (30/837,3.6%). Six of the 30 patients (20%) achieved a stable remission by immunosuppressive adjustment or adding rescue therapies such as Everolimus or single dose of basliximab. None of these 6 patients had ductopenia in the liver biopsies. In 24 out 30 patients (80%) CR followed a progressive course, despite changing immunosuppression, ultimately leading to chronic allograft failure and to retransplantation (19/24, 79%) or death (5/24, 21%). All patients in the latter group had shown interlobular bile duct loss and ductopenia in liver histology.
Conclusion: Our data indicate that ductopenia in liver histology predicts a very low chance of reversal of CR upon adaptation of the

immunosuppressive regimen. Ductopenia should therefore lead to consider early retransplantation given the increased risk of sepsis and death during intensification of immunosuppression.

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FRI-469-YI

Sodium and lactate levels during hypothermic oxygenated machine perfusion as predictive biomarkers for early allograft dysfunction in liver transplantation

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Background and aims: Hypothermic oxygenated machine perfusion (HOPE) improves liver transplantation (LTx) outcomes, yet there is a critical need for simple and accessible biomarkers to assess graft viability during perfusion. Currently, no standardized parameters are broadly available for monitoring HOPE effectiveness.
Method: This retrospective study analyzed 158 patients who underwent LTx with HOPE-perfused liver grafts at the Medical University of Vienna (2018–2023). HOPE followed standardized protocols using University of Wisconsin machine perfusion solution. Blood gas analysis of perfusate was conducted at 30-minute intervals up to 120 minutes. Hospitalization data were prospectively documented. Early allograft dysfunction (EAD) was defined using Olthoff criteria. Receiver operating characteristic (ROC) curves were used to identify predictive biomarkers for EAD.
Results: Of the 158 patients, 44 (27.8%) developed EAD. Grafts with EAD had significantly lower sodium levels and higher lactate levels during HOPE, particularly at 90 minutes. Sodium (<85 mmol/L) and lactate (>4.3 mmol/L) at 90 minutes demonstrated predictive potential for EAD, with ROC areas of 0.741 and 0.633, respectively. Stratification by these cut-offs identified distinct risk cohorts with a low-risk cohort (high sodium, low lactate) with an EAD incidence of 17.6%, while the high-risk cohort (low sodium, high lactate) displayed an incidence of EAD at 69.2% ($p < 0.001$). Importantly, both sodium and lactate remained as significant parameters in a multivariable model next to cold ischemia time and donation after circulatory death as donor type.
Conclusion: Monitoring perfusate sodium and lactate levels at 90 minutes during HOPE offers a simple and effective method for assessing liver graft viability. This approach enables the identification of high-risk grafts before transplantation, paving the way for improved patient outcomes through personalized graft utilization strategies. The findings support integrating routine blood gas analysis into HOPE protocols to enhance decision-making in liver transplantation.

FRI-470

Retrospective study on simultaneous liver kidney transplantation: renal outcome and prevalence of acute cellular rejection

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Background and aims: There has been a long-standing hypothesis that SLK has an immune protective effect for the transplanted kidney from the hepatic allograft. This hypothesis was challenged when recent data showed increased rejection rates for both liver and kidney grafts in patients with pre-existing DSA, particularly against class II HLA with mean fluorescence intensity (MFI) of >10000. In 2014 the immunosuppression protocol in our unit was changed following a case of antibody-mediated rejection (ABMR) and renal graft loss after SLK related to DSA to class II HLA. This study aims to evaluate liver, kidney, and overall survival outcomes in SLK recipients over a 5-year follow-up period following the protocol change. Additionally, the study assesses the incidence of acute and chronic rejection episodes in kidney grafts within the first 5 years post-SLK.
Method: We retrospectively collected clinical, biochemical, and outcome data on patients receiving SLK from 2014 to 2019 in King's College Hospital Londen.
Results: After a follow-up of 5 years, 18 patients (50%) achieved an estimated glomerular filtration rate (eGFR) greater than 45 mL/min/1.73 m². Only one patient (2.9%) needed renal replacement therapy (RRT) after 5 years, two patients (5.3%) were deceased. Additionally, renal allograft outcomes were analysed based on the presence or absence of acute rejection within the first year. The mean eGFR was compared between these patient groups. At 1 month post-transplant, the mean eGFR was significantly higher in the non-AR group (52 mL/min/1.73 m²) compared to the AR group (33 mL/min/1.73 m²; $p = 0.022$). However, the mean eGFR at the 5-year benchmark in the non-AR group was 50 mL/min/1.73 m² compared to 40 mL/min/1.73 m² in the AR group and was not statistically significant anymore ($p = 0.081$) and one patient in the non-AR group required RRT. AR of the kidney transplant was observed in 9 patients (22%), while no episodes of chronic rejection were recorded during the follow-up period. Both acute TCMR and ABMR occurred in 5 out of 36 patients (13.9%), with one patient with both TCMR and ABMR. The length of stay was longer in the AR group, with a mean of 36 days compared to 26 days in the non-AR group ($p = 0.027$). The presence of pre-transplant anti-HLA antibodies was analysed. Of the nine patients with an AR episode, two patients (22%) had class I anti-HLA antibodies, four patients (44%) had both class I and II anti-HLA antibodies, and three patients had no preformed DSA.
Conclusion: Our findings show that SLK is a viable and effective treatment option for patients with concurrent liver and kidney diseases. Patients who are deemed high risk for ABMR due to the presence of preformed DSA class II HLA antibodies should receive the enhanced immunosuppression protocol and close monitoring of their DSAs after transplant. Our study showed that despite the occurrence of an AR episode, renal outcome does not differ significantly after a 5-year follow-up period when managed properly.

FRI-471

Comparison of the effects of tenofovir alafenamide and entecavir on renal function and serum lipids in liver transplant recipients: a retrospective observational study

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Background and aims: Antiviral treatments can impact serum lipids as well as kidney function. We conducted a retrospective observational study with a 48-month follow-up period, involving liver transplant recipients receiving either entecavir or tenofovir

alafenamide, to assess the effects of these antiviral medications on lipid profiles and renal function.
Method: The study was conducted with 47 patients at the Gastroenterology Department of Izmir Dokuz Eylül University Hospital. Research data were retrospectively collected. Serum creatinine and lipid levels were measured at least once per year for each patient. The Friedman test was applied to compare glomerular filtration rate and serum lipids.
Results: During the 48-month observation period, a mean decrease in glomerular filtration rate of 10 mL/min/1.73 m² was observed in the tenofovir alafenamide treatment group ($p < 0.001$), while a decrease of 8 mL/min/1.73 m² occurred in the entecavir group ($p < 0.001$). However, there was no statistically significant difference in the glomerular filtration rate decrease between the two groups ($p = 0.990$). Additionally, no patient required renal replacement therapy, and no hepatitis reactivation was noted. Although entecavir showed more favorable effects on total cholesterol compared to tenofovir alafenamide at the 12th and 24th months ($p = 0.025$ and $p = 0.023$, respectively), neither treatment demonstrated a lipid-lowering effect by the end of the 48-month observation period.
Conclusion: We found no significant difference in renal safety between tenofovir alafenamide and entecavir. Switching from tenofovir disoproxil to either tenofovir alafenamide or entecavir did not improve kidney function in the short or long term. Entecavir demonstrated fewer dyslipidemic effects compared to tenofovir alafenamide, with lipid-lowering effects observed during the first two years of treatment. Overall, both entecavir and tenofovir alafenamide have similar impacts on serum lipids and renal function, making them safe and effective treatment options for liver transplant recipients.

FRI-472

Factors associated with retransplantation-free survival in patients receiving TIPS after liver transplantation: results of a french multicenter retrospective study

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Background and aims: Portal hypertension (PH) after liver transplantation (LT) may warrant the use of transjugular intrahepatic portosystemic shunt (TIPS), but data on TIPS outcomes in this setting are limited. The aim of this study was to evaluate the impact of TIPS on 5-year retransplantation-free survival (reLT-FS).
Method: We retrospectively analyzed a cohort of 82 LT patients from 15 French teaching hospitals who underwent post-LT TIPS between 1999 and 2023 (65% male, median age 56 years). The primary endpoint was reLT-FS at 5 years. Secondary endpoints included reLT-FS at 1 year, overall survival (OS) at 1 and 5 years, and clinical and hemodynamic efficacy of TIPS as measured by hepatic venous pressure gradient (HVPG). Complications following TIPS were also analyzed. Multivariate analyses were performed using an age-adjusted Cox model.
Results: Of the patients, 79% received TIPS after 2010. All had symptomatic PH, primarily refractory ascites (74%) and hydrothorax (28%), with a median HVPG of 14.5 mmHg. Causes of PH included cirrhosis (n = 34), vascular disease (VD, n = 36), and unknown or unreported causes (n = 12). The median time from LT to TIPS was 42 months, longer in cirrhosis cases than in VD cases (70 vs. 15 months; $p = 0.016$). After TIPS, HVPG remained ≥10 mmHg in 17.9% of patients, although this did not predict clinical efficacy, which was achieved in 36.2% of cases. Clinical efficacy correlated with age <60 years (46.0% vs. 11.8%; $p = 0.011$) and end-to-end inferior vena cava anastomosis (100% vs. 33.3%; $p = 0.017$). Complications occurred in 36 patients within 7 days of TIPS. Twenty patients required reLT (median time 8.5 months post-TIPS). OS and reLT-FS were 73.9% and 62.0% at 1 year and 59.6% and 40.7% at 5 years, respectively. At 1 year, reLT-FS was lower in cases with cirrhosis (55.2% vs. 77.9%; $p = 0.037$) and early post-TIPS complications (48.3% vs. 79.2%; $p = 0.004$), where 7 reLTs and 16 deaths occurred. Notably, reLT following early post-TIPS complications was associated with a high mortality rate (43% at one year). At 5 years, reLT-FS was higher with clinical TIPS efficacy (64.9% vs. 27.7%; $p = 0.001$) and VD vs. cirrhosis (51.1% vs. 35.2%; $p = 0.048$). On multivariate analysis, early post-TIPS complications were the only predictors of OS (HR = 0.21; $p < 0.01$) and 1-year reLT-FS (HR = 0.28; $p < 0.001$). Clinical efficacy was the only factor influencing 5-year reLT-FS (HR = 3.96; $p = 0.002$).
Conclusion: In post-LT PH, TIPS may reduce the need for reLT at 5 years if clinical improvement is achieved. An end-to-end inferior vena cava anastomosis predicts TIPS efficacy, while early complications are common and worsen prognosis, even despite reLT. Identification of risk factors for these complications is essential for selection of appropriate TIPS or reLT candidates. A study comparing TIPS with reLT in this population is ongoing.

FRI-475-YI

The effect of dual hypothermic oxygenated machine perfusion on the incidence of post-transplant diabetes mellitus in recipients of livers donated after circulatory death

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Background and aims: New onset post-transplantation diabetes mellitus (PTDM) is a significant metabolic complication that effects 2.5–25% of liver transplant recipients, and results in poorer graft and patient survival, as well as an increased risk of cardiovascular events. A combination of modifiable and non-modifiable donor and recipient risk factors contribute to PTDM development. Especially, transplantation with a liver from a donor after circulatory death (DCD) has been associated with a significantly increased risk of PTDM, thought to be due to the deleterious effect of ischemia-reperfusion injury on insulin resistance of the graft. Dual hypothermic oxygenated machine perfusion (DHOPE) mitigates ischemia-reperfusion injury by improving mitochondrial function during preservation. We therefore hypothesized that DHOPE treatment of DCD livers reduces the risk of PTDM development.

Method: This is an post-hoc analysis of the recently published DHOPE-DCD Trial, in which DCD livers were randomized between DHOPE versus conventional static cold storage (SCS). All trial patients from our center were included in this study, except those with pre-transplant DM. The primary outcome was frequency and 1-year cumulative incidence of PTDM, defined as the need for diabetics to control sustained hyperglycemic blood levels. Transient PTDM (T-PTDM) was defined as PTDM that resolved within 6 months. Immunosuppressive protocols (tacrolimus monotherapy or reduced-dose tacrolimus + mycophenolate, and fixed 4-month steroid taper) were similar in both groups.
Results: A total of 41 DM-naïve patients were included, n = 18 in the DHOPE and n = 23 in the SCS group. None (0%) of the DHOPE patients developed T-PTDM, vs 4/23 (17%) of the SCS arm (p = 0.118). The 1-year cumulative incidence of PTDM was 11% (2/18) in the DHOPE and 41% (9/23) in the SCS group (p = 0.049) after a median of 36 (range 27–44) and 34 (10–166) days, respectively. All PTDM patients used anti-diabetics, with 55% being insulin dependent. Two SCS patients had tacrolimus monotherapy, while the other nine (82%) had reduced-dose tacrolimus + mycophenolate at the time of diagnosis.
Conclusion: The cumulative incidence of PTDM was significantly lower in recipients of a DHOPE preserved DCD liver, compared to SCS, and none developed T-PTDM, despite similar exposure to steroids and tacrolimus. All cases of PTDM occurred within 6 months post liver transplantation. Albeit small in sample size, these results are promising and warrant further research into the metabolic effects of DHOPE preservation on liver allografts.

FRI-476

Current status of endoscopic treatment for anastomotic biliary stricture after living donor liver transplantation at our institution

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Background and aims: Anastomotic Biliary stricture (ABS) at the biliary-biliary anastomosis occurs in 15–30% of cases after living donor liver transplantation (LDLT) and is often challenging to treat. This report examines the endoscopic treatment outcomes for ABS following LDLT at our institution.
Method: The study included 46 cases of ABS among 190 adult patients who underwent LDLT with biliary-biliary anastomosis at our institution between 2009 and December 2021. Endoscopic treatment involved the placement of either plastic stents (PS) or fully covered self-expandable metal stents (FCSEMS). The BONASTENT M-intraductal stent was used for 16 weeks, ensuring no blockage of bile ducts, and subsequently removed. Technical success was defined as successful stent placement at the stricture site, and clinical success was defined as confirmed improvement of the biliary stricture on cholangiography at the time of stent removal. Treatment outcomes for the above cases were analyzed. Cost comparison was performed over a two-year period between cases treated with FCSEMS and a random selection of cases treated with PS.
Results: The median age of the patients was 58 years (range 38–70 years), with 27 males and 19 females. The graft type was right lobe in 20 cases and left lobe in 26 cases. The median time to ABS onset was 4 months (range 0–42 months). Among the 46 cases, FCSEMS placement was attempted in 20 cases, with successful placement achieved in all cases. Of the 17 cases where the stent was removed, 16 showed resolution of the stricture. The technical success rate of FCSEMS was 100%, and the clinical success rate was 94.1%. Cumulative re-stricture rates among clinically successful patients were 6.25% at 6 months, 12.5% at 1 year, and 12.5% at 3 years, with a median follow-up period of 52 months (range 0–79 months). Complications associated with FCSEMS included transient cholangitis in 5 cases, obstructive cholangitis caused by FCSEMS in 1 case, and stent migration in 1 case. There were no cases of post-ERCP pancreatitis, bleeding, or perforation. Regarding costs, the median number of hospital admissions was 2 for FCSEMS cases and 3 for PS cases, with median total hospital stays of 27 days and 24 days, respectively. The median total medical fee were 3,050,840 yen for FCSEMS and 3,673,210 yen for PS, with no significant differences observed.
Conclusion: FCSEMS demonstrated high stent free rates in LDLT patients with ABS and showed comparable cost performance to PS. These findings suggest that FCSEMS may contribute to improved quality of life for these patients.

FRI-477-YI

Recurrence of primary sclerosing cholangitis after liver transplantation: a single centre experience

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Background and aims: Primary sclerosing cholangitis (PSC) is a progressive cholestatic condition which may lead to liver transplantation (LTx). Recurrence of PSC (rPSC) after grafting is estimated to occur in 25% of patients (Dyson, 2018) and may pose a significant challenge including graft loss and impaired survival. In this study we evaluated the incidence, risk factors, and post-transplant outcomes associated with rPSC.
Method: We analyzed a group of 69 patients who had their LTx done between July 2015 and January 2022 and followed our protocol of regular magnetic resonance cholangiopancreatography (MRCP) procedures after LTx. All of them had their first MRCP done within a median time of 14 months and 48 of them had following MRCP with median time of 35 months. Median follow-up period was 58 months. Clinical and laboratory data from pre- and post-transplant periods were analysed. Radiological features of rPSC were assessed with criteria proposed by Graziadei (1999). Chi-square test was used for categorical variables, and the Mann–Whitney U test was used for the comparison of quantitative variables.
Results: Analyzed group comprised 44 males and 25 females with median age 35 years. Forty-five of them had inflammatory bowel disease (1 had colectomy before due to advanced colitis). Seven had cholangiocarcinoma (CCa) not detected before LTx and 2 were transplanted after neoadjuvant radiochemotherapy following Mayo protocol. Radiological features of rPSC were diagnosed in 26/69 patients (38%) during their first MRCP. A second MRCP showed features of rPSC in 31/48 (65%) patients. Four patients lost their grafts due to rPSC and required retransplantation (reLTx) within a median time of 61 months. Overall survival of the analyzed group during the follow-up period was 91%. Four patients died due to recurrent CCa and 2 due to complications following retransplantation. There were no significant associations between rPSC and age, gender, concurrent inflammatory bowel disease, liver biochemistry or MELD score at the time of LTx in univariate analysis. Among patients diagnosed with radiological rPSC at their first MRCP, 9/26 (35%) had normal cholestatic enzyme activity. During the second MRCP 15/31 patients (48%) with features of rPSC also presented with normal cholestatic enzyme levels.
Conclusion: The recurrence rate of PSC following liver transplantation, as assessed with routine MRCP imaging, is higher than previously reported. No pretransplant risk factors for rPSC were identified. Our findings highlight the need for close and prolonged monitoring of LTx recipients with PSC, as radiological recurrence can occur even in patients with normal cholestatic enzyme levels.

FRI-478

Outcome and predictors of major adverse cardiovascular events after liver transplantation: a single center experience

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Background and aims: Liver transplantation (LT) is the only life-saving treatment option for end-stage liver disease. However, major adverse cardiovascular events (MACE) are a leading cause of morbidity and mortality after LT, accounting for over 40% of early deaths (<30 days) after surgery. The present study aimed to assess the incidence, predictors and outcome of post-LT MACE.
Method: All consecutive adult patients who underwent LT from January 2018 to February 2023 in our Center were retrospectively evaluated. Each patient was represented only once in the cohort. MACE were defined as: congestive heart failure, acute coronary syndrome, arrhythmia, ischemic stroke, peripheral artery disease. Continuous variables were shown as median (IQR) while categorical variables were shown as percentages. Logistic regression was used to evaluate association between variables and outcomes.
Results: A total of 235 patients were included in the analysis. The median age was 58 years and 69% were male. The most common indications for LT were HCV (23%) and alcoholic cirrhosis (24%). Arterial hypertension, diabetes and obesity were present, respectively, in 29%, 26% and 14% of patients. During a mean follow up of 33 months (range 1–60), 36 (15%) LT recipients experienced a MACE. The early mortality rate (<30 days from OLT) for cardiovascular events was 33% (4/12). 20% of MACE occurred during LT or less than 48 hours after surgery, reaching 80.5% within 30 days from OLT and 86% at 1 year post-LT. The most frequent event was arrythmia (56%), followed by acute coronary syndrome (22%) and congestive heart failure (19%). Previous history of arrhythmia (OR = 7.86, 95% CI 1.98–33.3, p = 0.003) and obesity (OR = 2.55, 95% CI 1.03–5.96, p = 0.035) were significantly associated with MACE occurrence both at univariate and multivariate analysis. The concomitant presence of more than one cardiovascular risk factor (diabetes + hypertension + age >60 years) was way more frequent in MACE cohort compared to no-MACE cohort (16% vs 5%, p = 0.02).
Conclusion: Despite the accurate patient's selection pre-LT, 15% of patients developed an early post-LT MACE, being arrythmias the most frequent event. Previous history of arryhtmia and obesity were strongly associated with MACE.

FRI-479

AI-driven prediction of fibrosis progression in liver transplant recipients using a temporal deep learning framework

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Background and aims: Improvements in surgical techniques and perioperative care in liver transplant (LT) recipients have resulted in improved short-term survival. With increasing graft survival, older recipient age, and increasing proportion of patients with steatohepatitis being transplanted, LT recipients today are at increased risk of allograft fibrosis. Given the lack of clinical decision tools, we aimed to develop a machine learning (ML) tool to identify patients at highest risk of progressive fibrosis over time.
Method: We included all patients with index liver transplants performed at the Ajmera Transplant Centre from 1 Feb 1985 to 31 Dec 2023 who had subsequent paired fibrosis measurements by liver biopsy or transient elastography (TE). Due to the superior accuracy of TE findings at the extremes of cut-offs, we only included fibrosis stages F0 and F4 and excluded measurements in the intermediate range. Clinical demographic, anthropometric, and serial biochemistry data such as liver enzymes, bilirubin, and creatinine were extracted from the year preceding the fibrosis measurement. Fibrosis stage was classified semi-quantitatively based on biopsy report or TE. We utilized deep ML methods such as recurrent neural network (RNN), long short-term memory model (LSTM) and our proposed Temporal attenuation Gated Recurrent Unit (GRU) model to assess accuracy in prediction of rate of fibrosis progression/regression. Assessment of each method was conducted using mean squared error (MSE) and Pearson's r.
Results: 1318 patients had paired fibrosis measurements post-LT: 2408 and 337 were from liver biopsies and TE respectively. Using longitudinal data from one year before fibrosis measurements, we compared our proposed deep learning-based Temporal attenuation GRU method with other temporal ML techniques to predict fibrosis progression/regression stage. The RNN and LSTM model had MSE 0.87 ± 0.03 and 0.83 ± 0.05, and Pearson's $r = 0.74 \pm 0.01$ and 0.81 ± 0.01 respectively. Using the Temporal attenuation GRU method, the MSE improved to 0.61 ± 0.03, $r = 0.84 \pm 0.01$. When a weighted MSE loss function was applied to allow more importance in the longitudinal data points closest to the fibrosis measurement, the temporal attenuation GRU MSE improved to 0.28 ± 0.01, $r = 0.92 \pm 0.01$. The top five variables identified as being associated with rate of progression were current fibrosis stage, time from LT, donor gender, pre-LT diabetes and leukocyte count.
Conclusion: Advanced ML techniques today can aid in non-invasive prediction of allograft fibrosis progression reliably. This can help select patients for whom biopsies are required for assessment of fibrosis progression/regression. While TE is also useful, it is not easily accessible in some. Our study demonstrates that using longitudinal clinical variables used in routine assessment can reliably predict post LT allograft fibrosis progression.

FRI-480-YI

Changes in sarcopenia and adipose tissue alterations do not predict post-transplant outcomes in patients with cirrhosis and hepatocellular carcinoma undergoing liver transplantation

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Background and aims: Sarcopenia and adipose tissue alterations may predict liver decompensation and reduced survival during the waiting period and after liver transplant (LT). However, the evolution of body composition from pre- to post-transplant and its association with patient outcomes are poorly understood. Therefore, we aimed to assess the evolution of sarcopenia and adipose tissue alterations from pre- to post-LT and their potential impact on patient outcomes.
Method: Adult patients with hepatocellular carcinoma (HCC) who underwent LT at Padua University Hospital between January 2015 and March 2022 were retrospectively included. Body composition was assessed via CT scans within six months pre-LT and at 3-, 6-, and 12-months post-LT. The Skeletal Muscle Index (SMI), Visceral Adipose Tissue Index (VATI), and Subcutaneous Adipose Tissue Index (SATI) were calculated. Uni and multivariate Cox regression analysis was used to evaluate the association with clinical outcomes.

Results: 164 patients (85.3% male, median age 62 years) were included. HCV infection was the most common aetiology of liver disease, followed by alcohol-related liver disease (20%); indication to LT was HCC in 69% of patients. Prevalence of sarcopenia was 45% (median SMI of 50 cm^2/m^2; IQR 56.43–45.03), while VAT and SAT alterations were observed in 22.4% and 49.4% of patients, respectively. Sarcopenia prevalence slightly increased from 45.1% pre-LT to 56.1% at 12 months. VAT alterations increased consistently, from 40.6% pre-LT to 60% at 12 months post-LT, whereas SAT alterations remained largely stable. Pre-transplant body composition alterations were not associated with decreased survival at 1, 3, or 5 years (sarcopenia: p = 0.21; VATI alteration: p = 0.20; SATI alteration: p = 0.28). No association was found between changes in body composition and survival (sarcopenia: p = 0.43; VATI alteration: p = 0.50; SATI alteration: p = 0.43). In multivariate analysis, COPD (OR: 0.9; 95% CI 0.7–9.1; p = 0.042) and CKD (OR: 1.7; 95% CI 1.8–17.9; p = 0.003) were the only independent predictors of survival. In patients with HCC, no association was found between body mass composition or its evolution and the risk of HCC recurrence.
Conclusion: Sarcopenia and alterations of adipose tissue are highly prevalent in patients with cirrhosis and HCC undergoing transplantation; however, they are not linked to post-LT outcomes. Significant body composition changes occur within one-year post-LT but are not associated with post-transplant complications or survival. These findings would not support the assessment of body composition for LT evaluation nor early post-LT risk stratification in compensated cirrhosis with HCC.

FRI-481

Feasibility and effectiveness of liver transplantation following immunotherapy in patients with hepatocellular carcinoma

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Background and aims: Immunotherapy (IT) is an attractive strategy for downstaging and bridging hepatocellular carcinoma (HCC) to liver transplantation (LT). This multicenter study reports the feasibility and effectiveness of LT post-IT in HCC patients.
Method: The study cohort was identified in ten French liver transplant centers in the GRef2 research network. All patients were treated with IT between February 2019 and June 2023 and had their livers transplanted between May 2020 and March 2024. Clinical, biological, and radiological data were collected for each patient at the beginning of IT, the end of IT, and before LT. The primary endpoint was the tolerance and effectiveness of LT.
Results: Twenty-one patients [17 men/4 females; median age 62 years (57–64)] who underwent LT for HCC after IT were included. Fourteen/21 patients (66.7%) were BCLC-B at baseline, followed by 4 BCLC-A (19%), 2 BCLC-0 (9.5%), and 1 BCLC-C (4.8%). HCC was multinodular in 17/21 (81%) cases, with a median size of the largest nodule of 36 mm (21–60). Thirteen patients had an AFP score >2 (downstaging group) and 8 of ≤2 (bridging group). Patients in the downstaging group were beyond Milan criteria, and 3 in the bridging group (p = 0.006). Sixteen patients (76.2%) received Atezolizumab/Bevacizumab, and five (23.8%) other immune checkpoint inhibitors (ICs) alone or in combination with tyrosine kinase inhibitors during 8.5 cycles (4.7–14). At the end of IT, four patients had a CR (19%), eight PR (38.1%), six SD (28.6%), and three PD (14.3%) according to the mRECIST criteria. Most patients shifted to an early/intermediate BCLC stage (p = 0.001) and reached Milan criteria (57.1%, p = 0.023). Nineteen patients (90.5%) achieved an AFP score of ≤2, while 2 (9.5%) remained >2 (p = 0.003). The median interval between the last IT cycle and LT was 5.1 (2.7–9.3) months. All patients except 3 received standard immunosuppressive treatment (tacrolimus, mycophenolate mofetil, corticosteroids). Two cases (10%) of rejection occurred, resolved after increasing immunosuppression. Early serious adverse events occurred in 6 patients (28.5%), four of which were fatal (23.8%) and in the first 3 months post-LT. Four patients (19%) had late complications, and five (27%) died. Factors associated with lower overall survival were the onset of early complications (p = 0.00026), Child-Pugh B (p = 0.014), no treatment before ICIs (p = 0.012), and less than five cycles of IT (p = 0.037). Only one patient (5.2%) had an HCC recurrence post-LT. On explant pathology, 15 patients (71.4%) had viable tumors, and necrosis ≥50% was detected in 9 cases (42.8%). According to the R3-AFP score, 5 patients (27.8%) were at very low, 3 at low (33.3%), and 10 at high (47.6%) recurrence risk.
Conclusion: LT following IT is feasible in selected patients with HCC and has an acceptable risk of rejection. However, the high immediate mortality observed requires further exploration in prospective studies.

FRI-482

Coronary atherosclerosis progression in patients with cirrhosis: effect of liver transplantation and association with early post-LT kidney dysfunction

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Background and aims: Cardiovascular (CV) diseases are the second leading cause of long-term mortality in liver transplant (LT) recipients. Coronary artery calcium score (CACS) in computed tomography (CT) evaluates atherosclerotic burden and predicts CV events and mortality, and progression of CACS further identifies a subgroup of patients at higher risk of CV morbidity and mortality in the general population. Data on the progression of CACS in LT patients or patients with cirrhosis are scarce.
Method: Cohort study that included LT recipients and patients with cirrhosis that underwent LT evaluation but were eventually discarded from LT (non-LT). All subjects had a baseline (at LT evaluation) CACS ($CACS_{bl}$) and underwent a follow-up CACS ($CACS_{fu}$) 5 years thereafter. Progression of CACS was defined using the annualized difference between CACS and compared between the groups. In LT recipients, CV risk factors, renal function and immunosuppression including cumulative exposure to tacrolimus (CET) and steroids, all evaluated 12 months after LT, were studied as potential predictors of CACS progression by linear regression.

Results: Seventy-five LT recipients and 20 non-LT patients were included. $CACS_{fu}$ was performed 5.2 (IQR 4.7–6.2) years after $CACS_{bl}$. At baseline, there were no significant differences between the groups regarding the etiology of liver disease or CV risk factors. $CACS_{bl}$ and $CACS_{fu}$ were, respectively, 42 (0.5–333) and 208 (28–841) in LT recipients and 107 (1–290) and 371 (45–570) in non-LT (p = 0.801 for $CACS_{bl}$ and p = 0.887 for $CACS_{fu}$). Annualized progression of CACS was 23/year (2–86) in LT recipients and 30/year (4–57) in non-LT (p = 0.833). Twelve months after LT, LDL-cholesterol was 109 (88–121) mg/dL, eGFR was 61 (47–75) ml/min, and 87% and 73% of LT recipients had, respectively, HbA1c and blood pressure within range. Twelve-months CET corresponded to high exposure to tacrolimus only in 20% of patients. Age, $CACS_{bl}$, diabetes and eGFR 12 months after LT were significantly associated with the annualized progression of CACS on univariate analysis, while only $CACS_{bl}$ and 12 months eGFR persisted as independent predictive factors in multivariate analysis.
Conclusion: Over a 5 years period, CACS progression was not faster in a cohort of LT recipients with optimized control of CV risk factors and standard/low exposure to tacrolimus than in patients with cirrhosis. Pre-LT CACS and kidney dysfunction at 12 months after LT predict progression of CACS in LT recipients. Interventions aiming at preserving kidney function after LT may slow down the progression of atherosclerosis in this population.

FRI-483

Adherence to the mediterranean diet and physical activity levels among liver transplant recipients in Greece: relationship to the metabolic syndrome

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Background and aims: Liver transplant (LT) recipients have an increased cardiovascular risk due –among other factors– to the presence of Metabolic Syndrome (MS) in approximately half of them. One of the first-line therapeutic interventions for the MS is the adoption of a healthy dietary pattern, such as the Mediterranean Diet (MD), which has been widely recognized for its beneficial effects on metabolic profile, overall morbidity, and mortality. The aim of the present study is to evaluate the degree of adherence to the MD and the physical activity (PA) among LT recipients in Greece and to investigate its potential association with the development of MS components.
Method: The study comprises 135 clinically stable patients who underwent LT at least one year prior to their evaluation and are being followed at the outpatient clinic of our hospital. Adherence to the MD was assessed using the MEDAS questionnaire, which provides a scoring range from 0 to 14, with higher scores indicating greater compliance. Physical activity (PA) was evaluated through the IPAQ-short form questionnaire, categorizing activity levels into low, moderate, or high. Data analysis and dependency testing were performed using linear and logistic regression models, both univariate and multivariate.
Results: 93 of the participants were males, (69%), with a median age of 61 years (IQR 18) and a median time from transplantation of 11 years (IQR 10.5). The most frequent underlying etiology for LT was viral hepatitis (46%), with 20% of cases involving coexistent hepatocellular carcinoma, ethanol abuse, or a combination of these. Regarding viral hepatitis, hepatitis B virus was present in 53 of 61 patients (87%). Concerning PA levels, the majority of participants demonstrated moderate activity (82 patients, 61%), while only 1 exhibited high activity levels. The degree of adherence to the MD was moderate (median score: 8, IQR 2). Overall, 64% of the participants presented at least one new (de novo) MS parameter after LT. Specifically, 45 patients developed Arterial Hypertension, 58 Dyslipidemia, 38 Diabetes Mellitus, and 5 Coronary Artery Disease (3.7%). Older age was associated with higher MD compliance in the multivariate linear regression model. No statistically significant association was identified between the degree of MD adherence and the newly developed MS components.
Conclusion: Adherence to the MD and PA levels among LT recipients are moderate, potentially leading to beneficial effects on metabolic profile, and thus overall mortality. The lack of association between MD compliance and the development of MS components suggests the involvement of additional contributing factors, emphasizing the necessity for more comprehensive investigations in LT recipients.

FRI-484

Machine learning in predicting 3-month mortality for liver transplant candidates with HCC: a paradigm shift

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Background and aims: Predicting waitlist mortality in liver transplant (LT) candidates with hepatocellular carcinoma (HCC) is both critical and challenging. Traditional scores, like MELD scores, assess liver disease but ignore tumor risks, while HCC-specific models such as AFP model focus on tumors but overlook liver failure. This creates an unmet clinical need for an approach that evaluates both risks to optimize prioritization for transplantation. We address this gap using machine learning (ML) to predict 3-month mortality by combining liver dysfunction and tumor progression features.
Method: We used the OPTN/UNOS data registry to compare ML models with traditional scores to predict 3-month mortality in LT candidates with HCC. Inclusion criteria were adult patients listed for LT who (i) either died or were delisted due to clinical deterioration within 3 months, or (ii) survived beyond 3 months. Patients listed for multi-organ transplants were excluded. The cohort included 25 clinical, laboratory, and disease-related variables, with an additional 6 dynamic variables derived from changes in laboratory values, leading to 31 variables. Logistic Regression and Random Forest (RF) models were assessed using both feature sets. To address class imbalance, a down-sampling strategy was applied, and performance was assessed using 3-fold cross-validation.
Results: 11,641 patients were included, of whom 448 died or were removed from the waitlist within 3 months (mean: age 60, raw MELD 22) and 11,193 surviving on the waiting list beyond 3 months (mean: age 60, raw MELD 14). The AFP model performed the worst (AUC: 0.601). ALBI outperformed the Child-Pugh score (AUC: 0.710 vs. 0.699), while MELD scores demonstrated superior performance: MELD 3.0 achieved the highest AUC (0.752) compared to MELD (0.736) and MELD-Na (0.745). However, all traditional scores showed imbalance between sensitivity and specificity. ML models using 25

variables outperformed traditional scores, with RF achieving an AUC of 0.800. Incorporating 31 dynamic variables further improved performance, with RF achieving an AUC of 0.825 and balanced sensitivity (76.06%) and specificity (76.21%). Gini importance analysis identified new key predictors beyond MELD components, including largest tumor size, alpha-fetoprotein dynamics, BMI, and ascites severity.
Conclusion: RF outperformed traditional scores in predicting 3-month waitlist mortality for LT candidates with HCC, by integrating both liver dysfunction and tumor progression risks. This approach, pending validation, could enhance organ allocation.

FRI-485
Development of an explainable machine learning model for predicting waitlist mortality in liver transplant candidates
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Background and aims: Predicting waitlist mortality for liver transplant (LT) candidates remains a critical challenge due to the complexity of patient profiles and competing risks. Traditional models such as MELD, MELD-Na, and MELD 3.0, while effective in assessing liver dysfunction, lack the precision needed to capture dynamic, patient-specific factors. This study aims to evaluate the performance of an explainable ML model over traditional Model for End-Stage Liver Disease (MELD) scores in predicting 3-month mortality among adult LT candidates. By integrating Light Gradient Boosting Machine (LightGBM) with SHapley Additive exPlanations (SHAP), we sought to identify and analyze the most significant predictive variables, thereby proposing new factors for enhancing liver transplant allocation systems.
Method: We conducted a retrospective cohort analysis using data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing registry, covering patients listed for liver transplantation (LT) from February 27, 2002, to September 30, 2023. Employing LightGBM, we compared its performance against MELD, MELD-Na and MELD 3.0 scores in predicting waitlist mortality. SHAP was used to improve model explainability and to identify critical predictive factors.
Results: Among 94,891 patients, 11,466 died or were delisted within 3 months (mean age 55, raw MELD 31) and 83,425 surviving on the waiting list (mean age 53, raw MELD 16). MELD, MELD-Na and MELD 3.0 achieved AUCs of 0.881 (95% CI: [0.880, 0.882]), 0.888 (95% CI: [0.887, 0.889]) and 0.884 (95% CI: [0.882, 0.885]), respectively. LightGBM demonstrated superior predictive performance over MELD scores, with an AUC of 0.934 (95% CI: [0.933, 0.935]). This corresponded to a sensitivity of 85.51% (95% CI: [85.23, 85.79]) and specificity of 85.77% (95% CI: [85.44, 86.09]). SHAP analysis revealed new key predictors of mortality, beyond traditional MELD components, including patient's functional state, age at registration, degree of ascites, and bilirubin changes over time.
Conclusion: Our explainable machine learning model outperforms traditional MELD-based scores in predicting 3-month waitlist mortality for liver transplant candidates. By integrating dynamic and static factors such as bilirubin changes, functional state, and degree of ascites, this model provides a comprehensive and personalized risk assessment. It represents a promising tool to refine organ allocation strategies and improve patient outcomes, pending prospective validation.

FRI-486
NT-proBNP predicts the development of acute-on-chronic liver failure and mortality in patients with cirrhosis listed for liver transplantation
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Background and aims: Acute-on-chronic liver failure (ACLF) is a severe complication of cirrhosis characterized by high mortality and limited access to liver transplantation (LT). NT-proBNP has been proposed as a biomarker, but its ability to predict ACLF development and waiting list (WL) mortality has not been studied.
Method: This observational study included 277 patients with cirrhosis on the WL between 2014 and 2020. Clinical data, such as sarcopenia, cystatin C (CysC), and NT-proBNP were collected at listing. A competing risk analysis was performed, considering LT and death as risks for ACLF development and LT as a competing risk for WL mortality. The NT-proBNP threshold was set at ≥125 pg/mL based on prior studies.
Results: Over a median follow-up of 9 months, 89 (32%) patients developed ACLF, 58 (30.8%) underwent LT without ACLF, and 10 (3.6%) died or were delisted. Patients with elevated NT-proBNP levels exhibited worse liver function (higher MELD-Na and Child-Pugh scores) and increased sarcopenia. NT-proBNP showed a modest correlation with kidney markers, such as creatinine and CysC (r^2 = 0.47 and 0.45; $p < 0.001$), as well as with MELD-Na ($r^2 = 0.58$, $p < 0.001$) and CLIF-C AD ($r^2 = 0.52$, $p < 0.001$). In contrast, no correlation was observed with systemic inflammatory markers, such as WBC count. Higher NT-proBNP levels were associated with ACLF [81 (42–163) pg/mL vs. 300 (141–600) pg/mL; $p < 0.001$] and death on the WL [108.5 pg/mL (49–204) vs. 300 pg/mL (142–600), $p < 0.001$]. NT-proBNP levels also increased with ACLF severity and organ failure. NT-proBNP ≥125 pg/mL was associated with higher ACLF incidence at 3 and 12 months (28.5% and 49.2% vs. 3.6% and 6.1%, respectively; $p < 0.001$) and higher 1-year mortality (22.3% vs. 4%; $p < 0.001$). Multivariate analysis revealed that NT-proBNP ≥125 pg/mL independently predicted ACLF development (sHR 4.00; 95% CI: 1.76–9.10; $p = 0.001$), after adjusting for clinically relevant variables such as MELD-Na (sHR 1.16; 95% CI: 1.11–1.21; $p < 0.001$) and CysC (sHR 2.72; 95% CI: 1.43–5.14; $p = 0.002$). Similarly, NT-proBNP ≥125 pg/mL predicted WL mortality (sHR 3.89; 95% CI: 1.28–11.79; $p = 0.016$), adjusted for MELD-Na (sHR 1.00; 95% CI: 0.94–1.05; $p = 0.992$) and CysC (sHR 5.89; 95% CI: 2.17–15.99; $p < 0.001$). The combination of NT-proBNP with MELD-Na and CysC demonstrated a predictive accuracy for 3-month mortality on the WL, with an AUC of 0.82 (95% CI: 0.73–0.91, $p = 0.045$).
Conclusion: NT-proBNP level ≥125 pg/mL is an independent predictor of ACLF development and WL mortality. Its use may facilitate preventive interventions and improve WL prioritization.

FRI-487

Treatment of grafts not meeting criteria for transplantation with nor-ursodeoxycholic acid during normothermic machine perfusion reduces apoptosis and biliary injury markers

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Background and aims: Normothermic machine perfusion (NMP) allows for viability assessment in livers at risk for higher post-operative morbidity and provides a platform for ex vivo therapeutic intervention. Nor-ursodeoxycholic acid (norUDCA) is an agent with anti-inflammatory and antifibrotic properties that was used in phase II trials in patients with primary sclerosing cholangitis and metabolic dysfunction-associated steatohepatitis. We aimed to investigate the effects of norUDCA during NMP on livers that did not meet the criteria for transplantation during viability assessment.
Method: We evaluated apoptosis markers in perfusate and bile composition in samples of 18 normothermic perfused grafts that did not meet criteria for transplantation. Nine livers received treatment of 1500 mg of norUDCA after two hours, perfusion duration was 12 hours. Apoptosis markers (active caspase-3, Bcl-2, cleaved PARP, Cytochrome c, p53) were measured on the Luminex platform. To account for donor heterogeneity, the relative dynamic of apoptosis markers was determined for individual grafts after application of norUDCA. Blood gas analysis of perfusate and bile, as well as additional measurements including alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) were performed every two hours.
Results: NorUDCA treatment after two hours lead to a significant reduction of apoptosis markers cleaved PARP (6 h: p = 0.0142) and p53 (6 h: p = 0.0106; 12 h p = 0.0400), additionally to a significant reduction in delta 2 h–6 h values compared to control livers: active caspase-3 (p = 0.0188), Bcl-2 (p = 0.0400), cleaved PARP (p = 0.0244) and Cytochrome c (p = 0.0304). Of note is the overall dynamic reduction of apoptosis markers in the treatment group, whereas the control group increased or remained constant. Further, treated grafts presented with improved biliary viability and reduced biliary injury markers, evident in higher bile bicarbonate concentration (3 h: 0.026; 4 h: p = 0.016; 5 h p = 0.030), as well as lower bile transaminases AST (8 h: p = 0.017) and ALT (8 h: p = 0.004; 12 h: p = 0.026).
Conclusion: The present data suggests an anti-apoptotic effect as well as an improvement in bile compostition after treatment of extended criteria donor grafts with norUDCA during NMP. NorUDCA might be able to ameliorate the detrimental effects of bile toxicity on the ischemia-injured biliary tree. Therefore, therapeutic application of norUDCA prior to transplantation seems promising, especially for liver grafts at risk for biliary complications.

FRI-488

Concomitant sarcopenia and myosteatosis in patients with cirrhosis is associated with longer recovery and mortality after liver transplantation

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Background and aims: Skeletal muscle abnormalities, such as sarcopenia (low muscle mass) and myosteatosis (pathological fat accumulation in muscle) are well-established predictors of worse outcomes in patients with cirrhosis. Still, their impact on the post-liver transplantation (LT) course is unknown. We aimed to assess the association between sarcopenia and myosteatosis and recovery time and negative clinical outcomes in patients who underwent LT.
Method: In this cohort study, we evaluated patients with cirrhosis who underwent LT and had computed tomography (CT) imaging performed within three months before LT. Body composition analysis was assessed using Slice-O-Matic software (V4.2; Tomovision) to measure the skeletal muscle index (SMI) in cm^2/m^2 and muscle radiodensity in Hounsfield Units (HU). Sarcopenia was defined as SMI <39 cm^2/m^2 in females and <50 cm^2/m^2 in males. Myosteatosis was defined as mean skeletal muscle radiodensity <28 HU for females and <33 HU in males. Cox regression models were built to estimate and measure associations between skeletal muscle abnormalities and post-LT clinical outcomes.
Results: We evaluated 302 patients, 67.9% (n = 205) were males with a mean age at LT of 51.6 ± 11.6 years, and a MELD score at LT of 21.2 ± 9.7. The main indications for LT were alcohol-associated liver disease (38.4%, n = 116), hepatitis C (28.1%, n = 85), autoimmune liver diseases (19.2%, n = 58), and metabolically-associated steatotic liver disease (7.6%, n = 23). Hepatocellular carcinoma was present in 27.2% (n = 82) patients. Sarcopenia was identified in 51.3% (n = 155) and myosteatosis in 41.1% (n = 124). Concomitant sarcopenia-myosteatosis were present in 26.2% (n = 79). After LT, patients with concurrent sarcopenia and myosteatosis tended to have longer post-LT ICU median length of stay (LOS) (4 [IQR 8] vs 3 [IQR 5] days; p = 0.082) and substantially longer post-LT hospital LOS (28 [IQR 33] vs 20 [IQR 21] days; p = 0.017). Patients with concurrent sarcopenia-myosteatosis had worse 1- and 5-year post-LT survival (83.5% and 68.3% vs. 89.7% and 83.0%, log-rank p = 0.005). The 5-year post-LT survival was only 56.9% in patients with concomitant sarcopenia-myosteatosis and older than 60 years. In addition, concomitant sarcopenia-myosteatosis was associated with higher post-LT mortality (HR 1.86, 95%CI 1.19–2.87, p = 0.006) and was more pronounced in those older than 60 years (HR 2.61, 95%CI 1.06–6.43, p = 0.038). The association between concurrent sarcopenia-myosteatosis and overall mortality remained significant after adjusting for age, sex and MELD score at LT (HR 4.82, 95%CI 1.10–21.09, p = 0.037).
Conclusion: Concurrent sarcopenia-myosteatosis is present in over a quarter of cirrhotic patients who received LT and is linked to prolonged recovery times and reduced post-LT survival, particularly among older patients. Integrating this objective assessment into clinical practice could serve as a valuable criterion for evaluating the futility of LT.

FRI-489-YI

Coronary angiography in the preoperative work-up for liver transplantation (LT): a multicenter italian cohort study

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Background and aims: Evaluating coronary artery disease (CAD) is critical in liver transplant (LT) candidates due to increasing age and comorbidities. Coronary angiography (CATH) is the gold standard for CAD diagnosis but is not feasible for routine screening due to cost and invasiveness. Data on CATH in European LT cohorts are limited. We aimed to assess the role of CATH in a multicenter pre-LT cohort.
Method: 18/21 adult LT centers in our Country participated, enrolling adult cirrhotic patients (pts) who underwent CATH during cardiac work-up between 2018–2022. We evaluated: indications for CATH, rate of significant coronary stenosis (SCS: ≥50% major vessels or ≥70% moderate branches), post-LT major cardiovascular events (MACEs) and survival.
Results: Between 2018–2022, the 18 centers performed 5336 LT from deceased donors. 305 pts underwent pre-LT CATH and constituted our study cohort. Median age 62 years (y); 85% male; BMI 27 kg/m²; 68% smokers; 57% diabetes; 55% arterial hypertension; 13% CAD history, 9% peripheral artery disease, 26% CAD family history. Liver disease etiology was 34% viral, 27% alcohol, 15% MASLD, 12% alcohol+MASLD, MELD score 13 (IQR 9–18), 61% HCC. Indications for CATH were: 31% positive coronary CT (CCTA), 25% ≥3 cardiovascular risk factors, 12% cardiac consultation, 11% positive myocardial scintigraphy, 9% positive stress echocardiography (Echo), 8% CAD history, 4% resting echocardiographic abnormalities. CATH complications occurred in 16 pts (5%) (6 anaemia, 4 pseudoaneurysms, 1 acute kidney injury, 1 allergic reaction, 2 wound bleeds, 1 arrhythmia, 1 coronary spasm). SCS was detected in 120 pts (39%), 65 (54%) underwent revascularization. At univariate analysis, SCS was associated with male (OR = 2.02, CI: 1.00–4.09, p = 0.049) and smoking history (OR: 1.92, CI: 1.07–3.47, p = 0.029). At multivariable analysis, active smoking (OR 2.02, CI: 1.07–3.88, p = 0.037) and MASLD (OR 1.89, CI: 1.02–3.55, p = 0.044) were independent predictors of SCS. Positive predictive value (PPV) of CCTA and Echo was 57% and 35%, respectively. After CATH, 46/305 pts were excluded from LT list, 259/305 pts placed on LT waiting list. By June 2023, 230 underwent LT [49 (21%) after pre-LT revascularization]. 28 (12%) MACEs occurred within 2 y after LT (12 heart failure, 9 ischemic, 7arrhythmia), with 3 related deaths. Among 9 ischemic events, all had pre-LT SCS, and 67% (6/9) underwent pre-LT revascularization. 1- and 2-y cumulative survival rates were 92% and 90%, respectively.
Conclusion: Cardiac work-up varies across our 18 LT centers. CCTA showed a PPV of 57%. 39% of pts selected for CATH had SCS, 54% requiring revascularization. Smoking and MASLD were independent predictors of SCS. Post-LT MACEs occurred in 12% of selected patients, with cardiac-related mortality rate of 9%. National efforts should be made to share a unified cardiac work-up protocol tailored for our LT recipients.

FRI-490

Reintegration into working life for liver transplant recipients: cross-disciplinary evaluation of risk factors for unemployment

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Background and aims: The return to work of liver transplant (LT) recipients is essential, yet specific guidelines for this process are lacking. The BRIC-2022-ID25 project investigates the impact of liver disease and transplantation on work ability by examining correlations among clinical, social, and occupational factors before and after LT, with the aim of enhancing professional reintegration.
Method: In collaboration with the occupational medicine department, we enrolled patients who underwent LT in our Centre between 2018 and 2023, aged 18 to 68 years, who were not retired prior to LT. Participants completed the WHODAS 2.0 (World Health Organization Disability Assessment Schedule) and Work Ability Index (WAI) questionnaires, and results were merged with clinical and occupational data from both pre-LT and post-LT follow-ups. We performed interim analyses on patients interviewed from January to June 2024.
Results: A total of 140 recipients participated; 76% had liver cirrhosis (49% with hepatocellular carcinoma - HCC), and 19% were diagnosed with hepatic/hepato-renal polycystosis. The mean age was 55 years (range 24–69), with 64% males and an average interval of 42 months between LT and the interview. Notably, 50% had a middle-school education. Post-LT, 49% were unemployed, with 62% indicating that health issues hindered their job search. Significant correlations were identified between unemployment and factors such as pre-LT alcohol abuse (p = 0.005), age over 60 at LT (p = 0.02), having a caregiver outside the household (p = 0.004), working before LT (p < 0.001) and a greater number of post-LT hospitalizations (p = 0.05). A low self-assessment of work capacity (WAS) correlated with being over 50 years old (p = 0.02), lower education levels (p = 0.04), pre-OLT HCC (p = 0.02), and a MELD score <14 at LT (p = 0.04). Total WAI score was lower in non-Italian patients (p = 0.001). Poorer disability scores (WHODAS) were associated with female gender (p = 0.02), having a caregiver outside the family (p = 0.04), and non-Italian nationality (p = 0.002).
Conclusion: Interim analyses reveal a 49% of unemployment rates following LT, with health status affecting 62% of cases. Factors such as caregiving responsibilities, education level, nationality, and gender, along with age, pre-LT HCC, and complications, significantly impact work ability. Enhanced efforts are needed to ensure equitable employment opportunities for transplant recipients.

FRI-491

Outcomes of ABO-incompatible deceased donor liver transplantation in adults with acute liver failure: a study from a Costa Rican hospital

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Background and aims: The acceptance of ABO-incompatible organs (ABOi) has increased with the development of desensitization strategies, which have shown complication rates similar to those of ABO-compatible (ABOc) deceased donor liver transplantation (DDLT). This approach is particularly relevant in countries with low organ donation rates and limited resources, such as in Latin America (LATAM), although no outcome reports from the region are currently available. The aim of this study is to analyze the medical outcomes of ABOi DDLT at a Costa Rican hospital.
Method: A retrospective, comparative analysis was conducted on the clinical characteristics and outcomes of a cohort of patients >12 years with acute liver failure who were received ABOi or ABOc DDLT at the Liver Unit of Calderon Guardia Hospital from 2009 to 2024.
Results: 8 DDLT (3 ABOi and 5 ABOc) were performed for Wilson disease (n = 6) or drug induced liver injury (n = 2), with a median age of 22.5 years. 87.5% of the recipients were female. The median MELD-Na score was 37 (range: 34–40) in the ABOi group and 27 (range: 21–40) in the ABOc group (p = 0.11). ABOi pre-LT desensitization strategies consisted of plasmapheresis (PP) (n = 3) and rituximab (n = 2); and immunosuppression (IS) on basiliximab (n = 3), tacrolimus (n = 3), mycophenolate (n = 2) and steroids (n = 3). Quantification of isoagglutinin was performed in 2 ABOi cases (pre-LT titers 1:64 and 1:16), and post-LT titers peaking at 1:128 within 3 weeks in both cases, no PP was performed to lower these titers. The second patient had histological evidence of antibody mediated rejection (AMR) within 10 days post LT, leading to PP and immunoglobulin treatment, reducing titers to <1:16. In the 1-year follow up, the patient had 2 more episodes of AMR resulting in adjustment of IS. The incidence of cytomegalovirus and bacterial pneumonia was similar among groups, while fungal infections arose only in two ABOc DDLT cases, both with Aspergillosis, one of which also had Candidemia. Anastomotic biliary stenosis occurred in 3 ABOi and 2 ABOc patients, with earlier onset in ABOi DDLT (median time 4 vs 20 months, respectively). Protocolized endoscopic management was performed in all cases; however, stenosis complete resolution at 1 year was documented in only 2 patients, one from each group. No vascular complications occurred in the ABOi group. Regarding patient and graft survival rate, the 1-year survival rate for the 8 patients (3 ABOi, 5 ABOc) was 100%. At 3 years, all 5 transplanted patients (1 ABOi, 4 ABOc) had a 100% survival rates. At 5 years of the 4 transplanted patients (1 ABOi, 3 ABOc) the survival rate for ABOi was 100% vs 66.6% for ABOc.
Conclusion: Despite the use of heterogeneous desensitization strategies, ABOi DDLT was associated with 1-year patient and graft survival comparable to ABOc DDLT, with no significant differences in complication rates. These findings emphasize the importance of protocolized therapeutic approaches for ABOi DDLT, especially in regions with low donation rates and restricted resources, such as LATAM.

FRI-492

Torque Teno virus as a biomarker of immune status and attenuated immune response to vaccination in liver transplant recipients

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Background and aims: Liver transplant recipients (LTRs) are at higher risk for SARS-CoV-2 infections and often exhibit suboptimal responses to vaccination. Our aim was to characterize the immune status of LTRs, focusing on Torque Teno Virus (TTV) as a biomarker, and to evaluate humoral and cellular responses after the primary vaccination series (1st and 2nd doses) and the booster dose (3rd dose) against SARS-CoV-2, compared to healthy controls (HC).
Method: This multicenter, prospective study included 122 LTRs from August 2021 to March 2022. Humoral response was assessed by anti-Spike (anti-S) and neutralizing antibodies (anti-N) against SARS-CoV-2 variants (Wuhan, Delta, and Omicron). Cellular response was evaluated using an ELISPOT assay to measure IFN-γ-producing cells after stimulation with SARS-CoV-2 Wuhan and Omicron peptides. Additionally, the frequency of T and B cell populations was analyzed, and TTV viral load was quantified by qPCR as a surrogate marker of immune status.
Results: Following both the primary vaccination series and booster dose, LTRs showed a lower proportion of anti-S positivity compared to HC (1st and 2nd doses: 57.4% vs. 81.5%, p = 0.019; 3rd dose: 75% vs. 100%, p = 0.003). Anti-S levels were significantly lower in LTRs compared to HC after the 1st and 2nd doses (62.60 IU/mL vs. 619.2 IU/mL, p < 0.001), and the booster dose (406.6 IU/mL vs. 1350 IU/mL, p = 0.007). Similarly, anti-N levels were markedly lower in LTRs. Cellular responses, measured by IFN-γ-producing cells, were diminished in LTRs after the 3rd dose (Wuhan: 29.2% vs. 83.3%, p = 0.017; Omicron: 39.6% vs. 83.3%, p = 0.078). LTRs exhibited an altered CD4/CD8 ratio (2 vs. 2.8, p = 0.02), a lower percentage of naïve CD4+ (59.40% vs. 71.05%, p = 0.003) and CD8+ (20.75% vs. 42.45%, p = 0.01) cells, but a higher proportion of CD4+ and CD8+ effector memory (16% vs. 4.96%, p < 0.001; 12.40% vs. 9.52%, p = 0.228) and terminal effector cells (2.09% vs. 0.66%, p = 0.01; 46.65% vs. 23.25%, p = 0.002). TTV viral load (log10 copies/mL) was higher in LTRs compared to HC (5.45 vs. 4.10, p < 0.001), in non-responders after the primary vaccination series (5.94 vs. 4.90, p < 0.001), and after the booster dose (6.26 vs. 5.30, p = 0.005). Multivariate analysis identified the use of mycophenolate [OR: 0.16 (0.03–0.70), p = 0.022] and TTV [OR: 0.17 (0.05–0.43), p = 0.001] as independent predictors of humoral response to the 3rd dose in LTRs.
Conclusion: LTRs exhibit significantly reduced humoral and cellular responses to SARS-CoV-2 vaccination. Our findings highlight an immunosenescent state in LTRs, with a diminished ability to effectively respond to novel antigens. Emerging biomarkers, such as TTV, could provide valuable insights into the immune status of LTRs and support the development of individualized vaccination strategies.

FRI-493

Conversion from standard-release to prolonged-release tacrolimus mitigates calcineurin-induced nephrotoxicity in patients after liver transplantation

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Background and aims: Chronic calcineurin inhibitor (CNI)-induced nephrotoxicity is a major complication in the management of patients after liver transplantation (LT) since it is associated with an increased risk of both morbidity and mortality. While conventionally released tacrolimus (standard-release Tac) is mostly used in post-LT management, tacrolimus can further be administered with a modified galenic using MeltDose® technology (LCPT) leading to an extended drug release. In this context, the tacrolimus concentration-dose ratio (C/D ratio) is of particular value for investigating nephrotoxicity-related renal outcomes since an increased C/D ratio might prevent renal dysfunction by improved drug bioavailability. The aim of the study was to investigate the effects of switching from standard-release Tac to LCPT on the C/D ratio and renal function.
Method: This monocentric, retrospective observational study included adult LT recipients from the University Hospital Münster (August 2010–March 2022) who underwent at least 2 years of Tac-based therapy. Patients who were switched from standard-release Tac to LCPT formed the LCPT group (n = 63), while the control group (n = 107) continued to receive standard-release Tac. The day of the conversion was considered to be the baseline (t0). Clinical data were collected at three-month intervals over a total of 24 months. Statistical analysis included binary logistic regression to determine predictive factors for improvement of estimated glomerular filtration rate (eGFR).
Results: At t0, comparable median C/D ratios were observed in both groups (p = 0.553). After conversion, significantly higher median C/D ratios were observed on average in the LCPT group for both the first (p = 0.003) and second (p = 0.004) year of the study. At the same time, an increase in mean eGFR compared to t0 was found in the LCPT group over the entire study period, although this increase of 2.9 ml/min/1.73 m² was no longer significant 24 months after t0. In contrast, the control group showed a significant decrease in the mean eGFR compared to t0 at each measurement time point over the observation period; after 24 months, the mean decrease was −5.4 ml/min/1.73 m² (p < 0.001). In multivariable binary logistic regression, only eGFR at t0 (OR 0.985, 95%CI 0.972–0.997, p = 0.018) and use of LCPT (OR 3.334 95%CI 1.717–6.475) formulation were predictive factors of eGFR increase. Median serum bilirubin and GOT levels were all statistically significant lower in the LCPT group, while there were no significant differences for GPT and INR at all visits.
Conclusion: In comparison to standard-release Tac, LCPT appears to stabilize renal function in liver transplant recipients over a two-year period, potentially offering long-term nephroprotective benefits without compromising graft function.

FRI-494
Graft rejection and biliary complications affect liver stiffness measurements in the first year after liver transplantation

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Background and aims: Liver stiffness measurement (LSM) is an easy and non-invasive tool to assess graft function in the long-term management after liver transplantation (LT). The early period post-LT is characterized by well-known complications that could also affect LSM, however this relationship has not been established. The aim of this study is to evaluate the association between early post LT complications (≤12 months) and LSM changes.
Method: This single centre study retrospectively enrolled all consecutive patients undergoing LT between 2015 and 2023. Exclusion criteria were death within 6 months post-LT, re-LT and lack of LSM at 6 or 12 months (namely T1 and T2). LSM was performed at T1 and T2 by vibration-controlled transient elastography (Fibroscan, Echosens, Paris). We investigated the association between the occurrence of early post-LT complications and LSM >8 kPa, defining presumed graft damage. All graft rejection episodes were biopsy-proven. Chi-square and T-test were used to analyse categorical and continuous variables, respectively.
Results: 326 LT recipients were enrolled, median age 58 (18–72) years, 73% males. Liver diseases pre-LT were viral hepatitis (54%), Met-ALD (29%), immune-mediated (10%) and others (7%). 179 LT-recipients were transplanted for HCC (55%), 125 for decompensated cirrhosis (38%). The immunosuppressive regimen was CNI-based in all LT recipients. Median LSM was 6.6 (2.5–30.5) kPa at T1 and 6.1 (2.5–24.1) kPa at T2 (p = 0.02). LSM was > 8 kPa in 87 patients (27%) at T1 and 65 patients (20%) at T2. Graft rejection was reported in 22% of LT recipients at T1 and 3% at T2, biliary complications in 17% at T1 and 9% at T2, vascular complications in 12% at T1 and 1% at T2. CMV reactivation occurred exclusively within the first 6 months post-LT (27%). Arterial hypertension (AH) was the most frequent comorbidity (67%), followed by steroid-induced diabetes (32%) and chronic kidney disease (CKD; > grade 3; 15%), both at T1 and T2. By univariate analysis, among all early complications/comorbidities analysed (biliary, graft rejection, vascular, CMV reactivation, steroid-induced diabetes, AH and CKD) only graft rejection was significantly associated with LSM > 8 kPa at T1 (37% in LSM > 8 *vs* 17% in LSM ≤8, p < 0.01), whereas biliary complication (15% in LSM > 8 *vs* 7% in LSM ≤8, p = 0.03) and CKD (25% LSM > 8 *vs* 13% in LSM ≤8, p = 0.02) were significant at T2.
Conclusion: Our results demonstrate that LSM increase observed in the first 6 months post-LT is mostly associated with graft rejection, while in the second semester correlates with biliary complications and CKD. These results support the integration of LSM monitoring in the work-up of early post-LT complications.

FRI-495-YI
Hypothermic oxygenated machine perfusion (HOPE) treatment prior to organ transplant alters key immune modulators in patients receiving liver transplantation

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Background and aims: Hypothermic oxygenated machine perfusion (HOPE) is recognized as a powerful strategy to protect allografts from ischemia-reperfusion injury. While its benefits on early graft function have been demonstrated in several trials, its specific impact on immune regulation post-transplant remains unexplored. This study aimed to investigate how HOPE influences key immune modulators in patients undergoing liver transplantation.
Method: A single-center study of 100 patients receiving liver transplantation at the University Hospital RWTH Aachen between 2019 and 2024 was conducted. Of these, 38 received HOPE-treated donor livers, while 62 received livers with standard preservation treatment. Soluble immune markers, including T-cell immunoglobulin mucin domain-containing protein 3 (sTIM-3), sCD163 and programmed death ligand 1 (sPD-L1), were measured in patients`

serum before surgery (baseline), within 24 hours post-surgery (POD1) and one week after surgery (POD7).
Results: Patients who received HOPE-treated livers experienced significantly fewer postoperative complications (p = 0.04). Post-surgery, these patients exhibited significantly lower sTIM-3 concentrations, a marker involved in T-cell activation, suggesting reduced immune activation (p = 0.04). The macrophage activation marker sCD163 was also significantly reduced in the HOPE group (p = 0.005). Conversely, sPD-L1, known to inhibit T-cell activation and to promote immune tolerance, was elevated in the HOPE-treated patients, potentially contributing to improved graft tolerance (p = 0.004).
Conclusion: Our findings demonstrate that HOPE treatment has an immediate impact on the host immune response in patients following liver transplantation. The observed changes in sTIM-3, sCD163, and sPD-L1 provide early insights in immunomodulatory effects of HOPE and its potential to improve post-transplant outcomes by influencing key immune pathways.

FRI-496
Impact of donor-recipient age disparity on survival and recurrence in liver transplantation for hepatocellular carcinoma
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Background and aims: The age disparity between liver transplantation (LT) recipients and donors may influence long-term outcomes, including survival and recurrence of hepatocellular carcinoma (HCC). This study evaluates the impact of donor-recipient age combinations on post-transplant outcomes in HCC patients.
Method: A cohort of 586 HCC patients who underwent LT between 2000 and 2022 was classified into four groups based on recipient and donor age: Group 1 (recipient ≤65 years, donor ≤65 years; n = 319), Group 2 (recipient ≤65 years, donor >65 years; n = 130), Group 3 (recipient > 65 years, donor ≤65 years; n = 87), and Group 4 (recipient > 65 years, donor > 65 years; n = 50). Survival and recurrence rates were compared using Kaplan-Meier analysis and log-rank tests.
Results: During mean follow-up periods of 89 ± 68 months, the cohort has 82.4% males and 17.6% females with a mean age of 58.9 ± 8.7years.The main aetiologies of underlying cirrhosis were alcoholic-associated liver disease (29.2%), HCV (28.3%), MASH (15.5%) and HBV (13%).
The mean MELD score at time of LT was 13.6 ± 7.4. 79.9% of the patients were within Milan criteria at time of LT. 42.7% of donors were females. The mean age of donors at time of LT was 54 ± 20 years. At time of LT, tumours among 4 groups were within Milan criteria (78%, 81.7%, 77.1% & 85.4%, respectively, P = 0.765). MVI (p = 0.853) and tumour differentiation (p = 0.26) could not differ between the 4 groups. Recurrence incidence was significantly different among 4 groups (21.4%, 20%,16.1% and 26%, respectively, p = 0.037). Group 4 had the highest cumulative HCC recurrence rates at 1, 3, 5 and 10 (13.1%, 23.4%, 26.5% and 37.0%, respectively), while Groups 1 and 3 had the lowest recurrence rates (log-rank p = 0.033). Group 1 demonstrated the best long-term survival rates at 1, 3, 5 and 10 years (93.7%, 82.1%, 73.2% and 59.6%, respectively), while Group 4 showed significantly lower survival at all time points (78.0%, 61.8%, 31.5% and 21.0%, respectively; log-rank p = 0.020).
Conclusion: Donor-recipient age disparity significantly impacts long-term survival and recurrence in HCC patients undergoing liver transplantation. Younger recipients (≤65 years) paired with younger donors (≤65 years) demonstrate superior outcomes, while older recipients (> 65 years) paired with older donors (>65 years) exhibit the poorest outcomes. These findings highlight the importance of considering age compatibility during donor selection to optimize post-transplant outcomes in HCC patients.

FRI-497
Steatotic liver disease is associated with frailty, but this does not influence transplant listing outcomes: a retrospective study
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Background and aims: Steatotic liver disease (SLD) has emerged as a primary driver for liver transplant assessment. Frailty is increasingly recognised as critical in the assessment and management of patients with chronic liver disease. Our aim was to identify whether frailty was more prevalent in SLD and whether this influenced transplant listing outcomes.
Method: We identified all adults >18 years assessed for liver transplantation between September 2023 and September 2024 at King's College Hospital. SLD was defined as MASLD, alcohol, or MetALD. All other aetiologies (viral, autoimmune, vascular, genetic, cryptogenic) were combined as non-SLD. Those with HCC, variant indications, or re-do liver transplantations were excluded. Age, sex, liver frailty index (LFI), UKELD, hepatic encephalopathy, ascites, diabetes, BMI, and transplant listing outcome were identified for all patients. Chi-squared and t-tests assessed associations between SLD and clinical characteristics.
Results: 197 individuals with CLD were assessed for liver transplantation, of whom 110 (55%) had SLD. Median age at assessment was 55 years (Q1 46, Q3 62) with 40% female. Median UKELD was 54 with no significant difference between SLD and non-SLD (p = 0.7). Fifty (57%) of those in the non-SLD group and 38 (34%) of those with SLD were listed. Patients with SLD were more likely to have a prohibitive comorbidity profile (n = 26; 37%) than non-SLD (n = 7; 21%) but also more likely to lack a clinical indication for transplant (n = 24; 34% v n = 6; 18%). Psychosocial contraindications were similar in SLD (n = 7; 10%) to non-SLD (n = 3; 9%). Obesity (BMI > 30) was more common in SLD (38% v 22%; p < 0.05) as was ascites (60% v 31% p < 0.01) but rates of encephalopathy were not statistically different between the two cohorts. Within the SLD cohort, for those not listed, there was no difference in LFI based on reason for not listing (36% frailty for those not listed due to comorbidities vs 38% for those not listed due to lack of indication p = 0.41). Frailty was significantly associated with SLD (odds ratio [OR] 4.2; 95% confidence interval 1.4–12.1). However, frailty was not significantly associated with transplant listing (p > 0.4).
Conclusion: SLD is the leading cause for transplant referral but not transplant listing. The prevalence of frailty is higher in SLD as compared to other aetiologies of chronic liver disease. Predictably, SLD patients are more likely to have ascites, diabetes, and elevated BMI. The prevalence of frailty was equivalent in SLD patients declined for comorbidities and those declined for lack of indication. This suggests that frailty is prevalent in SLD and not a driver for listing. This further supports the need for intervention to improve frailty in the SLD population and to seek greater clarification on the role of frailty assessment in the transplant process. Future studies will explore how frailty differentially impacts transplant waiting list and post operative outcomes in SLD.

FRI-498

Prognostic impact of multi-resistant bacteria gut colonization in patients undergoing liver transplantation

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Background and aims: Patients with decompensated cirrhosis are prone to gut colonization by multi-resistant bacteria (MRB). Whether MRB gut colonization could impact post-transplant outcomes is yet to be ascertained.
Method: Retrospective observational study including a consecutive cohort of adult patients undergoing liver transplantation in a single center between January 2019 and October 2024. Patients with human immunodeficiency virus infection, retransplantation, or combined organ transplantation were excluded. A rectal swab was obtained from all patients immediately before liver transplantation to determine BMR colonization. We studied the impact of BMR colonization on the risk of infections, length of hospital stay, and mortality. Logistic regression, Kaplan Meier curves and Cox regression were used as appropriate.
Results: We included 272 patients undergoing liver transplantation among whom the prevalence of BMR colonization was 9.2% (n = 25). The most frequent microbiological agents were extended-spectrum beta-lactamases (ESBL) producing E. coli (n = 12) and carbapenemase-producing Klebsiella pneumoniae (n = 6). Sex, alcohol, tobacco use, and liver function (MELD) showed no association with the risk of colonization. MRB-colonized patients had received systemic antibiotic therapy more frequently in the months prior to transplantation (48% vs. 27%; p = 0.028), and had a more frequent history of spontaneous bacterial peritonitis (20% vs. 4.5%; p = 0.010). Patients receiving a liver transplantation due to non-tumoral MELD exceptions, particularly refractory ascites, had doubled prevalence of MRB gut colonization (16.9% vs. 5.8%; p = 0.004). Having two or more hospital admissions within the previous year was a risk factor for BMR colonization (23.1% vs. 7.7%; p = 0.021). After liver transplantation, MRB-colonized patients were at increased risk of bacterial infections during admission (36% vs. 15.4%; p = 0.022) and had a trend towards higher cytomegalovirus reactivation (16% vs. 6.1%; p = 0.083). Patients with and without BMR colonization had comparable length of hospital stay (19.3 days in colonized vs. 17.9 days in non-colonized; p = 0.63). Overall survival at 1 and 5 years was 89.6% and 80.7%, respectively in non-colonized patients, compared to 73.9% and 65.7%, respectively, in the BMR-colonized group (log rank p = 0.038).
Conclusion: Pre-transplant gut MRB colonization in liver transplant candidates increases the risk of infections early after liver transplantation and negatively impacts survival. These patients should benefit from minimized immunosuppression and individualized protocols of antimicrobial prophylaxis. Funding: "Instituto de Salud Carlos III" (grant reference PI22/00312) and European Union.

FRI-499

Hepatic artery atherosclerosis is a risk factor for biliary strictures after liver transplantation

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Background and aims: The aging of liver donors and transplant candidates, along with the growing prevalence of metabolic comorbidities, may increase the prevalence of hepatic artery (HA) atherosclerosis. Since the biliary epithelium relies exclusively on hepatic arterial flow, HA atherosclerosis could increase the risk of biliary complications after liver transplantation (LT).
Method: Retrospective observational study including all adult patients undergoing LT in a single institution between 2012 and 2023 who had a blinded pathological evaluation of the donor and recipient hepatic arteries. Patients receiving a retransplantation, combined organ transplantation, or showing hepatic artery thrombosis after transplantation were excluded. Risk factors for biliary complications were analyzed using univariate and multivariate Cox's regression, censoring events at 24 months post-transplantation.
Results: Among 322 included patients, 63 (19.6%) developed biliary complications after a median follow-up of 44 months (IQR 17–22 months). The incidence of biliary strictures was 11.8% (n = 38) at 12 months and 14.3% (n = 46) at 24 months. Neither age nor LT indication modified the risk of biliary complications (p = 0.88 and p = 0.38, respectively). There was a non-significant trend toward higher risk of biliary complications in male patients (16.7% vs. 8.5%, p = 0.057). Cardiovascular risk factors were comparable between patients with and without biliary complications at 24 months: hypertension (34.8% vs. 33%, p = 0.81), diabetes (28.3% vs. 28.6%, p = 0.96), and dyslipidemia (15.2% vs. 21.4%, p = 0.34). Liver grafts from donation after circulatory death were associated with higher risk of developing biliary strictures at 24 months compared to grafts from brainstem-death donors (23.6% vs. 12.4%, p = 0.03).
Histological analysis of intraoperative artery biopsy samples revealed atherosclerosis in 54% of donors and in 5.6% of recipients. Patients with atherosclerosis either in the donor or the recipient hepatic arteries (58.4%) showed a higher risk of biliary complications (17.6 vs 9.7%, p = 0.047). After controlling for age, sex, transplantation indication (hepatocellular carcinoma), donor steatosis, and cardiovascular comorbidities in the multivariate Cox's regression analysis, hepatic artery atherosclerosis (HR = 2.18 [95%CI 1.12–4.21; p = 0.021]) and donation after circulatory death (HR = 2.43 [95%CI 1.25–4,76; p = 0.009) were the only independent predictors of biliary complications after LT.
Conclusion: Donor or recipient hepatic artery atherosclerosis is associated with an increased risk of biliary strictures after liver transplantation. In such patients, the use of antiplatelet therapy could be considered to reduce the risk of biliary complications. Funding: "Instituto de Salud Carlos III" (grant reference PI22/00312) and European Union.

FRI-500

Association between pre-transplant body mass index and survival after liver transplantation in an adult recipient cohort from Johannesburg, South Africa

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Background and aims: There is uncertainty regarding associations between recipient pre-transplant body mass index (BMI) and survival after liver transplantation, particularly whether obesity is associated with increased mortality. There are no studies investigating associations in Africa which has limited liver transplant services. Currently, there are two liver transplant units in South Africa. The study aimed to determine the association between recipient pre-transplant BMI and survival after liver transplantation amongst adults in Johannesburg, South Africa.
Method: Adults 18 years or older, who received an index liver transplant for chronic liver disease from August 2004 to January 2024 at Wits Donald Gordon Medical Centre, Johannesburg, South Africa were included in this cohort study. Secondary data analysis was performed using an institutional review board approved database. Multivariable Cox regression determined adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of recipient pre-transplant BMI at listing and all-cause post-liver transplant mortality. Survival at 1- and 5 years post-transplantation was also assessed. BMI (kg/m^2) was categorised using the World Health Organisation classification: underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese: class I (30.0–34.9); class II (35.0–39.9); class III (> = 40). Potential confounders adjusted for were age, sex, self-reported ethnicity, aetiology of cirrhosis, Model for End-Stage Liver Disease (MELD) score, ascites, diabetes, waitlist duration, and postoperative complications. Effect modification by age, sex, self-reported ethnicity, and MELD were assessed.
Results: Among 489 adults, the median (IQR) age was 53 (43–60) years, 290 (59.3%) were male, 8 (1.6%) Asian, 89 (18.4%) Black, 35 (7.2%) Indian, 15 (3.1%) Mixed, and 338 (69.7%) White ethnicity. Of these, 21 (4.3%) were underweight, 168 (34.4%) normal, 169 (34.6%) overweight, 93 (19.0%) class I, 32 (6.5%) class II, and 6 (1.2%) class III obesity. After a median (IQR) of 5.3 (1.3–8.9) years follow-up, there were 187 (38.2%) deaths post-liver transplantation. After adjusting for potential confounders, compared to adults with normal BMI, only class III obesity was positively associated with post-liver transplant mortality (HR, 3.95; 95% CI, 1.49–10.47). BMI categories were not significantly associated with mortality at 1- and 5 years post-transplantation. There was no effect modification.
Conclusion: Overall, among adults receiving an index liver transplant for chronic liver disease in Johannesburg, South Africa, there was no significant association across BMI categories except for class III obesity which was positively associated with post-liver transplant mortality. Due to limited participants with class III obesity, larger studies are needed to reliably evaluate associations at extremes of BMI.

FRI-501
Extensive portal vein thrombosis in patients with cirrhosis undergoing liver transplantation : results of a national multicenter retrospective study

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Background and aims: Portal vein thrombosis (PVT) significantly impacts patient outcomes during liver transplantation (LT) and post-transplant survival, with an even greater impact in cases of extensive PVT. Portal vein (PV) recanalization using transjugular intrahepatic portosystemic shunt (TIPS) has been proposed in patients with PVT awaiting LT to facilitate LT and, consequently, improve post-transplant outcome. However, specific studies focusing on patients with extensive PVT are lacking. Aims: to evaluate the outcome of patients with extensive PVT undergoing LT, identify pre-transplant prognostic factors, taking into account patients management.
Method: Retrospective study performed in 12 French LT centers. All patients with cirrhosis and extensive non tumoral PVT (defined as either Yerdel grade ≥III or cavernoma of the main PV) listed for LT from 2010 to 2023 were included. All CT scans were retrospectively reviewed. Evolution of PVT from listing to LT was assessed using the VALDIG-PVT criteria. Primary endpoint was transplantation-free survival (ReLT-FS) at 1 year after LT.
Results: Among 1308 patients with cirrhosis and PVT on the waiting list, 131 had an extensive PVT (75% men, median age 57 years). 74% of the patients had a chronic PVT (known for ≥6 months). PVT was classified Yerdel grade I, II and ≥III in 6%, 50% and 43% of the patients, respectively. A cavernoma was present in 81% and calcifications of the main PV were present in 47% of the patients. 61% of the patients were treated with anticoagulation (AC) before LT. 88 out of 131 patients received a LT. From listing to LT, improvement of PVT, PVT stability and progression of PVT occurred in 13%, 73%, and 15% patients, respectively. 17 (14%) patients had received a TIPS before LT, while 26% could have been considered as potential candidates for TIPS placement (i.e progression of PVT under anticoagulation and MELD < 18, no hepatic encephalopathy nor hepatocellular carcinoma) Porto or mesenterico-portal (PPA), reno-portal (RPA), gastro-portal (LGA) and cavoportal (CPA) anastomoses were performed in 75%, 14%, 6%, and 5% of the patients, respectively. 34% of the patients received AC after LT. At one year after LT, 18% were dead, 6 had had undergone re-transplantation. Overall, one-year ReLT-FS after LT was 76% (95% CI: 67.1–84.9). One-year ReLT-FS was 78% (95% CI 67.8–88.2), 67% (95% CI 40.4–93.6), 100%, and 25% (95% CI 0–67.4) in patients who had a PPA, RPA, LGA and CPA, respectively. By multivariable analysis, the only factor associated with ReLT-FS at one year after LT was a Yerdel grade III PVT (p = 0.02). Neither TIPS performed before LT (p = 0.28), nor the type of anastomosis (p = 0.18), nor pre (p = 0.56) nor post LT AC (p = 0.78) were associated with ReLT-FS at one year.
Conclusion: Extensive PVT remains associated with a high short-term mortality after LT. Even when it is potentially feasible, TIPS is performed in a small proportion of the patients. Whether TIPS in patients with extensive PVT improves post-LT will deserve further, prospective evaluation.

FRI-502
An audit to assess adherence to local guidelines for prophylaxis and monitoring of herpes simplex virus (HSV) in patients following orthotopic liver transplant in a tertiary transplant centre

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Background and aims: Herpes simplex virus (HSV) can cause severe clinical manifestations in immunocompromised patients post liver transplant (OLT) leading to significant morbidity and mortality. OLT patients at high risk (HRPs) of developing primary HSV (P-HSV) following transplant, i.e. HSV seropositive or unknown HSV serostatus allografts transplanted to a HSV seronegative recipient, are given HSV prophylaxis (HSVPx) with antiviral medication for 1 month post OLT to reduce the risk of P-HSV. This audit aimed to review if all HRPs were given HSVPx and monitored by weekly HSV DNA testing in

blood as per local protocol (LP). All patients post OLT were reviewed for development of HSV within 30 days of OLT.
Method: A retrospective review of patients who had OLT between November 2021 and December 2023 at a single liver transplant centre was completed and HRPs were identified. Treatment and monitoring of HRPs was evaluated using electronic prescribing records. HRPs were reviewed for the development of P-HSV, while non-HRPs were reviewed for HSV reactivation i.e. HSV PCR positive blood test or high clinical suspicion for HSV. Patients who developed HSV were audited for appropriate management as per LP. Data from only the most recent OLT was collected for patients retransplanted within 30 days.
Results: 210 patients underwent OLT over the study period, 35/210 (17%) were HRPs. 32/35 (91%) HRPs were prescribed HSVPx as per LP. 1/35 (3%) did not receive HSVPx and had detectable HSV DNA 4 days following OLT (P-HSV). The donor allograft had detectable HSV DNA. 1/35 (3%) HRP was prescribed HSVPx via the wrong route for 4 doses before switching to the correct formulation for the remainder of the prophylactic course. This patient did not develop P-HSV. 1/35 (3%) did not complete the 1-month course due to developing pancytopenia on HSVPx. A clinical decision was made to discontinue the HSVPx and monitor the patient. The patient did not develop P-HSV. 1/35 (3%) had HSV DNA monitoring as per LP. 12/35 (34%) had no HSV DNA testing within the 30 days post OLT, the remaining 22/35 (63%) had HSV DNA monitored less than outlined in LP. 17/35 (49%) of HRPs had HSV DNA tested on day 30 post OLT. Available data may have been limited to lack of access to testing that may have been carried out at other centres. No HRPs receiving HSVPx who were monitored developed P-HSV. Overall, 9/210 (4%) OLT recipients developed HSV in the 30 days following OLT and all were treated as per LP. 1/9 (11%) was a HRP who developed P-HSV. 8/9 (89%) were non-HRPs who developed HSV reactivation. 1/8 (13%) reactivations tested positive for CMV DNA and so was treated as per the local CMV protocol.
Conclusion: This audit identifies that 17% of the population studied were at risk of developing P-HSV. With 91% of HRPs given HSVPx and despite limited monitoring, rates of P-HSV were low. The single case of P-HSV was donor derived. The remaining HSV cases were reactivations, underscoring the importance of HSV monitoring in the post OLT cohort.

FRI-503-YI
Pre-transplant hepatorenal syndrome as a predictor of recurrent post-transplant cirrhosis and portal hypertension-related complications
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Background and aims: HRS is a devastating complication in cirrhosis patients with severe portal hypertension. Here, we have hypothesized that patients who develop HRS prior to transplant and recurrent cirrhosis after transplant may experience worse portal hypertension complications post-transplant.
Method: Using the TriNetX database, which includes 115,676,318 patients from 66 US healthcare organizations, we examined patients aged ≥18 years with cirrhosis who underwent liver transplantation and developed HRS within a year prior to transplantation, from January 2010 to October 2024. New diagnoses of recurrent post-transplant cirrhosis, ascites, SBP, HE, variceal bleeding, and liver transplant rejection were captured. We propensity matched cirrhosis patients with pre-transplant HRS to those without pre-transplant HRS using age, sex, essential hypertension, and type II diabetes mellitus (T2DM) as matching variables. Diagnoses were identified using ICD-9 and ICD-10 codes and data were analyzed using built-in functions of the TriNetX Analytics Platform (R, version 4.0).
Results: 71,460 patients underwent liver transplantation, including 7,821 (11%) with HRS within one year of transplantation. The average age was 54 years (SD: 12), with the majority being male (62%) and Caucasian (69%); the mean pre-transplant MELD was 36 (SD: 8). In cirrhosis patients without HRS, demographics were similar, but the mean MELD was 25 (SD: 8). Essential hypertension and T2DM were equally common in both groups (hypertension: 54%; T2DM: 37%). Patients with pre-transplant HRS had a higher risk of developing recurrent post-transplant cirrhosis than those without HRS (30% vs. 14%; OR 2.2, $p < 0.001$). Of the common complications of portal hypertension, ascites after transplant was the most strongly associated with pre-transplant HRS (OR: 2.5, CI 2.2–2.9, $p < 0.001$), but SBP (OR: 1.9, CI 1.5–2.3, $p < 0.001$), HE (OR: 1.7, CI 1.2–2.0, $p < 0.001$), and variceal bleeding (OR: 1.2, CI 1.1–1.3, $p < 0.05$), were also associated with pre-transplant HRS. Pre-transplant HRS was also strongly associated with acute or chronic rejection after liver transplantation (OR: 1.7, CI: 1.6–1.9, $p < 0.001$). Over a median follow-up period of 5 years following liver transplantation, patients with HRS pre-transplant had a higher risk of mortality than patients without pre-transplant HRS (OR: 1.2, CI 1.1–1.2, $p < 0.001$).
Conclusion: Cirrhosis patients with HRS prior to liver transplantation have an increased risk of recurrent post-transplant cirrhosis and portal hypertension complications following transplant and greater post-transplant mortality rates. These data raise the possibility that severe portal hypertension persists in some patients even after transplantation, and contributes to the development of cirrhosis.

FRI-504
Nephrocheck as a predicitve tool for post-operative acute kidney injury following liver transplant for chronic liver disease
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Background and aims: Post-operative AKI (po-AKI) occurs within 7 days of an index procedure and is associated with adverse outcomes. Due to the physiological changes of advanced liver diseases and the surgical stress response, substantial injury may occur prior to detection by Kidney Disease Improving Global Outcomes (KDIGO) criteria in these cohorts. The cell-cycle arrest proteins TIMP-2 and IGFBP-7, have been proposed as early renal injury biomarkers that may detect patients at high-risk of po-AKI prior to rises in creatinine (Kashani, 2013). Nephrocheck, already validated for the detection of AKI in the critically ill, is a urinary point of care test based on these biomarkers (Hoste, 2014). The aim of this study was to identify the incidence of po-AKI following LT in our unit and the utility of Nephrocheck in this setting compared to conventional criteria.
Method: A prospective pilot observational study was performed in 45 patients undergoing liver transplant (LT) for chronic liver disease at the Liver Unit, Birmingham UK between August 2019-January 2020. Exclusion criteria: pre-existing AKI, stage 5 chronic kidney disease, previous renal transplant, pre-planned use of renal replacement therapy (RRT), acute liver failure and multi-visceral transplantation. Patient characteristics, biochemical parameters, donor details, daily serum creatinine and use of renal replacement therapy were collected from the electronic patient record. Standard definitions were used for defining po-AKI occurrence. Nephrocheck was performed on urine samples collected within 24 hours of the LT and po-AKI risk defined when a value > 0.3 (ng.ml-2).1000–1 was obtained.
Results: 40% (18/45) developed po-AKI following LT and had significantly longer Intensive Care Unit stays than those who didn't ($p = 0.004$). 89% (16/18) developed po-AKI within the first 48 hours, and 11% (2/18) developed a later po-AKI after four or more days. 5/18 (27.8%) required RRT within seven days of their LT. The median Nephrocheck score in those with po-AKI was higher than those without po-AKI ($p < 0.001$). Those with higher severity po-AKI also had a significantly higher Nephrocheck score ($p < 0.001$). In total 29/45 (%) patients met the pre-defined cut-off identifying them as "at-

risk" of po-AKI. This included all 18 patients (%) who developed KDIGO po-AKI ($p < 0.0001$). Sensitivity was calculated at 1.0 and specificity 0.6; AUC-ROC 0.88 (95% confidence interval 0.78–0.91).
Conclusion: Our results suggest that using the Nephrocheck acute kidney injury cut-off of 0.3 (ng.ml-2).1000–1 can predict po-AKI in patients undergoing LT for chronic liver disease without pre-existing renal injury. The benefits of this include instigation of reno-protective strategies in at risk patients and earlier detection of renal insults, potentially preventing progression to higher grade renal injury.

FRI-509
Assessing the safety and efficacy of advanced therapies to treat inflammatory bowel disease in patients with a liver transplant
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Background and aims: Primary sclerosing cholangitis (PSC) is associated with inflammatory bowel disease (IBD). Up to 80% of patients with PSC have IBD. The only life extending intervention for end-stage PSC is liver transplant (LT). Poorly controlled IBD post-LT increases the risk of recurrent PSC, highlighting the importance of adequate IBD control. IBD with LT presents a complex dilemma between disease control versus risks of immunosuppression. The proliferation of advanced therapies (AT; biologic or small molecule) for IBD have unknown efficacy and safety in the setting of LT. We describe our experience of IBD patients with a LT, requiring AT.
Method: Patients with IBD, who underwent LT at King's College Hospital were included. Retrospective data was collated, including demographics, IBD, AT and LT details.
Results: 81 patients with IBD and a LT were identified, and 39 (48.1%) required AT. Of the 39 patients, 30 patients were initiated post LT. Aetiology of liver disease was PSC (50/81), PSC/AIH (22/81) and other (9/81). IBD subtypes were ulcerative colitis (UC;89.7%), Crohn's disease (7.7%), and IBD-U (2.6%). Median age at first LT was 30 years (IQR 21–39), and second LT was 41 (IQR 30–45). Anti-rejection medications were tacrolimus and steroids. There was no significant difference in immunosuppression regimens in those who developed IBD post-LT ($p = 0.70$). There were 17 patients (43.6%) that received one AT, 22 patients received 2 or more. In the majority of patients with PSC, treatment with AT was first initiated post LT: 16/18 with PSC/IBD and 12/18 with PSC/AIH/IBD. First-line AT initiated post-LT was Vedolizumab in the majority (48.2%). Pre-LT, 15% of patients required AT; mean time between starting AT and LT was 48 months with an anti-TNF being initiated in 77.7%, and Vedolizumab in 11.1%. Acute cellular rejection (ACR) occurred in 16 patients on AT within the first 12 months after first LT, but only one had initiated AT within this time frame. IBD subtype did not influence incidence of ACR. In patients requiring AT (39/81); 36.8% of patients developed cholangitis post-LT. 50% were on an AT at the time of cholangitis (unable to extrapolate data in 28.5% of patients).
Conclusion: In our cohort of post LT patients with IBD, 37% of patients required initiation of an AT post LT, and over half of patients requiring AT required escalation of therapy beyond first line treatment. It is unclear whether this reflects the natural course of IBD, or influence of LT. Almost 40% of patients developed cholangitis post-LT, of whom 50% were on AT at the time of cholangitis. As the incidence of IBD and AT use increases, multi-centre experience will be invaluable, to collate larger numbers to assess the safety and efficacy of patients with IBD with LT, on AT. In conclusion, AT is initiated in a large proportion of patients with IBD after LT, and this cohort of patients require close monitoring for development of cholangitis.

FRI-510-YI
Acute pancreatitis in emergency liver transplantation for acute liver failure: prevalence, predictors and consequences
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Background and aims: Acute pancreatitis (AP) may contraindicate emergency liver transplantation (ELT), but biochemical and radiological biomarkers for AP perform variably in patients with acute liver failure (ALF) and the consequences for those who proceed to ELT are not well-defined. We aimed to describe AP prevalence, the relationship between biomarkers and intra-operative findings and the consequences for those who undergo ELT.
Method: Consecutive patients admitted for ALF to a specialist critical care unit who did (1/2013–12/2023) or did not (1/2018–1/2022) undergo ELT were studied. In ELT recipients, those with an intra-operative diagnosis of AP were matched by age, sex and disease aetiology to those without (1:2 ratio). Pre-ELT CT imaging was re-reviewed by 2 HPB radiologists unaware of the operative findings.
Results: 227 patients with ALF were identified (120 transplanted, 107 non-transplanted). Median age was 37 years; 65% were female. Aetiologies included paracetamol (37%), seronegative hepatitis (16%) and drug-induced liver injury (13%). Serum amylase above 100 IU/L was present in 49% (92/189) and above 300 IU/L in 15% (28/189). Radiological evidence of AP was contemporaneously reported on CT in 5% of ALF admissions (10/191). Serum amylase was significantly higher in those with radiological AP (median 261 (IQR 139–571) IU/L versus 73 (45–153) IU/L, $p < 0.001$), but was under 300 IU/L in 60% (6/10). AP was found intra-operatively in 8% of those transplanted (9/120); its presence was not associated with age, ALF aetiology or clinical presentation. Serum amylase alone was a poor discriminant test for intra-operative AP (AUROC 0.62); a level above 300 IU/L was specific (89%) but poorly sensitive (22%). Comparing intra-operative AP cases to matched controls, cases had increased organ dysfunction (SOFA score 19 (IQR 17–21) vs 15 (8–16), $p = 0.001$) and lower platelets at time of ELT (44 (IQR 38–86) vs 96 (49–136), $p = 0.02$). On re-review of imaging, pancreatic abnormalities were common in both case and control groups (78% vs 65%, $p = 0.5$). Pleural effusions were more common in those with intra-operative AP (89% vs 47%, $p = 0.05$) with no other radiological associations. AP patients had longer post-ELT on mechanical ventilation ($p = 0.008$) and renal replacement therapy ($p = 0.003$), increased rates of tracheostomy ($p = 0.037$), longer ITU and hospital lengths of stay ($p < 0.001$) and increased ITU readmission rates ($p = 0.003$). However, there was no significant difference in survival to discharge from ITU or from hospital and no significant difference in 1-year patient and graft survival.
Conclusion: Identification of AP in ALF is difficult. Hyperamylasaemia is common in patients with ALF, but biochemical and radiological diagnostic tests correlate poorly with presence of intra-operative AP, confounding ELT wait-listing decisions. Marked increases in morbidity follow an unexpected diagnosis of AP in patients transplanted for ALF, but without significant impact on mortality or graft survival.

FRI-511
QEL-001 LIBERATE study expansion cohort, CAR (Chimeric Antigen Receptor) T regulatory (Treg) cells engraftment and expansion following rATG (rabbit anti-thymocyte globulin) conditioning in post liver transplantation
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Background and aims: LIBERATE (NCT05234190) is an ongoing phase I/IIa, single-arm, open-label study to investigate the potential of QEL- 001, an autologous Chimeric Antigen Receptor (CAR) T regulatory (Treg) cell therapy to potentially induce allograft tolerance and allow the complete discontinuation of immunosuppression (IS) in post liver transplantation. QEL- 001 expresses an HLA -A2 specific CAR, a FOXP3 phenotype lock and an inducible safety switch. The Safety Cohort of the study has been completed (N = 3) and shown QEL - 001 was well tolerated, trafficked to and engrafted in the transplanted livers.
Method: The Expansion Cohort is being conducted in the UK and EU. Eligible subjects were aged 18–75 years and underwent liver transplantation 1–5 years prior to enrolment. Low dose rATG (rabbit anti-thymocyte globulin) was administered no less than 4 weeks before QEL- 001 infusion. A Data Safety Monitoring Board (DSMB) performed an independent review of the data.
Results: Eligible subjects received low dose rATG (2.5 mg/kg, up to 200 mg in total) at least 4 weeks prior to QEL - 001 infusion. Mild to moderate AEs were reported, such as fever, headache and infusion site swelling, attributable to ATG administration, which resolved within a few days with minimum or no intervention. ATG mediated a significant reduction in CD4 and CD8 T-cell frequencies. Other immune populations appear to be mostly unaffected. Active ATG was cleared from circulation approximately 3 weeks post ATG administration. QEL- 001 CAR-Treg engraftment was observed and remained detectable in circulation for at least 2 months after cell infusion, significantly longer than those observed in the Safety Cohort without ATG conditioning. CAR-Tregs can be detected by digital polymerase chain reaction (dPCR) in the post QEL- 001 infusion liver biopsy tissue. Clinical batches produced for all subjects were within the pre-defined product specifications, and without CD8 impurities. QEL- 001 CAR Treg maintained phenotypic stability, and consistently across batches in vivo, post-infusion.
Conclusion: QEL- 001 infusion after rATG conditioning was well tolerated in patients treated to date. Specific T-cell lymphodepletion was apparent one week post ATG which subsequently enhanced QEL-001 engraftment and durability in circulation compared with previous data in the safety cohort. Additional clinical and mechanistic data will be presented at the Congress.

FRI-512
TAVI in liver transplant candidates: a retrospective analysis from a high-volume transplant center

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Background and aims: Percutaneous treatment (transcatheter aortic valve implantation, TAVI) is less aggressive than surgical valve replacement (SVR) for severe aortic valve disease (AVD) and enables treatment for high surgical risk patients. In patients with cirrhosis that may be potential candidates for liver transplantation (LT) but have severe aortic valve disease that contraindicates LT, and in whom SVR is not feasible due to liver disease, TAVI could fix the valve condition and enable access to LT.
Method: Retrospective single-center study. We reviewed all patients evaluated for LT between July 2015 and December 2022 and identified those who underwent TAVI as part of pre-LT assessment. Patient characteristics, procedure details, complications, and final outcomes were analyzed.
Results: In the study period, 912 LT evaluations were conducted at our center. Among them, severe AVD requiring TAVI was identified in 4 (0.4%) patients: 3 men and 1 woman aged 59–69 years. Three TAVIs were performed for stenosis and one for post-endocarditis valve insufficiency. The indication for LT in all four cases was decompensated cirrhosis, with a combined liver-kidney transplant required in two of these cases. Pre-TAVI MELD-Na scores ranged from 14–29 and platelet count ranged from 35.000–130.000/microliter. All patients were prescribed aspirin for one month following the procedure. Two patients experienced gastrointestinal bleeding (one due to portal hypertension gastropathy and the other one from a gastric polyp), both cases resolved without complications, although they required blood transfusions. Arrhythmic events occurred in all four patients; three of them self-limiting without associated heart failure, and one of them persistent until death. This latter patient underwent TAVI as an emergency procedure due to acute pulmonary edema and passed away 10 days later while awaiting LT. Of the remaining three, two successfully underwent LT without perioperative complications 2 and 4 months after TAVI and remain asymptomatic with functioning TAVIs after 2 and 6 years of follow-up. In the fourth patient, LT was contraindicated despite a well-functioning TAVI, due to severe secondary pulmonary hypertension.
Conclusion: The need for TAVI in LT candidates is rare at out center. This procedure can help facilitate and give access to LT in patients with severe aortic valve disease, leading to excellent post-LT outcomes, although it carries risks, especially in emergency settings. Our data may serve as a basis to expand sample size through a multicenter study.

FRI-513
Clinical factors associated with non-tumoral portal vein thrombosis in liver transplant candidates and its impact on pre-transplant outcomes

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Background and aims: Portal vein thrombosis (PVT) can occur in liver transplant (LT) candidates, often associated with advanced cirrhosis. When severe, PVT may be a contraindication to LT. Features of metabolic syndrome (MS) are increasingly common in LT candidates and should be carefully considered during the evaluation process. Data on the possible association between MS features and PVT are controversial. This study aims to investigate clinical factors associated with the presence of PVT in LT candidates and its impact on access to the LT waiting list (WL) and to LT.
Method: 726 consecutive patients evaluated for LT were retrospectively enrolled (2008–2020). Data on the presence and extent of PVT, classified according to Yerdel, as well as clinical variables, were collected. Reasons for exclusion from listing and WL drop-out were also recorded. Multivariate binary logistic regression models were performed using the backward selection and bootstrap methods, considering presence of PVT, access to the WL, and LT as dependent variables, and clinically significant as covariates.
Results: PVT was identified in 11.4% of evaluated patients (n = 83), with advanced PVT (Yerdel stages 3–4) observed in 22% of PVT cases.

Two-hundred-eighty patients (38.6%) were listed and 161 transplanted (22.2%). Obesity was the sole independent factor associated with presence of PVT (p = 0.00028, OR 2.689, 95% CI 1.575–4.580) after adjusting for age, sex, MELD-Na, hepatocellular carcinoma, diabetes, dyslipidemia, and arterial hypertension. Among listed patients, those with PVT were more frequently excluded due to clinical contraindications compared to non-PVT patients in the univariate analysis (26% vs 14%, p = 0.042). However, multivariate binary logistic regression revealed no independent association between PVT and access to the WL. Similarly, among transplanted patients, PVT was not independently associated to LT. No significant differences were observed in the causes of WL drop-out. Nevertheless, advanced PVT was more prevalent among PVT non-transplanted patients compared to PVT transplanted patients in the univariate analysis (40% vs 20%, p = 0.04). No significant differences were observed in the causes of WL drop-out.

Conclusion: Among LT candidates, obesity is strongly associated with the presence of PVT, likely due to pro-inflammatory and pro-thrombotic stimuli from the gut-liver axis. However, PVT does not seem to be significantly independently associated with pre-transplant outcomes.

FRI-514

Dynamic changes of spleen stiffness in liver transplanted patients:preliminary findings from a single-center study

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Background and aims: Vibration controlled transient elastography (VCTE; Fibroscan®) is a non-invasive method to assess liver stiffness measurement (LSM) and evaluate liver fibrosis. VCTE has also been widely used in post-liver transplantation (LT) setting to identify graft damage. Spleen stiffness measurement (SSM) is known to improve non-invasive diagnosis of clinically significant portal hypertension (CSPH) but data in the post-LT setting is limited. The aim of this study is to evaluate changes in SSM, spleen size and liver stiffness following LT.

Method: From January 2022 to July 2024, all consecutive LT recipients transplanted at our centre with available SSM pre-LT were enrolled. Patients with re-LT, splenectomy or without SSM pre-LT were excluded. SSM was measured by VCTE Fibroscan® (Echosens, Paris) before LT and at 3–6–12 months after surgery when available, while LSM was assessed only after LT at the same time points. Ultrasonographic and biochemical data were also collected.

Results: Twenty-two recipients (median age 61.5 years, 55% males, 45% viral-etiology, 32% with HCC; 4 DCD grafts; donor age 58 years, 100% on CNI-based immunosuppression) were studied. Median SSM significantly decreased from 59 kPa pre-LT to 27, 22, 27 kPa at 3, 6, 12 months post-LT, respectively (p < 0.05), with 44% with >50% decrease already at month 3. Spleen diameter has reduced from 15 cm pre-LT to 14, 13, 11 cm at 3, 6, 12 months post-LT (p < 0.05), likewise platelet count significantly improved over time (65,000, 153,000, 148,000, 157,000/mm^3, p < 0.05). In the first year post-LT, LSM did not significantly change over time (~6–7 kPa at all post-LT time points, p = ns). A weak correlation was observed between spleen SSM values and spleen diameter at 3; the correlation progressively improves at 6 and 12 months (Spearman correlation 0.058, 0.262, 0.340 at 3, 6 and 12 months respectively, p = ns). No statistically significant correlation was found between the decrease in spleen stiffness and the increase in platelet count across the time points (Spearman correlation 0.360, 0.090, −0.205 at 3, 6 and 12 months respectively, p = ns).

Conclusion: Our study demonstrates a significant reduction of SSM and spleen diameter occurring within three months and remaining stable during the first year after LT. These results are consistent with the early reversal of CSPH after LT. The weak correlations found between SSM, diameter spleen and platelet count may be due to sample size. However, SSM could be a useful innovative tool to monitor liver transplanted patients.

FRI-515

Evolving trends and the role of mitigating performance status decline on the liver transplant waitlist

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Background and aims: Liver transplant (LT) candidates with low performance status (PS) face higher risks of mortality. Most studies on impaired PS and post-LT outcomes focus on static assessments measured at the time of LT, overlooking changes in PS during the waitlist period and potential selection bias.

Method: We conducted a nationwide retrospective cohort study using data from the Organ Procurement and Transplantation Network (OPTN), including adult LT candidates (age ≥18) listed between January 2015 and December 2023. Trends in the proportion of low Karnofsky Performance Status (KPS) listed for LT were assessed with logistic regression models. The impact of declining KPS before LT on post-LT survival was estimated with Cox proportional hazards models. Inverse probability censoring weighting (IPCW) was employed to mitigate selection bias resulting from death and drop-out while on the waitlist.

Results: A total of 57,917 candidates were listed for LT, of whom 39.5% had a low KPS (10–40%) at listing. While the likelihood of low KPS at waitlisting did not significantly change, fewer patients had a low KPS at the time of LT (p < 0.001). Each additional recent month of waitlisting was associated with a 0.4% increase in ΔKPS (change in KPS between waitlisting and LT), compared to the previous month (p < 0.001). A ten-percent increase in ΔKPS reduced the posttransplant hazard of death by 4% (HR 0.96, 95% CI 0.94–0.98). Absence of a decline in ΔKPS was associated with a 12% lower posttransplant hazard of death (0.88, 0.83–0.94). The sensitivity analysis confirmed robustness by testing different criteria for waitlist time (≤90 days), baseline functional status (only for those with the lowest KPS at listing), and the redefined binary category of ΔKPS.

Conclusion: The significant improvement in KPS at LT and the increasing ΔKPS over time may reflect more effective interventions during the waitlist period in the recent era. Our weighted survival model suggests that preventing and mitigating low KPS before transplantation could optimize post-LT outcomes, demonstrating the importance of focused efforts to improve overall functional status among LT candidates.

FRI-516

Impact of comorbidities on liver transplant outcomes: assessing sex-specific differences by using machine learning analysis

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Background and aims: Comorbidity plays a critical role in mortality of patients on both the waiting list for liver transplantation (LT), as well as in post-LT mortality. The aim of this study was to analyze the impact of comorbidities on survival through an intention-to-treat analysis.
Method: This prospective multicenter study included 1,504 consecutive patients on the LT waiting list across 18 Spanish hospitals. To classify patients based on comorbidities, unsupervised agglomerative clustering algorithms were applied using machine learning techniques. All analyses were stratified by sex.
Results: Comorbidities were more prevalent in males than in females ($p < 0.001$), with differing patterns between the sexes. The most frequent comorbidities and risk factors were smoking habit, arterial hypertension, obesity, and diabetes. Significant sex-based differences were observed for diabetes, renal insufficiency, cardiovascular disease, smoking habit, obesity, COPD, OSHAS, atrial fibrillation, and connective tissue disease. Patients were grouped into clusters based on differential comorbidities in both sexes. We identified clusters characterized by varying compositions of comorbidities, resulting in different overall survival outcomes. Kaplan-Meier curves of overall survival for clustering groups showed differences between the groups in both males ($p = 0.045$) and females ($p = 0.027$). Indexes derived from clustering were able to predict mortality for both sexes ($p < 0.001$, $p = 0.003$).
Conclusion: This study highlights the importance of comorbidities in LT outcomes and identifies clusters characterized by varying compositions of comorbidities that may affect overall survival. In addition, the findings underscore the need for sex-disaggregated analyses in patients with end-stage liver disease.

FRI-518-YI

Depression is highly prevalent amongst patients listed for liver transplant and unrelated to liver disease severity

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Background and aims: The prevalence of anxiety and depression is higher amongst patients with chronic liver disease (CLD) than the general population. Depression increases liver transplant (LT) wait-list mortality and negatively impacts post-LT survival. Patients on the LT wait-list are also under an immense psychological burden and experience increased illness uncertainty. We aimed to identify the prevalence of anxiety and depression amongst our diverse LT wait-list patient cohort and compare this to patients with CLD not on the wait-list.
Method: The Hospital Anxiety and Depression Scale (HADS) questionnaire was distributed to a sequential unselected cohort of patients attending the LT wait-list clinic and to non-wait listed patients with CLD attending hepatology clinics at King's College Hospital. An anxiety and/or depression sub-score (HADS-A, HADS-D) ≥8 was consistent with a probable diagnosis of current anxiety and/or depression.
Results: 30 patients on the LT wait-list (median time listed 297 days (interquartile range (IQR) 84–611) and 24 patients with CLD not wait-listed were assessed. Patients on the wait-list were younger (median age 45 years (IQR 34–58) than those in the CLD cohort (median age 56 years (IQR 50–62) ($p < 0.05$). There was no significant difference in Model for End-Stage Liver Disease-Sodium (MELD-Na) between the wait-list (median MELD 10.5 (IQR: 8–12)) and CLD cohorts (median MELD 9.5 (IQR: 7–12)) ($p = 0.6$). 47% of the wait-list cohort had a pre-existing mental illness diagnosis, compared to 50% of the CLD cohort ($p = 0.8$). More patients in the CLD cohort (33%) were on anti-depressants compared to the wait-list cohort (10%) ($p < 0.05$). 57% of the wait-list cohort screened positive for current depression compared to 25% of the CLD cohort ($p < 0.05$). Median HADS-D score was significantly higher in the wait-list cohort (8 (IQR 5–10)) than the CLD cohort (5 (IQR 1–8) ($p < 0.05$). Prevalence of probable anxiety was similar in the wait-list and CLD cohorts (47% vs. 50% respectively, $p = 0.8$), with no significant difference in median HADS-A ($p = 0.3$). Interestingly, 53% of the cases of probable depression in the wait-list cohort were not previously diagnosed, suggesting this may in part represent an adjustment disorder, whilst all cases in the CLD cohort who screened positive for depression had a pre-existing diagnosis of depression ($p < 0.05$). There was no correlation between HADS-D and MELD-Na scores.
Conclusion: The prevalence of anxiety and depression is high in CLD. The prevalence of depression is higher still in patients listed for LT. Depression in patients listed for LT is underdiagnosed and under-treated. A holistic approach is needed in the management of this patient cohort, including active screening for anxiety and depression, appropriate treatment and support where needed, and integration of

a dedicated psychologist into the multidisciplinary team pre- and post-transplant.

FRI-519

The post-operative recurrence rate is significantly higher in patients with HBV-HCC compared to those with HCV-HCC

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Background and aims: The survival outcome of HBV and HCV-related HCC (hepatocellular carcinoma) patients who received curative hepatectomy showed variable results in previous studies. However, most of the studies were conducted before introducing DAA (direct-acting antiviral) therapy for HCV patients. With the application of DAA for HCV patients, it remains unclear about the outcome of HBV and HCV-related HCC patients after curative hepatectomy.
Method: This prospective study enrolled HCC patients with positive HBsAg and anti-HCV who received curative hepatectomy from July 2015 to September 2024. Cox regression analysis was applied for independent predictors of HCC recurrence. The Kaplan-Meier method with the log-rank test was used to compare cumulative incidences of HCC recurrence and overall survival between HBV and HCV patients. A propensity score matching(PSM) at a 1:1 ratio was applied to adjust confounders between HBV and HCV patients such as age, sex, cirrhotic status, preoperative ALT levels and TNM clinical stage at first curative operation.
Results: There were 122 HBV patients and 55 HCV patients enrolling into the study with mean age of 63 years, 79% of male, 35% of cirrhosis, 85% of ALBI grade I, 60% of TNM stage I, and 57% having microvascular invasion. Among HBV patients, 95% were HBeAg negative, median HBV DNA level at operative date was 2.78 $\log_{10}$ IU/mL, and 43% received nucleos(t)ide analogue (Nuc) before curative surgery. While for HCV patients, 93% had undetectable HCV RNA and 62% had received DAA therapy before curative surgery. During the median follow-up of 3.4 years, a total of 58 patients (45 HBV, 13 HCV) had HCC recurrence. Multivariate Cox regression identified TNM stage ≥II (adjusted hazard ratio (aHR):2.648 (95% CI: 1.571–4.463), $p < 0.001$) was the only independent predictor of HCC occurrence. Of note, HCV patient was less likely to encounter HCC recurrence compared to HBV patients but the statistical difference did not reach significance (crude hazard ratio: 0.681 (0.367–1.264), $p = 0.223$) Before PSM, HBV-HCC patients had a higher 4-yr recurrent rate compared to HCV-HCC patients. (41% vs. 24%, $p = 0.073$). The 4-yr overall survival (OS) was similar (91% vs 87%, $p = 0.294$). After PSM (55 HBV and 55 HCV patients), the HBV-HCC patients still had a higher 4-yr recurrence rate than HCV-HCC patients(51% vs 24%, $p = 0.012$). Similarily, the 4-yr OS was still comparable in both groups. (90% vs 87%, $p = 0.473$).
Conclusion: Despite propensity score matching to adjust clinical and tumor factors between HBV and HCV-HCC patients, HBV-HCC still shows higher recurrence rates after curative resection. However, the OS remains comparable in both groups. These findings emphasize the distinct recurrence risk in HBV-HCC patients, suggesting the need for tailored management strategies in this population.

FRI-520

Rising global burden of liver transplants attributable to metabolic-associated steatotic hepatitis: trends from 68 countries (2009–2023)

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Background and aims: The global burden of metabolic-associated steatotic hepatitis (MASH) as a leading indication for liver transplantation (LT) outside the United States (U.S.) remains poorly characterized. Our aim was to use the Global Observatory on Donation and Transplantation (GODT) and other datasets to better understand the contribution of MASH as an indication for LT in different regions of the world.
Method: Data on the total number of LT from 68 countries (2009–2023) were obtained from GODT. The number of LT attributable to MASH [cirrhosis or hepatocellular carcinoma (HCC)] was calculated by using the estimated proportion of LT due to MASH for each country and for each year using mixed-effects models. These models included national data on LT-MASH from sources (when available) such as the U.S. Scientific Registry of Transplant Recipients and relevant literature. Country-specific factors, including etiological data for HCC and cirrhosis, as well as the Healthcare Access and Quality Index, were sourced from the Global Burden of Disease (GBD) 2021 dataset. Additional data about age, sex, income, and the prevalence of obesity and type 2 diabetes (T2D) were obtained from WHO, NCD-RisC, and the International Diabetes Federation (IDF). Forecasts for the etiology of HCC and cirrhosis for 2022–2023 were generated using Auto-Regressive Integrated Moving Average (ARIMA) models. Confidence intervals for the estimates were derived using the delta method. Temporal trends were analyzed using Joinpoint regression to calculate annual percentage changes (APC).
Results: In 2022, 37,436 LTs were performed in 68 countries, increasing to 41,024 in 2023. LT-MASH increased by +8.63% [from 5,152 (95% CI: 3,996–6,308) in 2022 to 5,598 (95% CI: 4,306–6,888) in 2023]. The median proportion of LT-MASH across countries was 12.07%, ranging from 6.67% to 20.6%. U.S. reported the highest number of LT-MASH in 2023 (1,945; 95% CI: 1,688–2,202), followed by China, India, Brazil, and Türkiye. The highest LT-MASH rate was also observed in U.S. (5.72 per 1,000,000 population). Other countries with rates ≥2.0 per 1,000,000 included Croatia, Türkiye, Canada, Belgium, Republic of Korea, Saudi Arabia, Mongolia, Sweden, Portugal, Spain, and France. Among the 57 countries with at least 10 years of data, 35 exhibited significant increases in MASH-LTs from 2009 to 2023. India, Saudi Arabia, Türkiye, China, and Brazil showed the highest APC in LT-MASH (APC > 5%). In the United States, the number of LT-MASH transplants increased annually by 3.82%, rising from 1,119 (95% CI: 1,002–1,236) in 2009 to 1,945 (95% CI: 1,688–2,202) in 2023.
Conclusion: The burden of liver transplants due to MASH has been rising steadily across different regions of the world. These findings highlight the growing public health impact of MASH and underscore the urgency of implementing targeted prevention strategies and interventions across the globe.

Liver tumours – Clinical aspects except therapy

TOP-093

Development and external validation of preoperative prediction model for early recurrence of intrahepatic cholangiocarcinoma

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Background and aims: Early recurrence (ER) of intrahepatic cholangiocarcinoma (ICCA) following surgical resection is clinically significant. This study aimed to develop and validate a preoperative risk scoring system to predict ER of ICCA after surgical resection, utilizing clinical and computed tomography (CT) features.
Method: This multicenter retrospective study included 365 patients who underwent curative-intent surgical resection for ICCA at six institutions between 2009 and 2016. Of these, 264 patients from one institution constituted the development cohort, while 101 patients from the other institutions constituted the external validation cohort. Logistic regression models were constructed to predict ER based on preoperative variables and were subsequently translated into a risk-scoring system. The discrimination performance of the risk-scoring system was validated using external data and compared to the American Joint Committee on Cancer (AJCC) TNM staging system.
Results: Among the 365 patients (mean age, 62 ± 10 years, 229 men), 153 had ER. A preoperative risk scoring system that incorporated both clinical and CT features demonstrated superior discriminatory performance compared to the postoperative AJCC TNM staging system in both the development (area under the curve [AUC], 0.78 vs. 0.68; $p = 0.002$) and validation cohorts (AUC, 0.69 vs. 0.66; $p = 0.641$). The preoperative risk scoring system effectively stratified patients based on their risk for ER: the 1-year recurrence-free survival rates for the low, intermediate, and high-risk groups were 85.5%, 56.6%, and 15.6%, respectively ($p < 0.001$) in the development cohort, and 87.5%, 58.5%, and 25.0%, respectively ($p < 0.001$) in the validation cohort.
Conclusion: A preoperative risk scoring system that incorporates clinical and CT imaging features was valuable in identifying high-risk patients with ICCA for ER following resection.

TOP-094-YI

Breaking barriers: intensive care admission in patients with advanced HCC on immunotherapy

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Background and aims: Intensive Care Unit (ICU) admission is usually denied in patients with advanced hepatocellular carcinoma (HCC) due to the perceived poor prognosis. However, immunotherapy based on immune-checkpoint inhibitors (ICI) has transformed the treatment landscape of these patients. With the increasing use of ICI-based therapies, the role of critical care is becoming more relevant in managing severe adverse events related to this therapy. The outcome of HCC patients requiring critical care requires to be revisited. Our aim is to assess the outcome of patients with advanced HCC treated with IT admitted to ICU.
Method: We evaluated patients treated with ICI combinations across 20 medical centers globally between November 2012 and April 2024. Demographic data, IT types, main causes of admission, organ support, and mortality in the short and medium term were recorded.
Results: Of 1,065 patients, 47 (4.4%) were admitted to the ICU. Most were male (76.6%) with cirrhosis (93.6%), and 59.7% received IT as first-line therapy. The primary reasons for ICU admission were immune-related adverse events (irAE) in 46.8% and variceal bleeding in 29.8%. Median time to ICU admission was 115 days after initiation of IT [38–202], with 51 days [31–137] for irAEs. Half of the patients required organ support, with a median SOFA score of 4 (2–8). ICU

mortality was 25.5%. Two thirds of the patients (66%) were alive 28 days post-ICU discharge, with 3- and 6-month survival rates of 83% and 69%. The 61.3% of survivors were rechallenged with IT or started new HCC therapy.
Conclusion: Immune-related adverse events are the main cause of ICU admission in patients with advanced HCC receiving IT. Despite the severity, 66% were discharged, and nearly half resumed the same cancer therapies. These findings highlight the vital role of ICU care in managing HCC patients, challenging the notion of excluding them from intensive care, and emphasizing the need to identify factors that improve prognosis.

TOP-107
Machine learning approaches for hepatocellular carcinoma risk stratification across various aetiologies
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Background and aims: New tools for HCC early detection are only cost-effective for patients with a high annual incidence exceeding 2%. The aim of this study was to develop Machine Learning (ML) models for risk stratification of HCC in prospective cohorts of patients with compensated cirrhosis and to compare their performance to traditional scoring systems.
Method: Data were collected from the HCC 2000 trial, the ANRS CO12 CirVir and CO22 Hepather cohorts, and CIRRAL cohort. All patients underwent semiannual ultrasound surveillance. The population was divided into a training group (two-thirds) and a validation group (one-third). The cumulative incidence of HCC was estimated within a competitive risk framework. A Fine-Gray regression model was constructed as a reference for comparison with the ML models, alongside the published FASTRAK and aMAP scores. A Single Tree (ST) model was developed using conditional decision tree methodology. Prognostic algorithms were derived using a Random Forest (RF) approach. The discrimination performance of the models was assessed in the validation set using the C-Index, and calibration curves were generated.
Results: 3,671 patients had either non-viral cirrhosis or cirrhosis related to resolved HCV or controlled HBV. After a median follow-up of 37.1 months in the training group, 182 patients (7.5%) developed HCC (1-yr incidence: 2.2%). 75 HCC cases occurred in the validation group (1-yr incidence: 2.4%). Non-viral causes of cirrhosis (alcohol and/or metabolic) were associated with a lower risk of HCC. The ST approach identified six main predictors, generating eight groups based on various combinations of these predictors, each with contrasting HCC risks. The most predictive factor at the root of the tree was age, which divided patients into two main subpopulations. Among younger patients, one group with slightly impaired liver function (despite a compensated status) showed moderate to high risks of HCC, while an extreme phenotype of young patients with resolved HCV infection and elevated GGT levels presented a particularly high risk despite normal liver function. RF models were constructed by aggregating 1,000 decision trees, confirming the results of the single tree analysis and identifying advanced age, GGT levels, thrombocytopenia, and elevated bilirubin as strong predictors of HCC. Comparisons of C-indexes indicated no significant advantage for the ML models over traditional short-term scores, although there appeared to be an improvement in long-term prediction (5-year C-index of 0.76 for RF versus 0.75 for all others). Calibration levels were similar between ML approaches and traditional models in the validation population.
Conclusion: ML algorithms highlight interactions between variables, aid in identifying patient clusters defined by varying risk levels, and highlight "extreme phenotypes" of patients with particularly high risks of HCC.

TOP-108-YI
Prevalence and impact of clinically significant portal hypertension (CSPH) in patients with hepatocellular carcinoma (HCC): a multicenter cohort study on the ITA.LI.CA database
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Background and aims: Clinically significant portal hypertension (CSPH) is an independent predictor for hepatocellular carcinoma (HCC) development and a key prognostic factor, influencing patient access to oncological treatments. This study aims to evaluate the prevalence of CSPH and its impact across different HCC stages according to the Barcelona Clinic Liver Cancer (BCLC) staging system.

Method: A retrospective analysis was conducted on HCC patients registered in the Italian Liver Cancer (ITA.LI.CA) database between January 1987 and December 2022. Patients with HCC in BCLC stage D or stage C without extrahepatic metastasis or macrovascular invasion and those with Child-Pugh score > B7, were excluded. The presence of CSPH in the remaining patients was assessed based on esophageal or gastric varices, tense ascites, or liver stiffness > 25 kPa on elastography.
Results: Of 10,907 total patients, 7,069 were included, with 2,652 diagnosed with CSPH. The prevalence of CSPH was highest in alcoholic etiology and BCLC stage C (44.7%), followed by stages A (39.1%), B (33.9%), and 0 (19.6%). CSPH was associated with reduced survival in the overall population. In univariate analysis, CSPH was linked to worse survival in BCLC stages A, B, and C, but not in stage 0. Multivariate analysis confirmed this association for stages A and B, but not for stage C. Only 9.7% of patients with CSPH were on non-selective beta-blockers (NSBB), and while NSBB use was associated with improved survival in univariate analysis, this effect was not seen in multivariate analysis.
Conclusion: Our study demonstrates that CSPH significantly impacts survival in the early and intermediate stages of HCC, but not in very early or advanced stages. These results may be explained by the milder underlying liver disease (or more frequent access to liver transplantation) in very early stages, or by a greater oncological burden in advanced stages, which may have a largely dominant impact on survival. Our study also shows that CSPH is particularly common in advanced HCC patients, who often require anti-angiogenic therapies that necessitate special precautions precisely due to the presence of CSPH. A further analysis considering subgrouping of BCLC-C according to presence or absence of venous invasion is underway.

WEDNESDAY 07 MAY

WED-083

Role of Child-Turcotte-Pugh and ALBI scores in patients with non-cirrhotic hepatocellular carcinoma

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Background and aims: While the Child-Turcotte-Pugh (CTP) as well as the albumin-bilirubin (ALBI) score represent important clinical tools for risk stratification in patients with cirrhosis and hepatocellular carcinoma (HCC), their prognostic abilities in patients with non-cirrhotic HCC is unclear.
Method: We included two cohorts of patients with HCC. Cohort I (Viennese HCC database) included non-surgical patients with BCLC stage A-C (non-cirrhotic: n = 132, cirrhotic: n = 773), and cohort II included patients with advanced HCC treated with atezolizumab/bevacizumab or durvalumab/tremelimumab from two large international databases (AB-/DT-Real: non-cirrhotic: n = 259, cirrhotic: n = 841). We evaluated the prognostic value of CTP/ALBI for overall survival (OS) by calculating Cox regression analyses as well as time-dependent AUROCs.
Results: Mean age in cohort I was 69 ± 12 in non-cirrhotic and 66 ± 11 years in cirrhotic HCC patients. Further baseline characteristics in the non-cirrhotic/cirrhotic cohorts were as follows: 83%/82% were male, 12%/46% as well as 39%/64% had CTP stage B and ALBI grade II. Most patients were classified as BCLC C (67%/46%). Patients received A/B (89%/89%) and D/T (11%/11%) in cohort II. Mean age was 66 ± 13/66 ± 11 years, 80%/82% were male. While 7%/23% had CTP stage B, 53%/57% had ALBI grade II and 3%/6% grade III. Median OS in cohort I in non-cirrhotic/cirrhotic patients was 19.0 (95%CI, 15.1–24.9)/22.4 (95%CI,

20.6–26.8) months in CTP-A, and 11.5 (95%CI, 3.4-NA)/10.2 (95%CI, 8.0–12.1) months in CTP-B. For ALBI grade I vs. II, median OS in non-cirrhotic/cirrhotic patients was 22.6 (95%CI, 14.6–29.3)/26.2 (95%CI, 21.5–30.7) months vs. 15.3 (95%CI, 11.6–24.7)/12.8 (95%CI, 11.1–14.7). While median OS in cohort II in non-cirrhotic/cirrhotic patients was 14.6 (95%CI, 11.7–19.2)/17.0 (95%CI, 15.6–19.6) months in CTP-A, it was 4.1 (95%CI, 1.8-NA)/7.7 (95%CI, 6.5–9.7) months in CTP-B. For ALBI grade I vs. II, median OS in non-cirrhotic/cirrhotic patients was 20.6 (95%CI, 15.0–23.1)/20.8 (95%CI, 17.8–26.3) months vs. 10.9 (95%CI, 8.9–14.5)/11.1 (95%CI, 9.7–12.6) months. In multivariable Cox regression analyses in non-cirrhotic HCC, CTP-B (cohort I: aHR, 2.65 [95%CI, 1.26–5.57], p = 0.010, cohort II: aHR, 3.24 [95%CI, 1.73–6.08], p < 0.001) and ALBI score (cohort I: aHR, 1.89 [95%CI, 1.11–3.21], p = 0.020, cohort II: aHR, 2.45 [95%CI, 1.71–3.52], p < 0.001) were independently associated with OS. Time-dependent AUROCs in non-cirrhotic vs. cirrhotic patients for CTP at 6 months (cohort I: 0.573 vs. 0.659 & cohort II: 0.679 vs. 0.672) and 12 months (cohort I: 0.538 vs. 0.630 & cohort II: 0.639 vs. 0.692) and ALBI at 6 months (cohort I: 0.598 vs. 0.671 & cohort II: 0.739 vs. 0.692) and 12 months (cohort I: 0.584 vs. 0.659 & cohort II: 0.635 vs. 0.720) were comparable.

Conclusion: CTP and ALBI scores can be used as clinical risk stratification tools in patients with non-cirrhotic HCC, and their prognostic power in non-cirrhotic HCC is comparable to that in patients with HCC and cirrhosis.

WED-084

Added-value of PET imaging to AFP score in predicting HCC recurrence after liver transplantation

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Background and aims: Despite the increasing use of positron emission tomography (PET) imaging in hepatocellular carcinoma (HCC) context, its utility in predicting recurrence post-liver transplantation (LT) is not clear, and PET is not considered among the selection criteria in LT for HCC. We investigated the correlation between HCC recurrence after LT and PET imaging characteristics before LT.

Method: We retrospectively analyzed 346 patients consecutively transplanted for HCC in Hepato-Biliary Center, Paul Brousse Hospital, between January 2017 and December 2023. Among them, 99 patients had available data before LT on 18F-fluorodeoxyglucose PET (FDG PET) and/or choline PET imaging and were included in the study. We collected pre-LT demographic data, characteristics of liver cirrhosis, HCC and PET imaging and post-LT data. At listing, all patients had an alpha-fetoprotein (AFP) score ≤ 2, according to French selection criteria for LT in HCC. Statistical analyses were performed using STATA 15.1 software and SPSS.

Results: The median age of patients was 63 years and 83 were males (83.8%). The main causes of liver cirrhosis were: viral hepatitis (41.4%), alcohol consumption (39.4%), and metabolic (14.1%). The median MELD (Model for End-Stage Liver Disease) score was 12. Most patients (89.9%) had a bridging treatment while waiting for LT. The median waiting time on waiting list was 5.1 months. The median follow-up post LT was of 36 months. 20 patients (20.8%) experienced HCC recurrence post-LT, with a median time to recurrence of 11.6 months post-LT. The 5-year disease-free survival (DFS) was of 57%, and the 5-year overall survival of 66%. Among the 99 patients with available PET imaging data, 44 patients underwent PET imaging before and after bridging therapy. 102 FDG-PET and 78 choline-PET were analysed, of which 27% of FDG-PET and 35% of choline-PET were positive (intrahepatic only), respectively. In these patients, the complete metabolic response to bridging treatment was associated with a better recurrence-free survival post LT (p = 0.047). Net reclassement index, based on AFP score and PET imaging at listing, was of 0.51, p = 0.02. We created a nomogram predicting HCC recurrence risk at listing, including PET features.

Conclusion: In our cohort, the recurrence-free survival after LT in HCC patients is better predicted when adding the PET imaging data to AFP score. We need to validate these data in external cohorts, but this could be an indication of a potential role for PET imaging in better selecting the best HCC candidates for LT.

WED-085

Bone mineral density predicts survival in patients with hepatocellular carcinoma and portal vein tumor thrombosis

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Background and aims: Low bone mineral density (BMD) has emerged as a risk factor in hepatocellular carcinoma (HCC). This study explores the potential of BMD as a prognostic indicator in patients with HCC complicated by portal vein tumor thrombosis (PVTT), which is characterized by an exceptionally poor prognosis.

Method: This retrospective study included 462 patients with HCC and PVTT at our tertiary care center between January 2005 and December 2020. BMD was ascertained by measuring the CT attenuation at the midvertebral core of the first lumbar vertebra using the established cut-off of 160 HU. Analyses were performed at initial HCC diagnosis and PVTT onset. We analyzed the impact of BMD on median overall survival (OS) and conducted multivariate analyses with established survival predictors.

Results: The median BMD was 136 HU (interquartile range [IQR], 113–160 HU) at HCC diagnosis and 134 HU (IQR, 109–159 HU) at PVTT diagnosis. At initial HCC diagnosis, the median OS was 10.4 months in patients with BMD ≥ 160 HU and 5.5 months in those with BMD < 160 HU (P < 0.001). Similarly, at PVTT diagnosis, the median OS was 8.5 months in individuals with higher BMD and 4.7 months in patients with lower BMD (P < 0.001). In multivariate analysis, BMD remained an independent prognostic factor alongside growth type and ALBI grade.

Conclusion: BMD is an independent prognostic marker of survival in patients with HCC and PVTT. Incorporating BMD into existing classification and scoring systems could enhance the accuracy of survival predictions and inform clinical decision-making processes.

WED-086

Clinical evaluation of multimarker algorithmic scores for detection of early stage hepatocellular carcinoma in high-risk liver patients

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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. Biannual ultrasound surveillance with or without a-fetoprotein (AFP) testing is recommended for at-risk patients, but its sensitivity for early stage HCC, for which potentially curative treatments exist, is suboptimal. We compared the clinical performance of GALAD (sex, age, AFP-L3, AFP and Protein induced by vitamin K absence-II (PIVKA-II)) and GAAD (sex, age, AFP and PIVKA-II) [Piratvisuth T, 2022, doi: 10.1002/hep4.1847] algorithms for differentiating early-stage HCC and benign chronic liver disease (CLD) in Japan.
Method: Adult patients ≥20 y.o. were retrospectively enrolled in a single-center, case-control cohort at Ogaki Municipal Hospital from January 1, 2010, to March 31, 2022. Eligible HCC cases had first-time HCC diagnosis confirmed by ultrasound or pathology as per the EASL guidelines. CLD controls had no HCC confirmed by imaging within 6 months. The recruitment we aimed for has a 4:1 ratio of cirrhotic to non-cirrhotic patients, equally representing viral and non-viral etiologies. Cirrhosis was defined as a FIB-4 index⩾3.25. Serum PIVKA-II, AFP and AFP-L3 levels were measured using Elecsys® assays on cobas® e 601. Same samples were also measured for AFP, AFP-L3, and PIVKA-II using the WAKO μTASWako i30 Immunoanalyzer. Established HCC detection cut-offs were 2.47 for GALAD and 2.57 for GAAD scores (range 0–10 for both Cobas algorithms) and –0.63 for μTASWako GALAD.
Results: A total of 902 patients (191 HCC; 711 CLD) were included: mean age 65.09 years, 547 males (61%), 901 of Japanese ethnicity, 704 (38.83%) had cirrhosis. Among HCC patients, 127 (66.5%) had early-stage HCC (BCLC 0/A). GAAD and GALAD algorithms showed similar performance for distinguishing HCC from CLD (area under the curve [AUC] both 85% for early, 96% for late and 89% for all stage HCC). At 90% specificity GAAD, GALAD (both Cobas) and μTASWako GALAD had comparable sensitivity for identifying all-stage HCC (71%(95%CI 0.64–0.77), 71%(0.64–0.77) vs 70%(0.63–0.76)). For early-stage HCC, AUCs were similar across cirrhotic viral 85.1%(78.5–91.7), 85.2%(78.6–91.7) vs 86.3%(80.5–92.2)) and non-viral (80.3%(70.4–90.1), 79.6% (69.7–89.5) vs 87.6%(80–95.3)) as well as non-cirrhotic viral (91.3% (83.7–98.8), 91.3%(83.9–98.7) vs 85.4%(75–95.9)) and non-viral (87.5%(67–100), 87.2%(67.3–100) vs 88.1%(67.5–100)) etiologies.
Conclusion: In a Japanese cohort, GALAD and GAAD showed similar performance in differentiating HCC and CLD controls, irrespective of etiology, presence of cirrhosis and tumor stages. The Elecsys AFP-L3 assay may have negligible impact within the GALAD algorithm. GAAD in vitro diagnostics tool offers a reliable and accurate way to aid the diagnosis of early-stage HCC, and may represent a more convenient alternative to GALAD by using only 2 assays while maintaining the diagnostic performance.

WED-087
Prognosis after resection or ablation of hepatocellular carcinoma: a danish population-based multi-state cohort study

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Background and aims: Hepatocellular carcinoma (HCC) has a high risk of recurrence, highlighting the need for adjuvant therapies to reduce this risk. We aimed to provide a comprehensive multi-state description of the prognosis after curative-intent treatments.
Method: Aarhus University Hospital is one of Denmark's three centers caring for patients with HCC. We offer all treatment modalities available and manage all HCC patients within a population of 1.9 million following EASL guidelines. The data was collected from our electronic patient records. We included all patients diagnosed with HCC between 1 January 2013 and 30 April 2023, and whose initial treatment was resection or ablation with curative intent, possibly in combination with transarterial chemoembolization (TACE). We followed patients from their initial treatment to death or censoring on 31 December 2023. To describe their prognosis, we used a multi-state model consisting of six states: index treatment, recurrence, locoregional (i.e., any non-systemic treatment) treatment post-recurrence, systemic treatment post-recurrence, death without recurrence, and death after recurrence. We used the Aalen-Johansen method to compute cumulative risks and state occupation probabilities, and we used Cox regression to identify prognostic factors.
Results: We included 296 patients (79% men, median age 69 years), of whom 115 were treated with resection and 181 with ablation. The largest tumor treated with ablation alone was 40 mm, and 29 tumors (median size 45 mm, maximum 78 mm) had been treated with ablation + TACE. Overall, the 2-year risk of recurrence was 55%, and the 5-year risk was 70%. Following the first recurrence, 76% received locoregional treatment,12% systemic treatment, and 12% did not receive either treatment. At 5 years after the initial treatment, 10% were alive and recurrence-free; 17% were alive and had experienced a recurrence treated with locoregional but not systemic treatment; 6% were alive and had experienced a recurrence treated with systemic treatment; 19% had died without a recurrence, and 47% had died following recurrence. At 5 years after the first recurrence, 18% were alive and had received locoregional but not systemic treatment; 7% were alive and had received systemic treatment; and 75% were dead. The 1-year mortality after initiation of systemic treatment was 43%. The prognosis was virtually identical for patients treated with resection or ablation: hazard ratio for recurrence for resection vs. ablation = 0.9 (95% CI 0.6 to 1.2) adjusted for sex, age, and presence of cirrhosis.
Conclusion: This population-based study showed that the risk of recurrence is very high after curative-intent treatments, and patients have a markedly higher mortality after a recurrence. Thus, interventions to reduce the risk of recurrence have great potential to reduce mortality.

WED-088
Prognostic influence of clinically significant portal hypertension in patients with compensated cirrhosis and hepatocellular carcinoma receiving systemic therapy: The HIPERIA study

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Background and aims: hepatocellular carcinoma (HCC) typically occurs in patients with cirrhosis, and its prognosis is influenced by both tumour stage and liver disease severity. Clinically significant portal hypertension (CSPH) represents a critical milestone in compensated cirrhosis, being associated with an increased decompensation risk and reduced survival following surgery for HCC. However, its prognostic significance in HCC patients on systemic therapy has not been established. This study investigates the impact of CSPH on overall survival and the systemic treatment window in patients with compensated cirrhosis and HCC.
Method: Multicentre retrospective study of patients with HCC and compensated cirrhosis receiving systemic therapy. The primary objective was overall survival and the secondary one: systemic treatment window, defined as the duration of treatment until symptomatic progression or death. Symptomatic progression was defined as severe hepatic decompensation and/or ECOG PS 3–4, warranting treatment discontinuation at the treating physician's discretion. CSPH was defined based on Baveno VII criteria. Mortality and the treatment window were analysed as time-to-event variables with adjusted hazard ratios (aHR) derived from Cox regression, accounting for prognostic variables (age, etiology of cirrhosis, MELD, ALBI, BCLC stage, and type of systemic treatment). Survival was analysed using Kaplan-Meier curves.
Results: Between January 2015 and January 2023, 663 patients were included (86.6% male, median age 66 years). Main cirrhosis etiologies were HCV (49%) and alcohol (40%). All patients were Child-Pugh A, with a median MELD score of 8, and ALBI grades 1 and 2 in 39% and 61%, respectively. Most patients were BCLC stages was B (39%) and C (56%). Systemic treatments included sorafenib (86.9%), atezolizumab-bevacizumab (7.6%), lenvatinib (3.9%), and nivolumab (1.7%). CSPH was present in 411 patients (62%), and esophageal varices in 280 (42%). The presence of CSPH was independently associated with decreased overall survival [median:13.0 (95%CI: 11.1–14.7) vs. 21.7 (18.8–25.9) months,] with aHR of 1.37 (95%CI: 1.07–1.77, $p = 0.014$). Additionally, CSPH was linked to a shorter treatment duration [median: 10.21 (95% CI: 8.70–11.76) vs. 18.82 (15.89–21.02) months], with aHR of 1.37 (95% CI: 1.05–1.79, $p = 0.02$).
Conclusion: The presence of CSPH stratifies the prognosis of patients with compensated cirrhosis and HCC undergoing systemic treatment. CSPH identifies a population of patients with compensated cirrhosis with poorer survival and a shorter therapeutic opportunity window across the different tumour stages.

WED-089-YI
Development and validation of PSU's AI-assisted ultrasound (AI-US) algorithm for focal liver lesion detection
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Background and aims: Ultrasound (US) is recommended as the primary imaging modality for hepatocellular carcinoma (HCC) surveillance, particularly in patients at high risk due to chronic liver disease (CLD). Current guidelines advocate biannual US surveillance, often combined with serum alpha-fetoprotein (AFP) measurement. However, US has limitations, including inadequate image quality in 20% of cases, operator dependence, and reliance on radiologist expertise, especially in patients with MASLD. AI-assisted US systems are emerging as a promising solution to improve the detection of focal liver lesions (FLLs), including HCC. This study aimed to develop an AI system to identify FLLs in patients with CLD.
Method: We used the YOLOv8 supervised deep learning algorithm. US images were collected from CLD patients, pre-processed by cropping and removing labels, and annotated by two blinded expert radiologists. Radiologists independently classified the images into five groups: normal, cysts, focal fatty sparing (FFS), focal fatty infiltration (FFI), and nodules/masses. Task 1 classified liver-specific images using a YOLOv8m-cls model. Task 2 detected fields of view with a YOLOv8m detection model, ensuring that only relevant areas were cropped for analysis. Task 3 performed multi-label classification of distinct liver lesions using YOLOv8m-cls. The model's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUROC) were evaluated.
Results: The algorithm was trained and tested on B-mode US images from 360 patients (mean age 58.9 ± 13.8 years, 37.1% male, cirrhosis 27.7%, fatty liver 24.2%). Of 3,798 images, 263 were classified as cysts, 308 as FFS, 56 as FFI, and 673 as nodules/masses. The model demonstrated strong performance, achieving an AUROC of 0.9046 for cyst detection, with a sensitivity of 27.59%, specificity of 99.23%, PPV of 53.31%, and NPV of 97.71%. For FFS, the AUROC was 0.8478, with a sensitivity of 55.88%, specificity of 88.89%, PPV of 15.97%, and NPV of 98.16%. For nodules/masses, the AUROC was 0.8355, with a sensitivity of 52.17%, specificity of 94.77%, PPV of 52.17%, and NPV of 94.77%. Normal classification yielded an AUROC of 0.8656. The confusion matrix showed true positive rates of 80% for cysts, 91% for FFS, 66% for nodules/masses, and 95% for normal findings, with minimal misclassification.
Conclusion: The results of this study highlight the potential of deep learning algorithms to assist radiologists in the accurate and efficient diagnosis of FLLs from US images. Incorporating clinical data enhances the performance of the algorithm, making it a valuable tool for improving diagnostic accuracy.

WED-090-YI
The mind and monitoring: The psychological impact of hepatocellular carcinoma surveillance
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Background and aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. HCC surveillance benefits patients with cirrhosis via early cancer detection, resulting in improved survival. There is a paucity of data on the potential harms of surveillance, particularly psychological implications. Baseline rates of anxiety (31.6%) and depression(28.9%) in the HCC surveillance population are nearly fivefold and eightfold higher than the UK population, likely due to comorbidities and pre-existing mental health diagnoses. This study aimed to explore the prevalence of psychological harms associated with HCC surveillance utilising the Hospital Anxiety and Depression Score (HADS), and to determine any potential change in psychological state of patients prior to and on receipt of surveillance.
Method: Administration was at two timepoints: (1) between surveillance episodes and (2) on the day of surveillance scan. We

compared HADS scores and the proportion of patients reaching thresholds for anxiety, depression, and psychological distress between timepoints. Sociodemographic data (sex, age, ethnicity, socio-economic status, aetiology of liver disease, prior mental health status) were obtained from electronic patient records.
Results: Patient demographics were as follows: the majority were male (60%); white (50%); most common aetiology Alcohol Related Liver Disease (44%); median age 61 years. Prior mental health diagnosis was identified in 17 (34%) patients, with the most common diagnosis being mixed mental and behavioural disorders (12%). Participants were asked to complete the HADS twice: firstly, on the day of surveillance ultrasound scan and secondly, at another time point in between surveillance episodes. 50 participants completed the surveillance HADS. 38 participants returned for baseline questionnaire(n = 12 lost to follow up). The prevalence of anxiety, depression and total psychological distress at baseline was 31.6%, 28.9% and 31.6%, respectively. Higher socioeconomic status was associated with prevalence of anxiety at baseline(OR 5.88; 95% CI = 1.30–26.51; p = 0.02). There was no statistical significance in the prevalence of anxiety and depression between timepoints (p = 1.00). Updated results will be presented at meeting.
Conclusion: There was no increase in anxiety or depression on receipt of HCC surveillance. There is a high baseline prevalence of anxiety and depression amongst patients undergoing HCC surveillance. However, this does not appear to be associated with receipt of HCC surveillance itself.

WED-091
Delta hepatitis versus HBV monoinfection associated hepatocellular carcinoma: spot the difference
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Background and aims: Hepatitis delta virus (HDV) was recently proved to be directly carcinogenic on the hepatocytes, via different mechanisms compared to hepatitis B virus monoinfection (HBV), leading to a different hepatocellular carcinoma (HCC) pattern. Hence, our aim was to describe the prevalence of HCC in HDV infection versus HBV alone and to highlight the differences between HCC behaviour in both groups.
Method: A retrospective study was conducted in a Hepatology Tertiary Care Centre. All HBsAg positive adult patients admitted from 1st of January 2021 to 31st of December 2023 were included. Statistics was performed using IBM SPSS 29.0. Patients were split in study group: HBV+HDV+HCC and control group: HBV+HCC.
Results: A total of 679 patients were included. The estimated prevalence of HCC in HDV infected population was 20.8% versus 9.1% in the control group, p = 0.000, with OR = 2.263, CI 1.536–3.333, p = 0.001. Younger patients were found to develop HCC in delta hepatitis (mean ± stdev, 59 ± 8.727 years vs 63 ± 11.28 years, p = 0.027). Patients in the study group have smaller tumors (maximum diameter: 32.66 ± 23.181 mm vs 56.75 ± 38.09 mm, p = 0.002), but with no difference in AFP values (177.24 ± 364.8 ng/ml vs 183.07 ± 336.77 ng/ml, p = 0.941) compared to the control group at HCC diagnosis. BCLC classification (p = 0.001) and AFP Duvoux score (p = 0.001) showed more advanced HCC in HBV monoinfection. Hence, treatment in the study group was predominantly loco-regional whereas in the control group was mainly systemic (p < 0.000). The presence of HCC in HDV infected patients was strongly correlated with advanced liver disease (measured by MELD, MELD Na and MELD 3.0, p = 0.001), higher HBsAg titre (p = 0.001) and lower HBV DNA viral load (p = 0.001).
Conclusion: HCC is more frequent in HDV infected patients, leading to a different HCC pattern, with smaller tumours, less advanced neoplasia and access to curative treatment, compared to HBV monoinfection associated HCC. HDV associated HCC occurs in patients with advanced liver disease, higher HBs Ag titre and lower HBV DNA viral load.

WED-092-YI
Lower allele frequency of the TERT-rs2242652 in sub-saharan african than american populations and hepatocellular carcinoma risk
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Background and aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. The single nucleotide polymorphism (SNP) rs2242652 in the telomerase reverse transcriptase (*TERT*) gene has been linked to a lower risk of HCC in individuals of European descent and Chinese Han populations. In sub-Saharan Africa, the earlier onset of HCC and higher incidence of this cancer suggest a potential role for inherited genetic predisposition or the absence of protective germline factors. In this study, we evaluated for the first time whether *TERT*-rs2242652 is associated with HCC in sub-Saharan African populations from Ghana, Nigeria, and Cameroon, and we compare the finding with a European descent-predominant population from the United States (U.S.).
Method: A total of 537 patients with pathology- or radiology-confirmed diagnosis of HCC were included, comprising individuals from the U.S. (n = 348), Ghana (n = 79), Nigeria (n = 43), and Cameroon (n = 67). The control group consisted of 2,872 cancer-free individuals from the same populations: U.S. (n = 2,399), Ghana (n = 323), Nigeria (n = 85), and Cameroon (n = 65). Whole-exome sequencing (Exome+, Helix, Inc.) was conducted using germline DNA from participants, and data for the *TERT*-rs2242652 were extracted for analysis. Unconditional logistic regression was used to calculate odds

ratios (ORs) and 95% confidence intervals (CIs). Protective allele frequencies (PAF) were assessed with chi-square tests.
Results: In the U.S. cohort, *TERT*-rs2242652 was significantly associated with a lower risk of HCC (OR = 0.75 for AG/AA vs. GG; 95% CI: 0.58–0.96; p = 0.021), with an overall PAF of 18.8% (15.4% in HCC cases vs. 19.3% in controls). In the combined sub-Saharan African population, no significant association was observed; however, a trend towards a decreased risk of HCC was noted (OR = 0.80; 95% CI: 0.53–1.22; p = 0.29), with an overall PAF of 12.2% (10.6% in HCC cases vs. 12.9% in controls). Separate analyses of the Ghanaian, Nigerian, and Cameroonian populations yielded similar non-significant trends with the protective allele and HCC risk. Overall, the PAF of the combined African populations was lower than the U.S. cohort (p < 0.0001 ; PAF = 12.2% in Africans vs. 18.8% in European Americans).
Conclusion: This study is the first to evaluate *TERT*-rs2242652 in sub-Saharan African populations, revealing lower PAF compared to European Americans. The reduced frequency of this protective allele might contribute to the younger HCC onset and higher mortality in sub-Saharan Africa. These findings highlight the importance of conducting diverse, multi-ethnic genetic studies to address disparities in the clinical application of genetic discoveries for HCC prevention, risk stratification, and treatment.

WED-095
Prognostic significance of tumor-associated endothelial B7-H3 expression in hepatocellular carcinoma
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Background and aims: B7-H3 (CD276), a newly identified member of the B7 family, is overexpressed in various solid tumors and acts as a T cell inhibitor that promotes tumor aggressiveness and proliferation. This study evaluated whether tumor or endothelial B7-H3 expression was associated with tumor behavior and prognosis in hepatocellular carcinoma (HCC) following surgical resection.
Method: We included consecutive patients with HCC who had undergone surgical resection (n = 624) or liver transplantation (n = 100) at two tertiary hospitals between 2009 and 2013. Tissue microarray (TMA) was used to assess B7-H3 expression in tumor and adjacent tissues. The primary outcome was overall survival (OS), and the secondary outcome was recurrence-free survival (RFS), analyzed according to B7-H3 expression levels.
Results: Among the 624 patients in the surgical resection cohort, moderate-to-strong B7-H3 expression was observed in 20.7% (129/624) of tumors and 54.8% (342/624) of endothelial tissues. The median follow-up duration was 6.8 (interquartile range [IQR] = 3.3–9.8) years. After balancing baseline characteristics using inverse probability of treatment weighting (IPTW), patients with the moderate-to-strong endothelial B7-H3 expression had significantly worse OS (adjusted hazard ratio [aHR] = 1.58, 95% confidence interval [CI] = 1.17–2.12, *P* = 0.003) and RFS (aHR = 1.33, 95% CI = 1.07–1.64, *P* = 0.009) compared to those with the none-to-weak expression. Similar findings were reproduced in the liver transplantation cohort, where higher endothelial B7-H3 group was indicative of unfavorable outcomes.
Conclusion: High endothelial B7-H3 expression in HCC was associated with aggressive tumor features and poor survival outcomes. Our findings suggest that B7-H3 could serve as a potential therapeutic target in HCC.

WED-096-YI
Diagnostic accuracy of novel serum biomarkers in predicting recurrence of hepatocellular carcinoma: a systematic review and diagnostic test accuracy meta-analysis
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Background and aims: High recurrence rates of hepatocellular carcinoma (HCC) remain a pressing issue, with early detection crucial for timely intervention. Alpha-fetoprotein (AFP) remains the standard biomarker to monitor patients post curative treatment – however, with poor sensitivity, other novel biomarkers have been trialed with varying efficacies. This meta-analysis aims to revisit the diagnostic accuracy of AFP and evaluate the efficacy of other biomarkers including AFP-L3, Protein Induced Vitamin K Absence or Antagonist-II (PIVKA-II) and circulating tumor cells (CTCs) in detecting recurrent HCC.
Method: We conducted a PRISMA-DTA adherent meta-analysis. PubMed, Embase and Cochrane databases were searched from inception to 1 November 2024 for relevant articles. Data on test accuracies of AFP, AFP-L3, PIVKA-II and CTCs were extracted. Prespecified cutoff values for AFP were determined at 0–10 ng/mL, 10–20 ng/mL, 20–50 ng/mL 50–200 ng/mL and 200–1000 ng/mL. For AFP-L3, at 15%. For PIVKA-II, at 40 mAU/ml. For CTCs, at 15 cells. Data at each cutoff were used to calculate the number of true positives, true negatives, false positives, and false negatives. A bivariate model was used to construct summary receiver operating characteristic curves and compute area under curves (AUC), sensitivities and specificities. Meta-regression was performed to explore the influence of patient and tumor factors on pooled sensitivities and specificities.
Results: 36 studies with 6104 patients were included. Sensitivities/specificities of AFP at varying cutoffs were 62.1%/78.1% (0–10 ng/mL), 52%/80.1% (10–20 ng/mL), 65.6%/74.9% (20–50 ng/mL), 50.8%/91.5% (50–200 ng/mL) and 38.6%/83.4% (200–1000 ng/mL). The highest diagnostic accuracy was observed at 50–200 ng/mL (AUC = 0.854). For PIVKA-II, sensitivities/specificities at varying cutoffs were 63.2%/89.1% (< 40 mAU/mL) and 58.5%/82.3% (> 40 mAU/mL). The highest diagnostic accuracy was observed at <40 mAU/mL (AUC = 0.848). For AFP-L3, sensitivity/specificity were 61.6%/89% at cutoff of < 15%. For CTCs, sensitivity/specificity were 67%/79.1% at cutoff of 15 cells. Meta-regression did not reveal any significant interactions between patient and disease factors, and the results.
Conclusion: The sensitivities of biomarkers for predicting HCC recurrence remain suboptimal, with PIVKA-II emerging as a promising non-conventional biomarker. Our results should be used to guide future studies in evaluating the effectiveness of combination of biomarkers. Further studies are necessary to validate these results and develop robust clinical algorithms.

WED-097
Identification of diagnostic markers based on spectral infrared fingerprints of bile samples from endoscopic drainage of patients with biliary stenosis due to extrahepatic cholangiocarcinoma or pancreatic adenocarcinoma
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Background and aims: Bile duct strictures present a diagnostic challenge in distinguishing between benign and malignant etiologies. Malignant strictures are primarily caused by extrahepatic cholangiocarcinoma (CCK) and pancreatic cancer (PK). Histopathology and cytology of bile samples are commonly used diagnostic tools in clinical practice but suffer from low sensitivity despite high specificity. This study aimed to determine whether infrared spectral fingerprints of bile samples could effectively differentiate between malignant and benign biliary obstructions.

Method: The study analyzed 198 bile samples from patients with biliary obstruction, including 39 CCK cases, 53 PK cases, and 106 benign cases. Bile samples were obtained during therapeutic endoscopic retrograde cholangiopacreatography (ERCP). High-throughput infrared spectroscopy (FTIR) was used to analyze the samples, with eight deposits per patient on silicon plates. After spectral acquisition, aberrant spectra were excluded, and the average spectrum for each sample was computed, baseline-corrected, second-derivative transformed, and normalized. Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) were employed as exploratory chemometric methods to analyze the spectral data.
Results: PCA and HCA analyses identified three distinct spectral groups: A group predominantly comprising malignant cases (20 CCK, 32 PK, and 11 benign). A group predominantly comprising benign cases (4 CCK, 0 PK, and 44 benign). An undifferentiated group (15 CCK, 21 PK, and 51 benign). Separate analyses of CCK and PK cases revealed two subgroups: one clearly distinct from benign cases and another undifferentiated. This segmentation may be attributed to cancer severity, intensity and duration of cholestasis affecting bile biochemical composition, and clinico-biological differences between CCK and PK cases.
Conclusion: This study demonstrates the potential of FTIR spectral analysis of bile samples to differentiate between benign and malignant biliary obstructions. However, advanced chemometric analyses are required to enhance diagnostic performance and facilitate the implementation of this method in clinical practice.

WED-098
Predictive microRNA panel of hepatocellular carcinoma occurrence in patients with chronic hepatitis C achieving sustained virological response after direct-acting antiviral therapy

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Background and aims: Direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection results in a sustained viral response (SVR) in over 95% of patients. However, hepatocellular carcinoma (HCC), occurs in 5–7% of cirrhotic patients who achieved SVR during the post-treatment follow-up period and predictive biomarkers have not been completely identified.
Aim of this study is to define a proteomic and microRNA (miRNA) transcriptomic profile to identify cirrhotic subjects after DAA therapy having a higher risk of developing HCC.
Method: Plasma samples were obtained from 8 cirrhotic subjects with sustained virological response (SVR) after direct-acting antiviral (DAA) treatment for HCV infection who developed HCC 1), and who did not develop HCC after therapy 2). Samples were obtained before starting DAA therapy (T0), at the end of the therapy (EOT), and three months after the end of the therapy (TF). Patients were matched for age, gender, and length of follow-up. MiRNA-sequencing and subsequent bioinformatic analysis were performed from total RNA extracted from plasma samples, while, for what concerns the proteomics analysis, LC-MS was precede by depletion and fractionation workflows to account for the large dynamic range f plasma proteins.
Results: among 794 miRNAs isolated, miR-3908 and let7-5f-5p were tendentially modulated at T0, miR-326, miR-484 and miR-98-5p were significantly modulated at EOT (p: 0,039), whereas miR-106b-5p and miR130b-3p were significantly modulated at TF (p:0,045). A survey on existing literature of gene targets from HCC patients' tumor tissues and HCC cell lines revealed that some of the identified miRNAs are potentially correlated to HCC progression. The proteomics results are currently undergoing bioinformatics analysis.
Conclusion The observation of significantly modulated miRNAs at the end of therapy and at follow-up deserves further analysis for a basic understanding of mechanisms of HCC progression as well as prognostic biomarkers.

WED-099
Insights into the GALAD Score: a new optimal cut-off for hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) affects 70–95% of people with chronic liver disease (CLD). Men aged 40 to 60 in Western countries, are more likely to develop HCC. Abdominal ultrasonography (US) is recommended as a semiannual screening method for patients at higher risk of HCC by various international guidelines, whereas serum alpha-fetoprotein (AFP) is inconsistently recommended. HCC surveillance could be improved by combining AFP, AFP-L3, and des-gammacarboxy prothrombin (DCP). These biomarkers, along with age and gender, were combined into an algorithm to create a GALAD score, which has a higher overall accuracy for early detection of HCC than the sum of its component biomarkers. However, no studies have established a standardized GALAD cut-off due to a lack of biomarker value comparisons between healthy people and those with cirrhosis or HCC.
Method: In this cross-sectional and multicenter Italian study with a prospective design, we examined four cohorts (n = 1411) and divided them into steadily (at two different long-term times) healthy individuals (n = 706), compensated liver cirrhosis of any aetiology (n = 511), and HCC (n = 194). These participants were drawn from an Italian historical cohort that included patients from the IRCCS "S. de Bellis" Gastroenterology Department, the University of Modena and Reggio Emilia Gastroenterology Department, and Padua University Hospital.
Results: Healthy subjects were significantly younger (50.79 ± 13.70 years) than those with cirrhosis or HCC (60.16 ± 12.03 and 67.11 ± 9.86 years, respectively). GALAD scores differed significantly between groups, with the healthy group having a lower level of −4.60 ± 1.66 compared to the values of the cirrhosis and HCC groups (−2.03 ± 2.33 and 1.06 ± 4.30, respectively). A GALAD score cut-off of −1.96 was determined, with sensitivity and specificity of 80.41% and 95.18%, respectively. Individuals with GALAD values >−1.96 have a moderate or high risk (approximately 90%) for developing HCC.
Conclusion: GALAD was the most effective score for discriminating HCC among patients with advanced CLD without HCC at a new optimal cut-off implemented for the first time in a large and "steadily healthy" population. We strongly recommend incorporating this cut-off into clinical national/international guidelines for high-risk patients undergoing HCC screening and surveillance.

WED-100

Prognostic value of a composite biomarker score for predicting overall survival in HCC patients

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Background and aims: Despite advances in diagnosis and treatment of Hepatocellular Carcinoma (HCC), its management remains challanging. Tumor stage and liver function, that impact overall survival (OS), currently guide treatment algorithms. Lacking histology in most cases, serum biomarkers might provide additional insights to characterize tumor biology. Alpha-fetoprotein (AFP), Prothrombin induced by vitamin K absence-II (PIVKA-II), and glypican-3 (GPC-3) have been separately used for diagnosis and monitoring, whether their measure can better stratify survival is unknown.
Method: In this retrospective cohort 275 patients admitted at the Hepatology Unit of the Pisa University Hospital and at the Gastroenterology Unit of the Molinette Hospital, Turin with a first diagnosis of HCC had AFP, PIVKA-II, and GPC-3 measured before treatment initiation. Setting pathological cut-offs (AFP > 10 ng/mL, PIVKA-II > 200 mAU/mL, GPC-3 > 100 pg/mL) each patient received a "bio-score" based on the number of elevated biomarkers (0–3). Kaplan-Meier and Cox regression analyses were used to evaluate the relationship between the bio-score and OS.
Results: The bio-score demonstrated a significant association with OS ($p < 0.001$), with higher scores correlating with worse outcomes. Patients with a bio-score of 3 had the poorest survival, while lower scores were associated with progressively better survival rates ($p < 0.001$). We performed a multivariate analysis including bio-score and the main HCC clinical-pathological features: the bio-score emerged as an independent predictor of OS ($p = 0.027$, HR = 5.316 for score of 3), surpassing the predictive power of individual biomarkers. The other independent variables associated with OS at multivariate analysis were the BCLC stage ($p < 0.001$), the presence of ascites ($p = 0.003$), ALBI grade ($p = 0.007$) and the number of lesions ($p = 0.036$).
Conclusion: The combined use of AFP, PIVKA-II, and GPC-3 as a composite biomarker score provides superior predictive accuracy for OS in HCC patients compared to individual biomarkers. This multi-biomarker approach could offer a valuable, noninvasive prognostic tool, allowing for more personalized management of HCC patients based on survival probability. Further studies are recommended to validate this model in larger cohorts.

WED-101

Hepatocellular carcinoma in the MENA region differs in presentation and outcomes: an analysis of 2736 patients from Saudi Arabia, Oman, Egypt and Turkiye

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Background and aims: To examine disease patterns and trends of hepatocellular carcinoma (HCC) from the MENA region, we analyzed an unselected patient (pt) population in the Middle East and North Africa (MENA) region.
Method: This retrospective, non-interventional cohort reports HCC (n = 2736) patterns in pts from Egypt, Oman, Saudi Arabia (KSA), and Turkiye from the period between Jan 2016–Dec 2023. We evaluated disease characteristics, treatment interventions, and median overall survival (mOS) assessed by Kaplan Meir analysis with survival defined as the time from diagnosis to death or last follow-up.
Results: The mean age was 66 ± 12 years, 74.7% were male, 99% were cirrhotic and 70.2% had viral etiology. HCC etiology differed across the region, with hepatitis C virus the commonest in Egypt (76%), whereas hepatitis B virus was more common in Oman (83%), Turkiye (53.9%) and KSA (26.4%). The majority presented with either advanced (BCLC 'C', 32.8%) or end-stage disease (BCLC 'D', 34.7%) or had Child-Pugh B/C (50.5%). Most frequent treatment decisions were transarterial chemo- (TACE) /radio-embolization (TARE) therapies (33.1%), followed by best supportive care (20.8%), ablative therapies (15.1%), systemic therapy (10.6%), resection (8.2%), combined therapies (6.8%) and liver transplantation (LT, 6.1%). Advanced stage (BCLC B/C) presentation was more frequent in KSA (46.6%), followed by Oman (35.6%), Egypt (33.3%), and Turkiye (27.6%), while Child-Pugh C disease was similar across the 4 countries (12.7%, 9.2%, 10.9% and 9.6%, respectively). Curative interventions (LT/resection/ablation) were most frequently undertaken in Oman (59%), followed by Turkiye (38.2%), Egypt (34.2%) and least in KSA (15.7%; $p < 0.001$), while embolization therapies (bland/TACE/TARE) were similar across the countries (34.1%, 33.3%, 33.7%, respectively; $p = 0.314$). Survival differed significantly across the countries, with the shortest mOS in KSA of 25 m (95% CI:18–32), followed by Turkiye 31 m (95% CI:27–

36), Egypt 69 m (95% CI:33–84) and Oman (not estimable; Hazard ratio 5.33 [95% CI:4.54 to 6.27] p < 0.0001).
Conclusion: Presentation of HCC differed significantly across the 4 countries of the MENA region in terms of disease etiology and characteristics, with the majority presenting in advanced stages and decompensated disease. Curative interventions were more common in Oman resulting in improved survival, while advanced stage presentation was common in KSA. Strategies to improve early diagnosis of HCC in routine care are needed across the MENA region to improve disease outcomes.

WED-102-YI

Impact of antibiotic therapy in patients with cholangiocarcinoma treated with chemoimmunotherapy

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Background and aims: Patients with biliary tract cancers (BTC) often require antibiotic therapy before starting systemic treatment that includes an immune checkpoint inhibitor. This study aims to evaluate the prognostic impact of antibiotic therapy administered in the 15 days prior to the start of chemoimmunotherapy in patients with BTC.
Method: The study population included patients with metastatic or locally advanced BTC from western and eastern populations treated with first-line chemoimmunotherapy. The aim of the study is to evaluate the impact of antibiotic therapy in the 15 days prior to starting oncological treatment (AT population) compared to patients who did not receive antibiotic therapy (NAT). Univariate and multivariate analyses were used to evaluate predictive factors for overall survival (OS) and progression free survival (PFS) while prognostic factors were analyzed by univariate and multivariate analysis using Cox regression model.
Results: 666 patients were enrolled in the study: 93 (14%) in AT cohort and 573 (86%) in NAT cohort. In the AT population, the incidence of cholangitis (p = 0.0017), ALT elevation (p = 0.0009), fever (p = 0.0021), decreased appetite (p = 0.0007), itching (p = 0.0081), and rash (p = 0.012) was significantly higher compared to the NAT. The median OS was 15.9 months (95% CI 13.8–18.3) in NAT cohort vs 10.1 months (95% CI 7.9–12.4) in AT cohort (NAT vs AT, HR 0.43,95% CI 0.27–0.70–15.6 p = 0.0006) while median PFS was 8.5 months in NAT cohort vs 5.4 months in AT cohort (NAT vs AT, HR 0.49,95% CI 0.34–0.71 p = 0.0001). Multivariate analysis confirmed the prognostic role of antibiotic for OS and PFS. Finally, NAT cohort showed better overall response rate compared with AT cohort (31.4% vs 20.4%, p = 0.03).
Conclusion: The use of antibiotic therapy in the 15 days prior to starting chemoimmunotherapy is an independent unfavorable prognostic factor for survival in our cohort of patients with advanced BTC treated with cisplatin, gemcitabine and durvalumab.

WED-103
Impact of statin therapy on survival in hepatocellular carcinoma: a single-center study

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Background and aims: Hepatocellular carcinoma (HCC) is the most common liver cancer. HCC incidence and mortality rates continue to rise worldwide. Statins are medications commonly used to reduce cardiovascular events. However, their anti-inflammatory effects have made them a possible option in the treatment of many diseases. The aim of this study was to assess whether statin therapy prior to HCC diagnosis had a positive impact on disease progression and patient survival.
Method: We retrospectively analyzed data regarding patients diagnosed with HCC at our center. Survival outcomes were analyzed using the Kaplan-Meier analysis, log-rank testing, and Cox proportional hazards models.
Results: A total of 136 patients (91.9% male; 36.8% active smokers) were included in our study. Patients had a median age of 67 years (IQR:59–75), BMI:26.1 kg/m² (IQR:23.7–28.7), AFP:203 ng/mL (IQR:66–1003), Child-Pugh score: 6 (IQR:5–7), and MELD-Na score:10 (IQR: 7–13). Statin treatment was prescribed to 23.5% of the patients prior to diagnosis due to elevated cardiovascular risk. At baseline, 70.6% of the patients had cirrhosis, and 25.7% had decompensated disease. Most patients had intermediate (stage B) or advanced-stage (stage C or D) HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system (stage 0: 6%, stage A: 22.4%, stage B: 45.7%, stage C: 18.1%, stage D: 7.8%). Treatment approaches included surgical hepatectomy (25.7%) transarterial chemoembolization (TACE, 47.1%), radioembolization (36%), and immunotherapy (44.5%). The median follow-up period was 24 months (IQR:8–54), with 66.2% of patients experiencing death. Kaplan-Meier analysis revealed that statin use was associated with improved survival (log-rank p = 0.041). Patients receiving statins had a median survival of 51 months (IQR: 23–124), compared to 31 months (IQR: 10–74) for those not receiving statins. In univariate Cox regression analysis, a higher BCLC stage (p < 0.001) and a higher Child-Pugh score (p = 0.002) were significantly associated with an increased risk of death, while statin use (p = 0.047) and the presence of viral hepatitis (p = 0.018) were associated with improved survival. In multivariate analysis, an advanced BCLC stage (aHR = 1.67, 95%CI:1.21–2.33, p = 0.002) and a higher Child-Pugh score (aHR = 1.24, 95%CI:1.02–1.52, p = 0.034) were independently associated with increased risk of death, whereas statin use was independently associated with improved survival (aHR = 0.37, 95%CI:0.14–0.95, p = 0.04).
Conclusion: Statin treatment prior to HCC diagnosis had a positive effect in overall patient survival. Further research is needed to determine whether statin therapy can prevent tumor progression in HCC patients, and its potential role in preventing the development of advanced chronic liver disease.

WED-104
Surrogate survival endpoint in hepatocellular carcinoma patients on first-line Atezolizumab-Bevacizumab: RECIST 1.1 vs modified RECIST

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Background and aims: Although modified RECIST (mRECIST) criteria have been recommended for evaluating response in hepatocellular carcinoma (HCC) patients receiving systemic therapy, the superiority of mRECIST to RECIST 1.1 is unclear. We aimed to compare the correlation of RECIST 1.1 and mRECIST with overall survival (OS) in HCC patients receiving first-line atezolizumab and bevacizumab (Atezo/Bev).
Method: This retrospective study analyzed HCC patients with at least one liver target lesion who received first-line Atezo/Bev between June 2020 and December 2022 at a tertiary center. Two radiologists evaluated responses using RECIST 1.1 and mRECIST, including best overall and target lesion responses. OS was compared by Kaplan-Meier analysis and log-rank tests. Subgroup analysis was performed for patients with liver-only target lesions.
Results: The study included 207 patients (171 men; median age, 63 years). Median OS was 10.7 months, with 152 deaths. mRECIST identified a higher overall response rate than RECIST 1.1 in all patients (44.0% vs. 16.9%) and in the 144 patients with liver-only target lesion (47.2% vs. 16.0%). Both RECIST 1.1 and mRECIST could stratify OS in all patients and in the liver-only target lesion subgroup. Multivariable analysis of this subgroup, however, found that, RECIST 1.1-based overall and target responses were independently associated with OS, while those of mRECIST were not. mRECIST-target responders

classified as RECIST 1.1-target progressors showed similar OS to target non-responders by both methods (8.1 vs. 9.1 months; p = 0.86) in the liver-only target lesion subgroup.
Conclusion: Both RECIST 1.1 and mRECIST can stratify OS in HCC patients receiving Atezo/Bev, but RECIST 1.1 is more reliable and correlates better with survival than mRECIST in patients with liver-only target lesions.

WED-106

Impact of metformin on the prevention of hepatocarcinoma in chronic hepatitis C with advanced fibrosis after sustained virologic response

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Background and aims: Metformin could show protective effects on the development of hepatocellular carcinoma (HCC) in chronic hepatitis C with advanced fibrosis after sustained virologic response (SVR) by enhancing immune response and modifying tumor metabolism. Using a Random Forest-based machine learning model, we evaluate the protective role of metformin in HCC adjusted for other HCC-associated risk factors.
Method: A Random Forest model was used for the prediction of HCC in chronic hepatitis C with advanced fibrosis after SVR. This method, based on an aggregation of binary decision trees, allows handling complex data and detecting nonlinear patterns. To interpret the importance of each variable in risk prediction, SHAP (SHapley Additive exPlanations) values were used to decompose the impact of each factor in the model. The database had 365 patients (FIB4 index > 3.25) in whom information was collected on demographic, clinical and biochemical factors, such as age, sex, smoking, alcohol consumption, clinically significant portal hypertension (CSPHT), type 2 diabetes mellitus, aspartate aminotransferase, alanine aminotransferase and platelet levels, international normalized ratio (INR), FIB4 index and metformin use. Results were compared for all patients, and subsets of patients with and without CSPHT (192 and 173 patients).
Results: The Random Forest model achieved an area under the curve of 0.72 for all patients. SHAP values revealed that factors such as increased FIB4, decreased platelet count, smoking, male sex and age have a significant impact on the development of HCC. Metformin treatment is associated with a reduced likelihood of developing HCC in patients with CSPHT. This finding suggests a possible protective effect of metformin in chronic hepatitis C with advanced fibrosis after SVR. For patients with CSPHT, the reduction in risk attributable to metformin is 8% with an OR 0.67 [0.65–0.68], while for the entire data set the attributable risk is 11% with OR 0.71 [0.70,0.73] and has little impact in those without CSPHT with attributable risk 2% and an OR 0.89 [0.88–0.90].
Conclusion: Using Random Forest, it is possible to generate predictive models of HCC development in patients with advanced fibrosis after SVR. The application of SHAP values provides a valuable tool for the clinical interpretation of complex predictive models. The results suggest that metformin could have a protective effect in those patients with FIB4 > 3.25 and CSPHT, which may be relevant for risk stratification and the development of preventive strategies. These findings may contribute to the development of personalized interventions in patients at risk of developing HCC.

WED-111

Use of a cGPT 4.0, a large language model in grading the Barcelona clinic liver cancer (BCLC) prognosis for patients referred for hepatocellular carcinoma management

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Background and aims: Large Language Models (LLMs) such as chatGPT (cGPT) are advanced artificial intelligence models. They were developed for natural language processing and have been helpful in classifying information for medical professionals. The Barcelona Clinic Liver Cancer (BCLC) staging system is a classification system for hepatocellular carcinoma (HCC) that stratifies the prognosis for patients to guide treatment decisions; they are used frequently in multi-disciplinary meetings. We aimed to determine the feasibility of using cGPT to determine the BCLC prognostic score for patients referred to an oncology clinic for hepatocellular carcinoma management.
Method: We evaluated 98 Oncology outpatient clinic visit notes in a tertiary centre where patients were referred for Hepatocellular carcinoma. Utilising redacted clinic notes from the visit, cGPT 4.0 was used to iterate through the dataset to extract pre-determined parameters relevant to the BCLC score. A rule-based algorithm was used to summarise the results with the suggested BCLC grading. The results generated by cGPT were studied qualitatively to assess for usefulness, validity and potential limitations.
Results: Out of 98 cases, 92 cases had valid results. 80% of the patients had preserved hepatic function. Majority of the patients (68%) had been classified as BCLC C, mainly due to vascular invasion. Qualitatively, the cases were summarised succinctly with headers for tumour characteristics, hepatic function and functional performance status relevant to decision making. Limitations included a "best guess" approach taken by cGPT. Notably, only 3 out of 98 cases in the data set contained the word "encephalopathy", while preserved hepatic function was often assumed based on serology and imaging results.
Conclusion: This serves as a proof-of-concept study in utilising cGPT in guiding BCLC grading, where concise summaries aid clinical decision making. While LLMs may work as tools to assist clinicians, we must be aware of potential pitfalls relating to the interpretation of results.

WED-112

Tumor burden score as a surrogate prediction marker in patients with hepatocellular carcinoma: prognostic role of performance status

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Background and aims: Size and number are major determinants of tumor burden in hepatocellular carcinoma (HCC). Recently, tumor burden score (TBS) was proposed to evaluate the extent of tumor involvement. On the other hand, the Eastern Cooperative Oncology Group (ECOG) performance status plays an important role in HCC treatment. However, the relationship between TBS and different performance status has not been evaluated in HCC. This study aimed to assess the role of HCC patients with different TBS and performance status.
Method: A total of 4185 treatment-naïve HCC patients were retrospectively analyzed. Multivariate Cox proportional hazards model was used to determine independent prognostic predictors.
Results: Tumor burden score tended to increase in poor performance status in study patients. There was significant survival difference between low, median and high tumor burden score in difference performance status groups (all P value< 0.001). In Cox model analyze, elderly, serum albumin <3.5 g/dL, serum bilirubin >1.1 mg/dL, serum creatinine ≥ 1.0 mg/dL, serum α-fetoprotein (AFP) level > 20 ng/mL, presence of ascites, presence of vascular invasion, performance status 1 to 2, performance status = 3 to 4, medium TBS and high TBS, were independently associated increased mortality in these patients. All P value < 0.001. In subgroup analyze of different performance status, higher tumor burden score is independently associated increased mortality in patient with ECOG = 0 and ECOG = 1–2.
Conclusion: Tumor burden score is a feasible new prognostic surrogate marker of tumor burden in HCC and can well discriminate survival in patients with different performance status.

WED-113
Targeted immunotherapy combined with TACE for conversion therapy of unresectable hepatocellular carcinoma: metabolomic biomarker insights
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Background and aims: Hepatocellular carcinoma (HCC), accounting for most liver cancer cases, presents significant treatment challenges when unresectable. Conversion therapy has emerged as a promising approach to downstage tumors, allowing for subsequent surgical resection. This study investigates metabolic biomarkers associated with the response to a combination therapy involving targeted immunotherapy and transcatheter arterial chemoembolization (TACE) for unresectable HCC, aiming to enhance precision in predicting therapeutic outcomes.
Method: Using untargeted metabolomics based on liquid chromatography-tandem mass spectrometry (LC-MS/MS), we analyzed serum samples from HCC patients undergoing combination therapy. We applied untargeted metabolomics analyses to identify significantly changed metabolites (SCMs). Receiver operating characteristic (ROC) analysis was conducted to evaluate the potential of key metabolites as non-invasive biomarkers for treatment response.
Results: A total of 44 significantly changed metabolites (SCMs) were identified, with 6 upregulated and 38 downregulated in patients who responded favorably to conversion therapy. The identified metabolic pathways with significant involvement include lipid metabolism, porphyrin metabolism, and arachidonic acid metabolism. ROC analysis highlighted several metabolites with high discriminatory power for predicting therapeutic responses in HCC. Among the upregulated metabolites were PC(16:0/20:4(5Z,8Z,11Z,14Z)), MG (18:1/0:0/0:0), Protoporphyrinogen, and Lys-Tyr-Ile-Glu. Downregulated metabolites included 9-OXO-11α,15S-DIHYDROXY-PROSTA-5Z,13E-DIEN-1-OIC ACID, (4-ACETYLAMINO) PHENYL ESTER, and Phe-Tyr-Gln-Lys.
Conclusion: This study identifies crucial metabolic pathways, particularly involving lipid and porphyrin metabolism, associated with the efficacy of combination therapy in downstaging HCC. The findings offer valuable insights into metabolic markers that may facilitate personalized treatment approaches and enhance conversion therapy outcomes in unresectable HCC.

WED-114
Outcome in patients with liver cirrhosis and hepatocellular carcinoma : comparing MRI and ultrasound for HCC surveillance
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Background and aims: Hepatocellular carcinoma (HCC) represents the fifth most prevalent malignancy globally, predominantly affecting patients with liver cirrhosis. International guidelines recommend bi-annual screening by ultrasound (US), although MRI has shown better sensitivity to detect small HCC lesions (< 2 cm). In 2018, HCC surveillance protocol changed at the study institution from a bi-annual US screening to annual MRI-based HCC surveillance protocol. The aim of this retrospective study was to compare patient outcomes in patients with HCC who underwent either MRI or US screening.
Method: Consecutive patients with liver cirrhosis who developed HCC between 2009 and 2023 at a single institution (MST) in the Netherlands were selected for analyses. All radiologic reports were evaluated, in addition to demographic and disease-specific data, and treatment and survival outcomes. The MRI surveillance protocol included T1 in and out of phase, T2, diffusion weighted and contrast enhanced imaging (abbreviated MRI protocol). In case of dysplastic noduli (LIRADS L3 and L4), MRI surveillance changed from an annual to a bi-annual screening module.
Results: Sixty-one patients with liver cirrhosis who subsequently developed HCC were included in this study; 29 (48%) patients underwent US screening (US-HCC) and 32 (52%) MRI screening (MRI-HCC). There were no significant differences at baseline between US-HCC and MRI-HCC patients, including MELD score (mean ± SD: 9.8 ± 3.6), child-pugh score (6.2 ± 1.3) and decompensation events (in 25 (41%) patients). The mean radiologic surveillance period was 3.83 ± 2.95 years before HCC. Annual screening frequencies were 2.28 ± 1.40 MRI/yr in MRI-HCC patients and 1.82 ± 0.64 US/yr in US-HCC patients (NS). MRI screening led to increased detection of dysplastic noduli ($p < 0.01$) as seen in 24 (75%) of 32 MRI-HCC patients. At time of HCC diagnosis, MRI-HCC patients had smaller HCC lesions than US-HCC patients (20.3 ± 10.5 mm versus (26.0 ± 12.7 mm, $p < 0.01$) and lower AFP values (8.27 ± 10.93 μg/l, versus 33.14 ± 67.96 μg/l, $p < 0.01$). A greater number of curative treatment options were observed in the MRI-HCC patients (MRI-HCC: 22 (69%), versus US-HCC: 15 (52%), $p = 0.88$). Overall, the benefits of MRI screening resulted in improved patient survival in MRI-HCC patients when compared to US-HCC patients after HCC diagnosis (i.e. at 1 year; 91% versus 68%, and at 5 year 62% versus 12%, $p < 0.001$).
Conclusion: Our study findings suggest clear clinical benefit of MRI screening when compared to US screening for HCC detection in cirrhotic patients, reflected by smaller HCC lesions at diagnosis, improved treatment options and prolonged patient survival. These study findings warrant further investigation to facilitate MRI screening as a routine diagnostic tool for patients with liver cirrhosis.

WED-115
Differential gene expression in hepatocellular carcinoma: a bioinformatic approach to correlate with HIF1A
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Background and aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and has one of the highest mortality rates worldwide. The hypoxic microenvironment contributes to treatment resistance and a more aggressive tumor phenotype. The cellular response to hypoxia is primarily regulated by hypoxia-inducible factor 1 alpha (HIF-1 alpha), which plays a crucial role in diverse tumoral processes. We aimed to identify differentially expressed genes (DEGs) in human HCC samples, examine their association to these tumor-related processes, and assess their potential correlation with HIF1A and the survival outcomes of HCC patients.
Method: We identified key tumor processes involving HIF1A, comparing its expression in HCC samples and analyzing its impact on overall survival (OS) in HCC patients. A screening of gene expression profiles from tissue samples of HCC patients in the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database resulted in 149 datasets. Thus, 54 provided general data on HCC samples, and after screening by gene expression data, 37 datasets were selected. Despite that 17 of them focused on tumor vs. non-tumor HCC samples, only 13 included gene symbols and were analyzed with GEO2R tool. Three datasets with the highest number of DEGs were selected for their functional analysis using GeneCards database and a Venn diagram, followed by research of the relationship between DEGs and HIF1A by TNMplot, and their association with the OS of HCC patients through Kaplan-Meier plotter.
Results: TNMplot database showed a significant increase in HIF1A expression in tumor vs. non-tumor HCC samples. Kaplan-Meier plotter database revealed a significant association between HIF1A overexpression and reduced OS in HCC patients, linked to angiogenesis, energy metabolism, and immune evasion. Analysis of the three gene expression profiles selected indicated that 10, 160 and 38 DEGs in HCC samples were respectively involved in the above processes, where the correlation with HIF1A was particularly strong. Finally, Kaplan-Meier OS analysis demonstrated that overexpression of 5 DEGs most correlated with HIF1A was associated with HCC prognosis, according to their positive or negative connection with HIF1A.
Conclusion: HIF-1 alpha is related to a worse prognosis in HCC patients. Its functional importance in angiogenesis, energy metabolism and immune evasion makes this factor a crucial therapeutic target for future treatments.

WED-116

Statin and its effects on hepatocellular carcinoma risk and liver fibrosis in chronic liver disease

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Background and aims: Hepatocellular carcinoma (HCC) incidence is rising globally, driven by metabolic and alcohol-related liver diseases. Statins may mitigate liver fibrosis progression, a key precursor to HCC, through anti-inflammatory and antifibrotic mechanisms. This study evaluated the association between statin use and risks of HCC and hepatic decompensation, with an emphasis on liver fibrosis progression.
Method: A historical cohort study was conducted using the Research Patient Data Registry (2000–2023), including 15,525 adults aged ≥40 years with chronic liver disease (CLD) and baseline FIB-4 scores ≥1.45. The cohort comprised 3,146 statin users and 12,379 nonusers. Statin use was defined as ≥30 cumulative defined daily doses (cDDDs). Outcomes included 10-year cumulative incidence of HCC and hepatic decompensation, as well as liver fibrosis progression, defined as a ≥25% sustained increase in FIB-4 score from baseline. Inverse probability treatment weighting method was applied for covariate adjustment, and competing risks were addressed using subhazard ratios (aSHRs) for comparison of the HCC risk between statin users and nonusers.
Results: Statin users had significantly lower 10-year cumulative incidence of HCC (4.8% vs. 9.3%; risk difference [RD], −4.5%; 95% CI, −5.7 to −3.2) and hepatic decompensation (12.9% vs. 23.1%; RD, −9.9%; 95% CI, −11.8 to −8.0). Statin use was associated with a 42% reduction in HCC risk (aSHR, 0.58; 95% CI, 0.40–0.83) and a 28% reduction in hepatic decompensation risk (aSHR, 0.72; 95% CI, 0.62–0.84). Among 9,403 patients with serial FIB-4 data, statin users showed significantly lower fibrosis progression rates (59.9% vs. 64.6%, $p < 0.001$) and stable FIB-4 scores, while nonusers exhibited significant increases. These effects were more pronounced among patients with advanced fibrosis. Lipophilic statins demonstrated greater reductions in HCC risk compared to hydrophilic statins.
Conclusion: Statin use, particularly lipophilic statins and longer durations of therapy, is associated with reduced risks of HCC and hepatic decompensation in patients with CLD. These benefits are likely mediated by attenuation of fibrosis progression, suggesting a potential role for statins as chemopreventive agents in liver disease.

WED-117

Challenges and adherence to hepatocellular carcinoma screening program in patients with advanced chronic liver disease

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Background and aims: Hepatocellular carcinoma (HCC) is a major global health issue among patients with Advanced Chronic Liver Disease (ACLD). International guidelines recommend biannual ultrasound (US) screening for HCC in cirrhotic patients classified as Child-Pugh (CP) A and B, as well as those listed for transplant with CP C. However, global adherence to screening programs remains low. This study aims to assess adherence to HCC screening among patients with ACLD, identify factors contributing to non-adherence, quantify the diagnostic yield of HCC screening, and evaluate the impact of adherence on early detection of HCC.

Method: This retrospective observational cohort study included adult patients with ACLD consulted during the year of 2022 at a tertiary hospital's Liver Unit in Portugal. Patients with an ECOG performance status of ≥ 3, CP C patients not eligible for liver transplant, patients with a previous diagnosis of liver cancer or metastatic liver disease, and those under personalized surveillance for previously identified liver nodules were excluded. Adherence to screening was defined as having two imaging tests within an interval of 150 to 210 days. Adherence rates, reasons for non-adherence, and the incidence of HCC during one year of screening were analyzed.
Results: A total of 621 patients were included for analysis after applying the inclusion and exclusion criteria. The global adherence rate to HCC screening was 54.8%, with a median interval between screening events of 189 days among adherent patients. In the remaining sample, hospital-related factors (41.6%), patient-related factors (29.9%), and hepatologist-related factors (28.5%) were identified as primary barriers to adherence. Lack of social/family support significantly increased the likelihood of non-adherence. However, the adherence rate among hepatologists was 87.1%. During US screening, 77 patients were identified with liver nodules, of which 20.8% (n = 16) were confirmed as HCC. Most HCC cases (10 out of 16) were confirmed after computed tomography (CT) scan, although 25 out of 60 patients who underwent CT required additional tests for clarification (22 magnetic resonance imaging; 3 biopsy). Despite higher odds for earlier BCLC stages at diagnosis among adherent cases, statistical significance was not achieved.
Conclusion: This study underscores the challenges in achieving optimal adherence to HCC screening among patients with ACLD. Factors related to the hospital, hepatologist, and the patient contribute to non-adherence. Addressing these barriers by improving hospital administrative processes, implementing alerts for attending hepatologists, providing patient reminders, and educating patients for the benefits of screening, is crucial. The overall adherence rate and the high adherence from the attending hepatologists in our study highlight the benefits of follow-up in dedicated liver units.

WED-118-YI
Shifting etiologies and emerging metabolic factors of hepatocellular carcinoma from 2005 to 2020: a german nationwide population-based study

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Background and aims: Hepatocellular carcinoma (HCC) is the most frequent primary malignant liver disease and it is associated with complications that ultimately lead to a high mortality rate. Liver cirrhosis represents the main risk factor for HCC development. However, the underlying etiologies of liver cirrhosis have shifted in the last decade. Therefore, in this German population-based study, we aimed to assess the effects of the changing etiological trends on HCC.
Method: 393,230 admissions of patients with HCC from 2005 until 2020 were included using the diagnosis-related-groups (DRG) system based on ICD and OPS codes. We focused concretely on the investigation of underlying etiologies and cardiometabolic risk factors associated with HCC development, as well as the all-cause in-hospital mortality rate of these patients. Trends were analyzed using linear regressions or Mann-Whitney U-tests.
Results: The number of recorded admissions of patients with HCC increased significantly during the last 16 years, rising by 21.8% from 19,594 in 2005 to 23,861 in 2020. However, the overall in-hospital mortality rate of these patients decreased notably from 13.4% in 2005 to 10.5% in 2020.
The most common underlying etiology in admissions with HCC was alcohol-related liver disease (ALD), accounting for 55.5% from HCC etiologies. Among non-alcoholic etiologies, viral hepatitis was the most prevalent (32.3%), followed by metabolic dysfunction-associated steatohepatitis and steatotic liver disease (MASH/MASLD), which represented 4.5% of etiologies. Notably, during the observed period patients with MASH/MASLD exhibited an increase of 3.7-fold in hospital admissions, the strongest growth among all etiologies. Additionally, admissions of patients with ALD raised by 22.8%, from 4,008 in 2005 to 4,921 in 2020, while their in-hospital mortality rate was reduced by 23.0%. In contrast, viral hepatitis showed a significant decrease in admissions, from 3,532 in 2005 to 1,580 in 2020, along with a 7.3% reduction in in-hospital mortality rate. Throughout the observational period, all cardiometabolic risk factors showed a significant increase in patients with HCC ($p < 0.001$). Remarkably, arterial hypertension, cardiac insufficiency, and dyslipidemia appeared to be significantly more associated with a higher risk of HCC diagnosis in non-cirrhotic admissions. Furthermore, HCC patients exhibited a greater burden of metabolic comorbidities compared to those with other malignancies.
Conclusion: This nationwide study highlights the increasing prevalence of ALD, MASLD and metabolic risk factors in patients admitted with HCC. Especially, metabolic risk factors seem to play a significant role as drivers of HCC development, even in absence of cirrhosis, emphasizing the need to specifically address these factors in future investigations.

WED-119-YI
Increasing prevalence of hepatocellular carcinoma in the Netherlands: changing etiologies, tumor characteristics and survival rates

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Background and aims: Hepatocellular carcinoma (HCC) represents a major health problem with its causes shifting from viral to non-viral, particularly metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to 1) investigate the etiology, tumor characteristics and survival rate of HCC in the Netherlands, and 2) study the association of screening and tumor characteristics and survival rates.
Method: Consecutive patients registered with a newly diagnosed HCC from 2014–2021 in the Netherlands Cancer Registry (NCR) were included. Data was gathered by trained registration clerks approximately nine months after diagnosis. Data on screening was available from January 2017 onward.
Results: Between 2014 and 2021 (n = 5,821), HCC diagnoses in the Netherlands increased 1.5-fold, with MASLD-related HCC increasing 2.43-fold. Cirrhosis was absent in 24.3% of patients overall and 14.8% of patients with MASLD-related HCC. Cirrhosis status was unregistered in many cases (27.8 and 14.8%, respectively). Overall median survival duration was 304 (IQR: 71–844) days. Multivariable Cox regression analysis showed better survival for patients with MASLD-related HCC compared to alcoholic liver disease (ALD)-related (HR: 0.70, 95% CI: 0.62–0.79) and for patients without cirrhosis compared

to with cirrhosis (HR: 0.81, 95% CI: 0.73–0.90). Between 2017 and 2021, 14.1% was diagnosed through screening. Screened patients had smaller tumor diameters (28 (IQR: 20–43) vs. 74 (IQR: 40–116) mm) and better survival probability (HR: 0.60, 95% CI: 0.52–0.69) than those presenting with disease complaints.
Conclusion: The prevalence of HCC is increasing in the Netherlands, partly driven by MASLD. Overall survival is poor but patients with MASLD-related HCC and those without cirrhosis have better survival probability. Patients diagnosed through screening had smaller tumors and better survival probability.

WED-120-YI
Machine learning-based survival analysis and risk stratification for patients with cholangiocarcinoma
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Background and aims: To identify prognostic factors for patients with cholangiocarcinoma (CCA) and assess the performance of novel machine learning (ML)-based survival analysis models in predicting outcomes and stratifying risk.
Method: A total of 693 treatment-naïve CCA patients diagnosed at Taipei Veterans General Hospital from 2014 to 2022 were retrospectively analyzed. Patients were randomly divided into a training cohort (n = 485) and a validating cohort (n = 208). The primary endpoint was overall survival (OS). Non-invasive biomarkers and image features obtained at diagnosis were analyzed using a Cox proportional hazards model to identify independent prognostic factors. Prognostic models were developed in the training cohort using Extreme Gradient Boosting (XGBoost), Random Survival Forest (RSF), Decision Tree (DT), and Logistic Regression (LR). Model performance was validated in the validation cohort and compared based on predictive parameters (accuracy, precision, recall and F1-score) and AUROC. Shapley Additive Explanations (SHAP) were used to identify key predictors in the ML-based models. Kaplan-Meier (KM) survival analysis was performed to validate the ability of the models to stratify patient risk groups.
Results: After a median follow-up of 33.0 months (interquartile range 29.6–36.4 months), 480 patients had died, with a 5-year OS rate was 12.0%. Independent risk factors for OS included advanced tumor stage, intrahepatic CCA, lack of treatment, non-surgical modalities, prothrombin time international normalized ratio (PT INR), serum cancer antigen 19–9 (CA 19–9) levels, serum gamma-glutamyl transpeptidase (GGT) levels, albumin-bilirubin (ALBI) grade, and fibrosis-4 (FIB-4) grade. Among the models, RSF demonstrated the best performance in predicting OS (AUROC 0.791, 95% CI: 0.717–0.865), outperforming XGBoost, DT, and LR. SHAP analysis highlighted surgery, advanced tumor stage, absence of treatment, serum GGT, and CA 19–9 levels as the top five predictors in the RSF model. KM survival analysis confirmed the RSF model's robust ability to stratify patients into distinct risk groups ($p < 0.001$).
Conclusion: Machine learning-based survival analysis, particularly the Random Survival Forest, provided accurate prognostic predictions and risk stratification for CCA patients. These tools could support individualized treatment planning and optimize disease management strategies.

WED-121
Comparison of clinical characteristics, risk factors and prognosis of HCC patients with lean and non-lean MASLD undergoing surgical resection
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Background and aims: Lean and non-lean metabolic dysfunction-associated steatotic liver disease (MASLD) exhibit distinct pathophysiological mechanisms and clinical characteristics, potentially affecting the prognosis of patients with concurrent hepatocellular carcinoma (HCC) differently. This study aimed to evaluate and compare outcomes and risk factors associated with overall survival (OS) and recurrence-free survival (RFS) in HCC patients with lean and non-lean MASLD undergoing surgical resection.
Method: This retrospective study included 410 HCC patients with MASLD who underwent surgical resection at Taipei Veterans General Hospital between 2016 and 2022. Patients were classified into lean MASLD and non-lean MASLD groups based on a BMI cutoff of 23 kg/m². Baseline demographics, serum biochemistry, imaging features at diagnosis, and pathological data from hepatectomy specimens were analyzed. Cox proportional hazards models were used to identify prognostic factors for OS and RFS. Kaplan-Meier survival analyses were performed to compare outcomes of the two cohorts.
Results: Lean MASLD patients exhibited smaller tumor sizes, lower serum albumin levels, higher fibrosis-4 (FIB-4) scores, and less fatty change in the non-tumorous liver compared to non-lean MASLD patients. After a median follow-up of 60.4 months, 79 patients had died, and 168 patients had HCC recurrence. The 5-year OS rates were 66.9% for lean MASLD and 79.4% for non-lean MASLD ($p = 0.150$), with no significant difference in RFS between groups ($p = 0.809$). Independent risk factors for poor OS in the lean MASLD group included lower serum albumin levels and larger tumor size. In the non-lean MASLD group, additional factors such as FIB-4, histological grade, and the presence of steatohepatitis significantly impacted OS. For RFS, prothrombin time international normalized ratio (PT INR), serum aspartate aminotransferase (AST), alpha-fetoprotein (AFP) levels, and microscopic small vessel invasion were significant prognostic factors in the lean MASLD group, while alanine aminotransferase (ALT), tumor number, Ishak modified histology activity index (HAI) score, and microscopic small vessel invasion were significant in the non-lean MASLD group.
Conclusion: HCC patients with lean and non-lean MASLD who underwent surgical resection demonstrated distinct clinical and pathological features, with different prognostic factors for poor OS and RFS. Despite these differences, the long-term outcomes in terms of OS and RFS were comparable between the two groups.

WED-123
Prognostic significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in hepatocellular carcinoma: a retrospective multicentre study on overall survival following hepatectomy or orthotopic liver transplantation
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Background and aims: Local and systemic inflammation are recognized as hallmarks of cancer, playing a critical role in the pathogenesis and progression of hepatocellular carcinoma (HCC). Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as potential prognostic indicators in HCC patients undergoing hepatectomy or liver transplantation. This study aimed to evaluate the prognostic significance of NLR and PLR in predicting overall survival (OS) among patients with HCC treated with either hepatectomy or orthotopic liver transplantation (OLT).
Method: We conducted a multicentre retrospective cohort study involving 74 individuals diagnosed with HCC (64 males; 86.5%). The mean age at diagnosis was 62.3 ± 10.2 years, with a mean MELD-Na score of 9.3 ± 15.9. A viral etiology was identified in 42 HCC patients (56.8%). Of the participants, 48 (64.9%) underwent hepatectomy, and 26 (35.1%) met the Milan criteria and received OLT. Baseline and longitudinal parameters were evaluated as potential prognosticators of overall survival (OS) using Cox proportional-hazards regression, both unadjusted and adjusted for surgical procedures (hepatectomy and transplantation), and BCLC stages (0/A vs. B/C). The performance of binary classifiers was analyzed using ROC curves. Repeated-measures ANOVA was applied to compare longitudinal data. Statistical analyses were conducted with SPSS 26.0.
Results: The most prominent predisposing factor for HCC development was chronic HBV infection, affecting 33 patients (44.6%), followed by MASH-related HCC (N = 21, 28.4%). At diagnosis, most patients had a very early (BCLC stage 0) or early stage (BCLC stage A) HCC (48 cases; 64.9%). The overall 30-day mortality rate was 8.1%. The pre-surgery PLR was a significant prognosticator for Clavien-Dindo classification ≥ 3 complications (AUROC: 0.667; 95% CI: 0.516–0.817; p = 0.030). Unlike NLR (p = 0.182), the PLR demonstrated significant variability over the first 12 months after surgery (p < 0.001). The NLR was a significant prognostic factor for OS after adjustment for surgical procedure and BCLC stage when measured 3 (HR: 1.294; 95% CI: 1.041–1.608; p = 0.020), 6 (HR: 1.410; 95% CI: 1.108–1.794; p = 0.005), and 12 (HR: 1.612; 95% CI: 1.205–2.158; p = 0.001) months post-surgery. The PLR measured 12 months post-surgery was also a significant prognostic factor for OS after adjustment for surgical procedure and BCLC stage (HR: 1.008; 95% CI: 1.002–1.005; p = 0.012).
Conclusion: Higher 3-, 6-, and 12-months post-surgery NLR and 12 months post-surgery PLR were independently associated with a substantially increased risk of shorter OS. These findings underscore the potential use of NLR and PLR in clinical decision-making as biomarkers for risk stratification and outcome prediction in HCC management, warranting further investigation in prospective studies.

WED-124
National burden of MASH-related liver cancer in the United States 1990–2021: a systematic analysis for trends and patterns of geographic variations of the global burden of disease study

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Background and aims: The epidemiology of metabolic dysfunction associated steatohepatitis (MASH)-related liver cancer has changed remarkably in recent past decades. We systematically reported temporal trends of disease burden from MASH-related liver cancer in the United States (U.S.) from 1990 to 2021.
Method: By the Global Burden of Disease (GBD) 2021 Study Database, we examined the incidence, mortality rate, and the disability-adjusted life-years (DALYs) of MASH-related liver cancer at a national and state level and age- and sex-specific disease burden.
Results: In the U.S., the incidence of MASH-related liver cancer showed a significant rise from 1990 to 2021; in 2021, there were 3,381 cases, representing a 371.6% increase since 1990, with an age-standardized incidence rate of 0.58 per 100,000 population. DALYs from MASH-related liver cancer rose by 324% to 59,666 in 2021, and deaths increased by 324.1% to 2,799. Geographically, Hawaii had the highest age-standardized incidence, DALY, and mortality rates, while Texas had the lowest. Oklahoma showed the largest increase in these rates since 1990. The age-standardized incidence of MASH-related liver cancer was higher in males than in females, with the highest incidence in individuals aged 85–89, DALYs peaking in those aged 75–79, and highest mortality in those aged 90–94 for both sexes. High fasting plasma glucose was a significant risk factor, contributing to 35.6% of DALYs in males and 32.5% in females, with smoking also contributing 11.8% in males and 8.9% in females.
Conclusion: The disease burden of MASH-related liver cancer has significantly increased so far, necessitating vigorous intervention for at-risk patients.

WED-125
The Liver Frailty Index predicts survival in hepatocellular carcinoma: an australian multicentre prospective cohort study (APriCa study)

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Background and aims: Frailty assessments have demonstrated promise in stratification of prognosis in cirrhosis, however prospective studies in hepatocellular carcinoma (HCC) are limited. We aimed to determine frailty characteristics of individuals with newly diagnosed HCC using the Liver Frailty Index (LFI).
Method: A multicentre prospective observational cohort study was conducted across seven hospitals in Sydney. LFI testing using hand grip strength, time to perform five chair stands and three position balance (side by side, semi-tandem, tandem) was performed, generating a continuous score and also classifying participants as robust (LFI < 3.2), pre-frail (LFI 3.2–4.4) or frail (LFI ≥ 4.5). The relationship between frailty, overall survival (OS) and Barcelona Clinic Liver Cancer (BCLC) parameters were compared.
Results: Among 93 individuals (82% male; median age 71.0 years (interquartile range (IQR) 65.0–76.0), LFI class identified n = 24 (26%) as frail, n = 64 (69%) as pre-frail and n = 5 (5%) as robust. The median follow-up was 7.0 months (IQR: 5.0–13.5). Frailty was associated with older age, metabolic dysfunction-associated steatotic liver disease and allocation to management with palliative intent. Poorer Eastern Cooperative Oncology Group score was weakly correlated with LFI score (Kendall rank correlation coefficient = 0.21, p = 0.013). LFI score was independently associated with death (adjusted hazard ratio (aHR) = 2.38, (95% CI: 1.15–4.91, p = 0.019) when adjusted for BCLC stage and alpha-fetoprotein (AFP) level. Likewise, LFI class was a significant predictor of death on multivariable analysis when adjusted for BCLC stage and AFP level including in subgroup analysis of frail vs pre-frail individuals (aHR = 3.73, 95%CI: 1.38–10.10, p =

0.034). The 6-month mortality rates for robust, pre-frail and frail individuals were 0%, 19% and 38% respectively. LFI score was a fair predictor of 6-month survival (area under the curve = 0.67, 95%CI: 0.53–0.81, p = 0.045). The maximum value of Youden's index was utilised to evaluate the optimal LFI cut-off, calculated to be LFI = 3.91 (sensitivity = 88%, specificity = 57%). At this cut-off 43 individuals (64%) were more frail with a 6-month survival of 67% compared to the 24 individuals (36%) less frail whom had a 6-month survival of 92%. The log-rank test showed individuals more frail than this cut-off displayed significantly poorer 6-month survival (p = 0.036). The model of BCLC stage and AFP level had a Harrell's C concordance statistic of 0.73 in predicting survival compared to the model with BCLC stage, AFP level and LFI score with a concordance statistic of 0.79. The likelihood ratio test highlighted a significant difference between these models (p = 0.005).

Conclusion: Frailty is prevalent in this cohort. The LFI is an independent predictor of death in HCC. The addition of the LFI to current BCLC staging may improve the prediction of survival.

WED-126-YI

Treatment of hepatocellular carcinoma according to multiparametric therapeutic hierarchy approach: a prospective multicenter validation study

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Background and aims: Treatment strategy of hepatocellular carcinoma (HCC) is a complex decision-making process that considers several variables in clinical practice. A "multiparametric therapeutic approach" has been proposed (*Lancet Oncol* 2023): the feasibility of all treatments is evaluated systematically in a hierarchical order, to match each patient with the optimal therapy. The aim of the study is to validate the reliability of the new multiparametric decisional framework (MPDF) and the impact of the several variables on the final treatment decision in clinical practice.

Method: This is a prospective ongoing study. Primary endpoints are: 1) adherence to MPDF for treatment allocation, 2) identification of the relative weight of variables involved in this MPDF for treatment decision, while secondary endpoints are overall survival and radiological response after treatment. The study includes all consecutive patients with HCC managed in our center from September 1st, 2023. The disease is staged according to Barcelona Clinic Liver Cancer (BCLC) classification, while patient's characterization is conducted by Charlson Comorbidity Index (CCI), Liver Frailty Index (LFI), skeletal muscle mass index by CT, Child-Pugh (CPT) and ALBI and MELD. Each patient is allocated to treatment according to MPDF, BCLC 2022 as the benchmark.

Results: As September 1st, 2024, 131 patients were recruited into the study [median age 69 (39–92) years, 74% male, 36% HCV, 37% first treatment for HCC]. Twenty-four (18%) patients were classified BCLC 0, 48 (36%) A, 21 (16%) B, 31 (23.6%) C and 7 (5.3%) D. The median CCI was 8 (4–15), the median LFI was 3.92 (2–5.95). One hundred and seven (81.6%) patients were in CPT class A, 17 (13%) in B and 4 (3%) in C, while 90 (68.7%) were classified ALBI grade 1 and 38 (29%) ALBI grade 2. The median MELD score was 8 (6–22). According to the MPDF, 15 (11.5%) patients were allocated to liver transplant, 6 (4.6%) to laparoscopic surgical resection, 33 (25.2%) to microwave thermal ablation (MWTA), 26 (19.8%) to transarterial treatments (17 TACE and 9 TARE), 6 (4.6%) to other locoregional therapies (5 MWTA+TACE and 1 electrochemotherapy), 32 (24.4%) to systemic treatment and 6 (4.6%) to palliative care only. In 6 cases, the MDT decided for reassessment at 3 months. Treatment allocation was coherent to the BCLC 2022 recommendations in 83% BCLC 0, 77% BCLC A, 90% BCLC B, 80% BCLC C and 71% BCLC D.

Conclusion: Preliminary data of our ongoing prospective study suggest that personalized approach for HCC treatment by MPDF is feasible in clinical practice and might help ensuring a customized approach in a standardized framework. Updated data will be presented at the meeting.

WED-131

Low FIB-4 in multinational hepatocellular carcinoma cohort

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Background and aims: The fibrosis-4 index (FIB-4) is recommended as one method to risk stratify people with chronic liver disease. However, it is unclear what proportion of people with hepatocellular carcinoma (HCC) have a low FIB-4. We aimed to assess the proportion of people with HCC of various etiologies who have a low FIB-4.

Method: This cohort study included 1,778 consecutive adults (26% female) with hepatocellular carcinoma (HCC) from seven international centers in Australia, India, Japan, South Korea, Singapore, and the United States. The primary objective was to determine the proportion of patients with a low FIB-4 for each etiology, defined as FIB-4 <1.45 for hepatitis B virus (HBV)- or hepatitis C virus (HCV)-related HCC, and FIB-4 <1.3 (<2.0 for Age >65) for metabolic dysfunction-associated steatotic liver disease (MASLD)- or alcohol-associated HCC.

Results: The median (IQR) age and body mass index were 73 (66–82) and 25.6 (22.3–28.0) kg/m^2. The median FIB-4 was 5.09 (2.60–9.96), and 952 (55%) had known cirrhosis. A total of 138 patients (8%) had a low FIB-4. 952 patients (55%) had known cirrhosis. The proportion of people with HBV-, HCV-, alcohol-, and MASLD-related HCC who had a low FIB-4 were 11%, 2%, 3%, and 11%, respectively. A low FIB-4 was associated with lower odds of receiving HCC surveillance (p = 0.002) but increased odds of receiving curative treatment (p = 0.002). After adjusting for confounders, a low FIB-4 was associated with lower mortality (adjusted HR 0.54, 95% CI 0.38–0.76).

Conclusion: The majority of people with alcohol- and HCV-related HCC have an elevated FIB-4, however, one in ten with HBV- and MASLD-related HCC have a low FIB-4.

WED-132

Serologic and immunologic biomarkers for the identification of patients with hepatocellular carcinoma with high tumour burden and poor survival

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Background and aims: The prognosis of patients with hepatocellular carcinoma (HCC) closely correlates with liver disease stage and tumour burden at diagnosis. However, no biomarker reflecting HCC behaviour and aggressiveness is currently available for patients' prognostication. Therefore, we investigated the prognostic value of selected immunologic (interleukin [IL]-6, IL-8, and IL-10) and serologic (alpha-fetoprotein [AFP], protein induced by vitamin K absence or antagonist II [PIVKA-II], and glypican-3 [GPC-3]) biomarkers in patients with HCC.
Method: A total of 285 patients (median age: 68, IQR 60–75 years; males: 231, 81.1%; HCV/MASLD: 130/155) with a new diagnosis of HCC were retrospectively enrolled. Most patients had an early-stage HCC (BCLC: 0/A, n = 184, 64.6%); patients with BCLC stage D were excluded from the analysis. Serum IL-6, IL-8, and IL-10 were measured at HCC diagnosis by multiplex immunoassays (Bio-Plex® 200, Bio-Rad, USA), AFP and PIVKA-II by CLEIA (Lumipulse® G600 II, Fujirebio, Japan), and GPC-3 by EIA (Fujirebio Diagnostics AB, Sweden). Literature cut-offs were used for biomarkers' dichotomization. The primary end-point was overall survival (OS).
Results: Patients' median OS was 32.9 (95%CI 29.0–47.7) months. At univariate analysis, all biomarkers were associated with OS. IL-6 > 4.28 pg/mL: HR = 1.97, 95%CI 1.37–2.83; IL-8 > 17.60 pg/mL: HR = 2.20, 95%CI 1.40–3.44; IL-10 < 1.00 pg/mL: HR = 1.62, 95%CI 1.08–2.43; AFP > 20 ng/mL: HR = 2.27, 95%CI 1.59–3.26; PIVKA-II > 200 mAU/mL: HR = 2.59, 95%CI 1.78–3.76; and GCP-3 > 150 pg/mL: HR = 1.61, 95%CI 1.10–2.35. Remarkably, the biomarkers' combination allowed stratifying patients into 3 risk categories with different OS: 0–2 biomarkers+ (mortality: 31/115, 27%; median OS: 58.9, 95%CI 48.9–109.5 months), 3–4 biomarkers+ (mortality: 60/125, 48%; median OS: 28.5, 95%CI 22.9–35.1 months), and 5–6 biomarkers+ (mortality: 31/45, 69%; median OS: 11.6, 95%CI 6.4–17.3) (Log-rank test: p < 0.001). This multi-parameter model was significantly associated with OS (aHR = 2.20, 95%CI 1.68–2.86) independently from BCLC stage (aHR = 1.96, 95%CI 1.59–2.42).
Conclusion: In patients with HCC, the combination of serologic and immunologic biomarkers may provide prognostic information and contribute to personalized treatment strategies. *Project PNC 0000001 D[3] 4 Health, The National Plan for Complementary Investments to the NRRP, funded by the European Union – NextGenerationEU.*

WED-133
A machine learning model to predict the treatment response of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma incorporating computed tomogram-derived imaging biomarkers

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Background and aims: Despite the growing number of patients receiving atezolizumab plus bevacizumab (Atezo/Bev) for hepatocellular carcinoma (HCC), reliable models to predict treatment response in advance remain lacking. We aimed to develop machine learning models that can predict objective response (complete or partial response) after Atezo/Bev therapy incorporating clinical data and imaging biomarkers derived from abdominal computed tomography (CT).
Method: A total of 500 consecutive patients with HCC who received Atezo/Bev as a first-line systemic therapy between 2020 and 2023 were included from 3 referral centers in Korea. Blood test results, including alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II), were collected right before initiating Atezo/Bev and at the first imaging follow-up visit, 6–9 weeks after the first therapy. In patients with available imaging biomarkers derived from baseline CT (n = 389), seven additional biomarkers were obtained using a deep learning-based CT auto-segmentation software: volume of abdominal visceral fat, muscle, liver, and spleen; total fat-to-trunk volume ratio; liver and muscle Hounsfield unit (HU). Patients were randomized 1:1 to either the training or test cohorts and gradient boosting machine algorithm was employed to develop the models.
Results: During a median follow-up of 9.6 (interquartile range [IQR] = 5.7–14.2) months, 129 patients (25.8%) achieved objective response. Model 1 was developed using eight clinical variables: MoRAL score ($2x\sqrt{AFP} + 11x\sqrt{PIVKA\text{-}II}$), ALBI score, neutrophil-to-lymphocyte ratio (NLR), and eosinophil count at the first imaging follow-up and change in these variables from baseline. This model demonstrated an area under the receiver operating characteristic curve (AUROC) of 0.748 (95% confidence interval [CI] = 0.764–0.812) in the training cohort and 0.747 (95% CI = 0.679–0.809) in the test cohort. Model 2, which incorporated seven imaging biomarkers in addition to clinical variables, showed improved predictive accuracy in both the training (0.789, 95% CI = 0.717–0.862) and test cohorts (0.769, 95% CI = 0.691–0.839).
Conclusion: Using the clinical data and CT-derived imaging biomarkers, these machine learning-based models can predict response and help determine future treatment plans in advance for HCC patients receiving Atezo/Bev therapy.

WED-134
Age differences in the association between alcohol consumption and risk of hepatocellular carcinoma: a nationwide cohort study

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Background and aims: The role of age in modulating the association between alcohol consumption and the risk of HCC has not yet been cleared. Accordingly, we aimed to investigate the dose-response association between alcohol consumption and subsequent risk of HCC according to age.
Method: We included 4,234,445 individuals age ≥ 20 years who underwent a national health examination in 2009. Cox proportional hazards regression models were used to investigate the dose-response association of alcohol consumption with the risk of HCC according to age.
Results: Among 3,869,084 participants, 18,444 patients were newly diagnosed with HCC during a median follow-up period of 11.3 years. When stratified by 20-year age groups, increasing alcohol consumption was significantly associated with an increased risk of HCC in the ≥ 60 age group compared to no alcohol consumption (*P* for trend < 0.0001), whereas no significant association was found in the 20–39 and 40–59 age groups (*P* for trend = 0.725 for 20–39 age group; *P* for trend = 0.0501 for 40–59 age group). Heavy alcohol consumption was significantly associated with an increased risk of HCC in the 40–59, and ≥ 60 age groups, with this risk trend showing a progressive

increase as age advanced (aHR, 1.11; 95% CI, 1.05–1.18 for the 40–59 age group, and aHR, 1.47; 95% CI, 1.38–1.57 for ≥ age group).
Conclusion: In conclusion, our findings suggest that age is a critical factor when considering the risks of alcohol consumption on the development of HCC.

WED-135-YI
Metabolic response to locoregional treatment for hepatocellular carcinoma measured by 18F-FDGal PET/CT
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Background and aims: Research on liver function before and after locoregional treatment for hepatocellular carcinoma (HCC), apart from surgical resection, is nearly nonexistent. This study aimed to use positron emission tomography (PET) with the liver-specific tracer [^{18}F]-fluoro-2-deoxy-D-galactose (^{18}F-FDGal) to explore the contribution of hepatocellular carcinomas to total metabolic liver function and to investigate the liver's regenerative potential to locoregional treatments for HCC.
Method: The study included 29 patients with an ^{18}F-FDGal PET/CT scan 0–40 days before locoregional treatment for HCC with surgical resection (n = 8), radiofrequency ablation (RFA) (n = 8), selective internal radiation therapy (SIRT) (n = 4), or transarterial chemoembolization (TACE) (n = 9) and an ^{18}F-FDGal PET/CT scan 31–147 days after the treatment. The total and mean metabolic activity in tumors larger than 3 cm in diameter and in liver tissue exempt from tumors larger than 3 cm in diameter were calculated before and after locoregional treatment as the percentage of the injected dose of ^{18}F-FDGal (%ID) and the percentage of the injected dose of ^{18}F-FDGal divided by the functional volume (%ID/L).
Results: In patients with tumors larger than 3 cm in diameter, the total metabolic activity of the liver was significantly higher when including the tumor compared to the surrounding liver tissue without the tumor ($p = 0.0002$). The median percent change in mean metabolic activity in the liver after locoregional treatment for patients without cirrhosis was 5.1%, compared to –6.0% for patients with cirrhosis ($p = 0.05$). After treatment, seven of the eight patients who underwent resection showed increased or stable mean metabolic liver function, while responses for those treated with RFA, SIRT, or TACE were mixed.
Conclusion: HCCs larger than 3 cm in diameter contribute substantially to the liver's galactose metabolism. The regenerative response in the liver to locoregional treatment is decreased in patients with cirrhosis, and the type of locoregional treatment seems to impact the response.

WED-136
Proton-pump inhibitors and gut microbiome are associated with survival in patients with hepatocellular carcinoma under immunotherapy
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Background and aims: The efficacy of immunotherapy may be influenced by the gut microbiome. Primary aim was to study the role of proton-pump inhibitors, antibiotics and gut microbiome composition on survival in patients with hepatocellular carcinoma under immunotherapy.
Method: This is an exploratory analysis of a multicenter phase I/IIa trial of patients with hepatocellular carcinoma treated with the regorafenib and nivolumab in second line. Fecal samples were collected before starting nivolumab and profiled by 16S ribosomal RNA sequencing. Main outcome was overall survival.
Results: Median age of the 40 patients analyzed was 65.4 years, 82.5% male, 60% with cirrhosis, all ECOG-PS-0 and 62.5% in BCLC-C stage. Twenty received proton-pump inhibitors before immunotherapy and 12 antibiotics within the 12 months prior to treatment start. Cox regression analysis showed that, BCLCpC2 (HR 3.0, 95%CI 1.1–8.3), AFP> 400 (HR 2.7, 95%CI 1.1–6.5), obesity (HR 3.1, 95%CI 1.2–7.8) and proton-pump inhibitors (HR 3.0, 95%CI 1.1–8.3) were associated with higher risk of death. Use of antibiotics within 12 months lowered mortality risk (HR 0.3 95%CI 0.1–0.99). After IPTW analysis and adjustment for confounders, proton-pump-inhibitors use (HR 4.4, 95%CI 1.6–12.1) was associated with higher risk of death. Multivariate analysis including microbiome profile showed that higher abundance of Streptococcaceae, Gemellaceae, Sutterellaceae and Synergistaceae families was associated with higher risk of death. Proton-pump-inhibitors use was associated with higher abundance of Streptococcaceae and lower abundance of Lachnospiraceae.

Conclusion: Use of proton-pump inhibitors and gut microbiome composition are associated with survival in hepatocellular carcinoma patients under immunotherapy. The use of this class of drug should be avoided in the absence of a mandatory indication.

WED-137-YI

Hepatocellular carcinoma after liver transplantation: development of a machine learning-based risk score for safely ruling out recurrence

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Background and aims: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality, with liver transplantation (LT) being a definitive treatment for select patients. Traditional prognostic models often fail in effectively ruling out the risk of post-LT recurrence. Screening for recurrence is costly and exposes the individuals to radiation. No standardized criteria for ruling out recurrence exists. We propose a machine learning-derived risk model that aims to improve the ability to rule out this risk.
Method: We conducted a retrospective cohort study at a single reference center, including patients with HCC who underwent LT between 2004 and 2024. Missing data were addressed using multiple imputation by chained equations. The dataset was randomly divided into a training set (70%) and a testing set (30%). Using elastic net regularization, we developed a model to identify key variables and evaluate their discriminative power. Three receiver operating characteristic (ROC) curves were constructed to predict 3-, 5-, and 10-year relapse-free survival (RFS), with the area under the curve (AUC) calculated and non-zero coefficients identified. Using these coefficients, we created a risk score and categorized patients into "high risk" and "low risk", using a threshold that maximized sensitivity with acceptable specificity in the training subset. We used Kaplan-Meier estimates to yield the relapse probability at time-points. Finally, a univariate Cox proportional hazards (PH) regression analysis was performed, adjusting for the newly developed risk score.
Results: A total of 424 HCC patients which underwent LT were included. From the input variables, the elastic net model identified five predictors with non-zero coefficients: age at LT, MELD score (pre-LT), the diameter of the largest nodule (pre-LT), Barcelona Clinic Liver Cancer staging, and the presence of microvascular invasion on the explant. Using these predictors, a risk score was developed, categorizing 214 patients as "low-risk" and 210 patients as "high-risk." The AUC for 3-, 5-, and 10-year RFS on the validation cohort was 0.717 for all. Using the optimal threshold, the positive predictive value and negative predictive value of the risk score for 5-year RFS were 7.2% and 99.5% in the whole cohort, respectively, with a sensibility of 93.8%. In the low-risk group, the relapse probabilities were 0% at 3, 5, and 10 years. In the high-risk group, the relapse probabilities were 10.4% at 3 years, 14% at 5 years, and 20.8% at 10 years. Low- and high-risk groups had significantly different RFS at all assessed time-points ($p < 0.001$). In the univariate Cox PH regression, low-risk patients had a relapse hazard ratio of 0.05 (95% confidence interval: 0.01–0.35) compared to high-risk patients.
Conclusion: Our risk score exhibited outstanding performance in ruling-out HCC recurrence post-LT. This model could be used to guide post-LT monitoring and follow-up strategies, ensuring that low-risk patients benefit from less frequent monitoring.

WED-138-YI

Somatic copy number alterations in circulating cell-free DNA as a predictive biomarker for hepatocellular carcinoma: insights from a proof-of-concept study

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Background and aims: Despite improvements in hepatocellular carcinoma (HCC) management, its prognosis remains poor. Diagnosis at advanced stages often precludes curative treatment options, and currently available biomarkers (e.g., alpha-fetoprotein (AFP)) offer limited utility in early diagnosis and prognostic stratification. Liquid biopsy has emerged as a promising tool for early HCC detection and prognostic evaluation, and the analysis of circulating cell-free DNA (ccfDNA) hold significant potential as a diagnostic tool. This proof-of-concept study aimed to investigate the potential role of tumor fraction (TF) within ccfDNA as a biomarker in HCC patients.
Method: A total of 60 patients were recruited, including 13 with chronic liver disease (CLD), 24 with cirrhosis, and 23 with HCC. Plasma samples were collected, and ccfDNA was extracted for genomic analysis. TF was calculated by focusing on somatic copy number alterations (SCNAs) within the ccfDNA.
Results: In patients with CLD and cirrhosis (n = 37), circulating tumor DNA (ctDNA) was undetectable with the exception of one cirrhotic patient, who presented a significant TF (17%) and displayed HCC shortly after. Conversely, 5 out of 22 HCC patients (21.7%) exhibited detectable ctDNA, with TF levels ranging from 3.0% to 32.6%. Patients with higher TF levels were characterized by more aggressive disease features, including elevated AFP levels, larger tumor sizes, multiple tumor nodules, and advanced-stage disease.
Conclusion: Preliminary evidence from this study suggests that the analysis of TF, specifically through the detection of SCNAs, could serve as a promising non-invasive tool for the identification and evaluation of HCC. The innovative approach has the potential to significantly enhance early diagnosis and may also improve prognostic stratification in HCC patients.

WED-139

Evaluating the performance of large language models at hepatobiliary tumor boards: a prospective study

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Background and aims: The growing use of artificial intelligence in daily life and clinical practice raises questions about the reliability of large language models (LLMs) in medical contexts. The objective of this study is to ascertain the reliability and reproducibility of recommendations provided by different LLMs in comparison to those of a multidisciplinary team meeting (MDM) for liver tumors.
Method: A prospective study was carried out on 102 cases with hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC) who were presented to the hepatobiliary MDM at Charité – Universitätsmedizin Berlin between April and October 2024. The analysis was conducted using the LM Studio software. The following

LLMs were utilized: Phi-3-Mini-4k (Phi), Llama 3.1 8B Instruct (Llama), Mistral-7B-Instruct-v0.2 (Mistral), Qwen 1.5 (Qwen), and Gemma. The LLMs recommendations were subjected to an evaluation process in which they were compared to the MDM recommendations. The following categories were subjected to comparison: surgery (resection; liver transplantation), intervention, systemic therapy, and surveillance (follow-up; diagnostic; best supportive care).

Results: The overall concordance rates (CR) for the LLMs were as follows: 57.8% for Phi, 61.8% for Llama, 60.8% for Mistral, 55.9% for Qwen, and 32.4% for Gemma. In the case of HCC, LLM yielded the following CR: For Phi, Llama, Mistral, Qwen, and Gemma the CR were 59.1%, 52.2%, 56.8%, 38.6%, and 18.2%, respectively. The CR for CCC were as follows: For Phi, Llama, Mistral, Qwen, and Gemma 56.9%, 61.5%, 63.8%, 69%, and 27.6%, respectively. For Qwen the CR was significantly associated with tumor entity $p = 0.002$. The CR of the remaining LLMs was found to be independent of the tumor entity. Llama demonstrated the highest CR (73.3%) when surgery was recommended. The CR for intervention was lower overall, with Llama and Mistral, achieving the highest rates (57.1%). When systemic therapy was recommended, Qwen demonstrated the most favorable outcomes, with a CR of 71.9%. The CR for surveillance was notably lower, with Mistral demonstrating the greatest accuracy (63.6%). We also investigated whether LLMs recommendations differed based on timing of MDM presentation before or after therapy. Despite low agreement rates, LLMs distinguished between the two and adjusted recommendations accordingly. For example, favoring surgery pre-therapeutic and systemic therapies post-therapeutic, a pattern seen across all LLMs ($p < 0.001$).

Conclusion: The overall CR between MDM and the examined LLMs for HCC and CCC are notably low. These results were somewhat more favorable for CCC. In conclusion, the reviewed LLMs do not appear to be suitable for MDM recommendations in complex treatment decisions for HCC and CCC. It would be beneficial to conduct a review of additional models or potential optimization processes for the LLMs in question.

WED-140

Liver function and tumor stage determines adherence to tumor board recommendation in HCC

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Background and aims: The range of treatment options for Hepatocellular carcinoma (HCC) is extensive and requires diligent assessment during multidisciplinary tumor board meetings (MDM). It has been demonstrated that patients with HCC who are discussed in MDMs have superior outcomes. Nevertheless, a considerable number of patients do not receive the recommended therapy. The objective was to evaluate the extent to which the stage of a liver disease has influence on adherence to MDM recommendations.

Method: The analysis is a retrospective, single-center study of patients with HCC whose cases were presented to the hepatobiliary MDM at Charité - Universitätsmedizin Berlin between January 2014 and December 2018. A total of 1164 cases from 643 patients were analyzed. Adherence and the potential influence of indicators for liver disease were examined. Moreover, a survival analysis was conducted.

Results: Overall adherence rate was 82.7%. The five-year survival rate was significantly higher for the adherent group across all BCLC stages (0-A, B, C, D) than in the non-adherent group (BCLC 0-A, $p = 0.05$; BCLC B, $p = 0.04$; BCLC, C $p < 0.001$; BCLC D, $p = 0.001$). Patients with good liver function (ALBI 1 and ALBI 2a) showed no significant difference in five-year survival probability between the adherent and non-adherent groups. In contrast, for patients with poorer liver function (ALBI 2b and ALBI 3), the difference in survival probabilities was highly significant, with the adherent cohort demonstrating significantly higher five-year survival rates (both ALBI 2b and ALBI 3, $p < 0.001$). Adherence was found to be significantly influenced by Child-Pugh score $p < 0.001$. Also compliance was significantly influenced by tumor stage, measured by the following parameters: distant metastases ($p < 0.001$), BCLC stage ($p = 0.004$) and tumor size ($p = 0.02$). Poor liver function also showed a significant decrease in overall survival (OS) with Hazard Ratio (HR) 1.41 (95% CI 1.02–1.94; $p = 0.04$) for ALBI 2b and HR 2.34 for ALBI 3 (95% CI 1.48–3.68; $p < 0.001$). Also highly significant effects on OS were seen for metastasis (HR 3.06, 95% CI 1.99–4.72; $p \leq 0.001$) and portal vein invasion (HR 3.12, 95% CI 1.97–4.95; $p \leq 0.001$) as well as for higher alpha-fetoprotein levels which were also associated with shorter OS (HR 1.8, 95% CI 1.37–2.46; $p \leq 0.001$).

Conclusion: Adherence to MDM recommendations has the potential to enhance patient survival. It is noteworthy that adherence is influenced by liver function and tumor stage in patients with HCC.

WED-141

MicroRNA profiling of hepatocellular carcinoma can improve the prediction of tumor recurrence after liver resection

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Background and aims: Hepatocellular carcinoma (HCC) diagnosed at an early stage may undergo liver resection with curative intent.[1] However, the 2-year recurrence rate after HCC resection can be up to 34%, even under optimal conditions.[2] Currently, reliable biomarkers for accurately predicting recurrence are lacking. In this study, we evaluated whether the microRNA (miRNA) profile in HCC tissue was associated with HCC recurrence after liver resection.

Method: Patients undergoing liver resection for HCC were prospectively included. At surgery, HCC tissue samples were snap-frozen for subsequent identification and quantification of their miRNA profiles using RNA sequencing. Clinical and histopathological parameters including 2-year recurrence, circulating plasma levels of alpha-fetoprotein (AFP), tumor size, microvascular invasion, resection margin, and satellite lesions were obtained from medical records.

The miRNA expressions were compared between HCCs from patients with and without recurrence within 2 years. Differential expression analysis and Lasso regression were used to select different panels of miRNAs. Using logistic regression, the ability to predict recurrence was tested for clinical and histopathological parameters, alone and in combination with miRNAs. Results were validated in an external cohort from The Cancer Genome Atlas (TCGA).

Results: A total of 67 patients had complete data and were included in the study. Four clinical and histopathological parameters (AFP, tumor size, microvascular invasion, satellite lesions) could differentiate between recurrence and no recurrence with an AUC of 0.715. Ten miRNAs were differentially expressed in HCCs from patients with and without a 2-year recurrence. The addition of these miRNAs to the clinical and histopathological parameters significantly increased the AUC to 0.824 (p = 0.02), a result which was confirmed when the same analysis was carried out in the TCGA cohort (n = 161 cases with complete data). Lasso regression obtained a 14-miRNA panel which alone had an AUC of 0.867, however results could not be verified in TCGA.

Conclusion: The miRNA profile in HCC tissue can improve the ability of clinical and histopathological parameters to predict HCC recurrence after liver resection. However, further studies are required to identify the optimal miRNA panel.

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WED-142

Impact of hepatocellular carcinoma surveillance on survival in a contemporary international cohort

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Background and aims: The etiologies of hepatocellular carcinoma (HCC) are changing. It is unclear if the beneficial impact of surveillance for HCC remains consistent given the changing epidemiology of HCC. We evaluated the impact of HCC surveillance on a large contemporary cohort of people with HCC.

Method: This cohort study included 1,185 participants with HCC from five international sites. Multivariable restricted mean survival time (RMST) analyses with lead time bias adjustments were conducted to assess overall survival, compared between participants who underwent any HCC surveillance compared to those who did not.

Results: RMSTs were consistently higher in participants who underwent HCC surveillance (n = 975) (RMST difference at 1 year, 0.102 years [95% CI: 0.055–0.150], p < 0.001; RMST difference at 3 years, 0.497 years [95% CI: 0.316–0.678], p < 0.001; RMST difference at 5 years, 0.960 years [95% CI: 0.635–1.286], p < 0.001) compared to participants who did not undergo surveillance (n = 210). RMSTs remained higher among participants with hepatitis B (HBV) and hepatitis C (HCV) patients who underwent surveillance, compared to no surveillance across all follow-up periods. Among participants with metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease, there were no statistically significant differences in RMSTs in the first three years of follow-up between HCC surveillance and no surveillance.

Conclusion: HCC surveillance is associated with improved survival. This survival benefit is more prominent in people with HBV- and HCV-associated HCC, compared to people with MASLD- and alcohol-associated liver disease.

WED-143-YI

Ki-67 and CK19 as predictors of hepatocellular carcinoma recurrence after liver transplantation

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Background and aims: Tumour recurrence after liver transplantation (LT) remains the dominant reason for poor post-transplant survival in patients transplanted for hepatocellular carcinoma (HCC). Improved risk stratification would enable targeted post-LT surveillance and treatment. Several prognostic tools based on demographics, serum markers and tumour configuration, including the recently published R3-AFP model, predict recurrence. However, none include molecular features of the explanted HCC, beyond AFP levels. Tumoral Ki-67 and CK19 expression may predict aggressive tumour biology. We examined the prognostic significance of tumoral Ki-67 and CK19 expression for HCC recurrence after LT. Secondly, we examined whether the addition of these biomarkers could refine the R3-AFP model.

Method: We conducted a retrospective analysis of sequential patients undergoing LT at Addenbrooke's Hospital, Cambridge, between January 2008 and December 2022. All patients had HCC on explant histopathology. Clinical and histopathological data was obtained retrospectively from a prospectively maintained database. Tumoral expression of Ki-67 (MIB-1) and CK19 was performed retrospectively by immunohistochemistry and scored by a specialist hepatobiliary histopathologist. Cox regression analyses were used to assess factors predicting post-LT recurrence-free and overall survival.

Results: 277 patients (238 male (85.9%); median age 59.8 years (min-max: 23.1–73.6)) underwent LT during the study period. The cumulative incidence of recurrence at 5 years post-LT was 10.5% (95% CI: 7.0–14.8%). Significant univariate predictors of HCC recurrence included viral hepatitis (HR = 2.54, p = 0.026), elevated pre-transplant AFP (HR = 1.17, p < 0.001), pre-transplant UKELD score (HR = 2.54, p = 0.026), number of lesions (HR = 1.15, p < 0.001), size of largest lesion (HR = 1.88, p < 0.001), tumour grade (p < 0.001) and microvascular invasion (p < 0.001). At univariate analysis, Ki-67 (HR = 1.38, p < 0.001) and CK19 expression were associated with HCC recurrence (HR = 3.09, p < 0.016). After multivariate adjustment

for other predictive factors neither Ki-67 (HR = 1.16, 0.98–1.38, p = 0.09) nor CK19 expression (HR = 1.66, 0.65–4.21, p = 0.29) were associated with HCC recurrence. Neither Ki-67 (HR = 1.13, 0.999–1.27, p = 0.05) nor CK19 (HR = 1.68, 0.86–3.32, p = 0.13) expression were associated with overall survival after liver transplantation. In our cohort, the R3-AFP score effectively stratified patient risk groups for recurrence, with a 5-year recurrence rate of 1.0% (95% CI: 0.1–4.8%) in very-low-risk patient and 32.6% (95% CI: 7.8–47.2%) in the very-high-risk group. Finally, Ki-67 (p = 0.077) and CK19 (p = 0.338) expression could not predict post-LT HCC recurrence independent of the R3-AFP risk score.
Conclusion: Tumoral Ki-67 and CK19 expression do not confer additional prognostic utility for recurrence-free or overall survival after LT for HCC, beyond commonly used clinicopathological variables or the R3-AFP score.

WED-144
Clinicopathological features of liver tumors in Guilin: a region with significant Aflatoxin contamination in food crops in China
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Background and aims: Aflatoxins, toxic metabolites produced by molds, are common contaminants of food crops. Chronic exposure to aflatoxins is strongly associated with liver diseases, including hepatocellular carcinoma (HCC). Guilin, located in southern China, has significant aflatoxin contamination in food crops. The Second Affiliated Hospital of Guilin Medical University (GMUSH) serves as a leading healthcare institution in the region. This study aimed to analyze recent liver tumor cases at GMUSH and investigate the pathological features linked to aflatoxin exposure.
Method: We analyzed 54 liver tumor cases from GMUSH that underwent surgical treatment between 2021 and 2024. Aflatoxin exposure was assessed by immunohistochemistry for aflatoxin B1 (AFB1) DNA-adducts (clone 6A10). Clinicopathological data, including tumor cell characteristics, background hepatocytes, fibrosis, and infiltrating cells, were evaluated by independent liver pathologists. Statistical analyses were performed to identify features associated with AFB1 exposure.
Results: Among the 54 cases, 38 were diagnosed with HCC, 14 with intrahepatic cholangiocarcinoma (ICC), and 2 with combined HCC-ICC. Of the 38 HCC cases, 28 (73.7%) were hepatitis B virus (HBV)-positive, while 5 of 14 ICC cases (35.7%) were HBV-positive. AFB1 DNA-adducts were found in the nucleus or cytoplasm of cells in 5 HBV-positive HCC cases. No AFB1 positivity was detected in ICC or combined HCC-ICC cases. There were no significant differences in pathological and clinical parameters between AFB1-positive and -negative cases, but the AFB1-positive group exhibited a higher incidence of glycogen deposition in both tumor cells and background hepatocytes.
Conclusion: Our immunostaining method for AFB1 detection revealed a 13% positivity rate in recent HCC cases from Guilin, with no significant clinicopathological differences between AFB1-positive and -negative cases. Detection of AFB1 DNA-adducts is a useful tool for identifying past exposure, even in the absence of aflatoxin in routine blood tests. Interestingly, the incidence of ICC in Guilin was higher than the national average, accounting for 25% of liver cancer cases. This elevated incidence may be linked to aflatoxin exposure, as animal studies have shown that aflatoxin administration can induce ICC. Furthermore, the TP53 gene mutation (R249S), a known aflatoxin signature, has been identified in ICC cases in China. We are currently conducting genetic analysis on ICC cases in parallel, and will also report these findings.

WED-145
Morphomolecular proliferative disease and microvascular invasion characterize PET-CT positive hepatocellular carcinoma cases: a single-center pilot study
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Background and aims: Positron emission tomography (PET) – computed tomography (CT) is a helpful diagnostic tool for excluding metastatic disease in patients with hepatocellular carcinoma (HCC). However, PET-CT is rarely used for the diagnosis of intrahepatic lesions in HCC, due to its low sensitivity, which is associated with relatively elevated Standard Uptake Value (SUV) in both normal and cirrhotic liver. PET-CT positivity for primary HCC has been associated with microvascular invasion and more aggressive tumour behaviour. We aimed to study the association between the SUVmax of primary HCC in PET-CT and HCC morphomolecular classification based on liver biopsy.
Method: Twenty-eight patients (22 males, 7 with diabetes, 17 with cirrhosis, 7 of viral aetiology, 9 with varices, 15 classified as ALBI-I, BCLC stage: 7 A, 11 B, 10 C) were included in the study. All patients had primary HCC lesions and underwent ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT examination and imaging-guided liver biopsy. We studied the SUVmax of all histologically proven HCCs. We divided HCCs into proliferative (pHCC, n = 14) and non-proliferative (npHCC, n = 14).
Results: Sixteen cases were PET-positive and the rest 12 PET-negative. Microvascular invasion was observed in 13 pHCC patients (92.8%) and in only 2 npHCC patients (14.3%) (p < 0.001). Baseline characteristics of the two groups were comparable for all variables studied (gender, age, diabetes, cirrhosis, etiology, varices presence, Albumin-Bilirubin/ALBI grade, α-fetoprotein serum values). Median SUVmax in pHCCs was significantly higher compared to npHCCs (8.5 vs. 4, respectively, p = 0.001). In multivariate analysis, SUVmax emerged as the only significant factor differentiating between the two groups (p = 0.033, OR = 2.5, 95% C.I. 1.077–5.940). SUVmax was strongly correlated with pHCC (Pearson r = 0.52, p = 0.005). SUVmax of 5.15 presented a sensitivity of 85.7% and specificity of 78.6% for the prediction of pHCC presence (AUROC 0.86, p = 0.001). In the subgroup of BCLC-A/B patients (n = 18), microvascular invasion was detected in 7/8 (87.5%) with PET-positive HCC compared to 2/10 (20%) with PET-negative HCC (p = 0.004). In BCLC-A/B patients with microvascular invasion, 8/9 patients (88.9%) presented with pHCCs, whereas absence of microvascular invasion presented only in patients with npHCCs (9/9, 100%) (p < 0.001).
Conclusion: Our pilot study highlights a significant relationship of SUVmax with histologically confirmed proliferative HCC, a finding requiring further investigation. PET positivity in primary HCC may be related to specific HCC histological/molecular subtypes and/or presence of microvascular invasion.

WED-146

HCC detection using LI-RADS ultrasound surveillance algorithms: a comparative analysis of v2024 and v2017

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Background and aims: The Liver Imaging Reporting and Data System (LI-RADS) Ultrasound (US) Surveillance Algorithm was updated in 2024, highlighting the need for studies to validate these changes. This study aims to compare the 2024 and 2017 versions of the LI-RADS US Surveillance Algorithms for hepatocellular carcinoma (HCC) detection in adults with cirrhosis.
Method: This retrospective analysis of a prospective clinical trial included adult patients with cirrhosis who underwent up to three rounds of semi-annual US surveillance with AFP testing; the first two rounds reviewed. Two radiologists independently assigned LI-RADS Surveillance US visualization scores (VIS-A, VIS-B, VIS-C) and categories (US-1, US-2, US-3), with any discrepancies resolved by a third reviewer. AFP positivity was assessed per LI-RADS/American Association for the Study of Liver Diseases criteria. Sensitivity and specificity in Round 1 were compared between the 2024 and 2017 versions, and univariable and multivariable logistic regression identified baseline predictors for VIS-C in Round 2.
Results: Among 407 patients (230 men; median age 56-years), 28 (7%) were diagnosed with HCC in Round 1. LI-RADS 2024 demonstrated significantly higher sensitivity for HCC detection compared to 2017 (64% vs. 39%, $p = 0.016$) but lower specificity (82% vs. 93%, $p < 0.001$). In 299 patients with negative Round 1 surveillance by LI-RADS 2024 who subsequently underwent Round 2 US, multivariable analysis indicated that baseline VIS-C (adjusted odd ratio = 22.8, [95% confidence interval, 12.0–43.3], $p < 0.001$) was the only significant predictor for VIS-C in Round 2.
Conclusion: Compared to the 2017 version, LI-RADS US Surveillance 2024 demonstrated improved sensitivity for detecting HCC, albeit with reduced specificity. Baseline VIS-C was the sole independent predictor of VIS-C in follow-up surveillance US.

WED-149

Machine learning-based decision tree model for predicting survival in patients with single-large hepatocellular carcinoma

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Background and aims: Single large hepatocellular carcinoma (SLHCC) exhibits substantial heterogeneity in clinical presentations and outcomes, distinguishing it from other hepatocellular carcinoma (HCC) stages. Conventional prognostic tools and staging systems for HCC provide limited accuracy and applicability in predicting outcomes for SLHCC patients. This study aimed to develop a machine learning-based prognostic model specifically to SLHCC.
Method: This retrospective study analyzed 477 treatment-naive SLHCC patients diagnosed at Taipei Veterans General Hospital between January 2012 and January 2023. The primary study endpoint was overall survival (OS). Patients were randomly divided into a training cohort ($n = 334$) and a validation cohort ($n = 143$). In the training cohort, multivariate analysis using the Cox proportional hazards model identified independent risk factors for poor OS. These factors were incorporated into a machine learning-based decision tree model, which was then validated in the validation cohort to assess its prognostic performance.
Results: After a median follow-up of 50 months, 234 patients had died, with a 5-year OS rate of 42%. The multivariate Cox model identified larger tumor size (>10 cm), serum creatinine levels, treatment modality, albumin-bilirubin (ALBI) grade, fibrosis-4 (FIB-4) score, and serum alpha-fetoprotein (AFP) levels as independent predictors of poor OS. The machine learning-based decision tree model demonstrated robust prognostic performance, with an area under the receiver operating characteristic curve (AUROC) of 0.706 (95% CI: 0.626–0.786).
Conclusion: The machine learning-based decision tree model, incorporating non-invasive biomarkers, imaging features, and treatment modalities, provides effective prognostic insights for SLHCC patients. This tool holds potential for aiding clinicians in optimizing treatment strategies and enhancing personalized patient care.

WED-150-YI

Cost-effectiveness of ultrasound plus alpha-fetoprotein and biomarker-based strategies for hepatocellular carcinoma surveillance in patients with chronic hepatitis B

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Background and aims: Currently, the standard program for hepatocellular carcinoma (HCC) surveillance is the combination of ultrasound (USG) with alpha-fetoprotein (AFP) every 6 months. However, there are limitations such as accessibility, radiologist shortages, and suboptimal cost-effectiveness data. This study evaluated the cost-effectiveness of traditional HCC surveillance methods compared to biomarker-based strategies, focusing on patients with chronic hepatitis B (CHB), a population at high risk for HCC in the Asia-Pacific region.
Method: A Markov model simulated a cohort of patients with CHB to compare cost-effectiveness of surveillance strategies, including USG +AFP, GAAD score (gender, age, AFP, and des-carboxy-prothrombin), GALAD score (gender, age, AFP-L3, AFP, and des-carboxy-prothrombin), ASAP score (AFP, sex, age, and Protein induced by vitamin K absence-II), and no surveillance. Data on utilities, transition probabilities, and costs were derived from literature reviews and the Thai healthcare system. A societal perspective and a lifetime time horizon were applied for the analysis. Incremental cost-effectiveness ratios (ICERs) were calculated as costs per quality-adjusted life-year (QALY) gained. Deterministic and probabilistic sensitivity analyses were conducted to evaluate the robustness of findings.
Results: ASAP every 12 months emerged as the most cost-effective strategy, with an ICER of 62,318 THB (~1,946 USD) per QALY gained compared to no surveillance. While ASAP every 6 months provided slightly greater QALY gains, it incurred significantly higher costs, resulting in an ICER exceeding the willingness-to-pay (WTP) threshold of 160,000 THB (~5,000 USD) per QALY gained. GAAD every 6 months and GALAD every 6 months achieved similar QALY gains to ASAP strategies but were dominated due to higher costs. The strategies adopting GAAD or GALAD with 12-month surveillance intervals improved cost-effectiveness but remained inferior to ASAP every 12 months. USG+AFP every 6 months had the highest ICER of 108,294 THB (~3,382 USD) per QALY gained, significantly exceeding the ICER of other strategies. Probabilistic sensitivity analysis confirmed ASAP every 12 months as the most cost-effective strategy, falling below the WTP threshold in over 90% of simulations. Tornado diagrams highlighted that biomarker costs, utility values for HCC stages, and HCC incidence were key drivers of cost-effectiveness.
Conclusion: ASAP every 12 months is the most cost-effective surveillance strategy for patients with CHB compared to other approaches. Its combination of cost-effectiveness and feasibility makes it a practical surveillance for resource-limited settings, particularly in regions with constrained access to radiologists. Policymakers should prioritize biomarker-based surveillance

programs, in particular ASAP, to improve HCC outcomes and ensure efficient resource allocation.

WED-151-YI

Development and external validation of a weakly supervised deep learning algorithm for the diagnosis of focal liver lesions on contrast-enhanced ultrasound

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Background and aims: Accurate characterization of focal liver lesions (FLL) remains a challenging task of routine clinical practice. Contrast-enhanced ultrasound (CEUS) is a reliable and comparatively inexpensive imaging modality, but its interpretation relies heavily on the expertise of the examiner. Previous studies have explored the application of AI to CEUS analysis; however, most are relying on resource-intensive preprocessing and lack external validation. This study aimed to classify FLLs applying a weakly-supervised attention-based multiple instance learning algorithm and to validate the model's performance using external cohorts.
Method: Retrospectively collected multicentric data from four FLL types were included: focal nodular hyperplasia (FNH), hemangioma, hepatocellular carcinoma (HCC), and metastasis. Deep learning features were extracted from CEUS video frames using a pretrained convolutional neural network. A class-balanced 20% test set was held out, and the remaining data was used to train a classification algorithm applying a hyperparameter grid search and five-fold cross-validation. The best hyperparameter set was selected based on the averaged area under the receiver operating characteristic curve (AUROC) across all cross-validation runs. The final model was created by ensembling the five models from the best run and then deployed on the held-out test set as well as two external cohorts from Germany (same ultrasound machine) and Switzerland (different ultrasound machine) for testing.
Results: The in-house dataset included 370 patients (FNH n = 52, hemangioma n = 149, HCC n = 67, metastasis n = 102). The final model achieved an average AUROC of 0.82 during cross-validation. On the test set, AUROCs were 0.85 for FNH, 0.87 for hemangioma, 0.92 for HCC, and 0.93 for metastasis. In external validation, AUROCs for the German cohort (39 patients) were 0.70, 0.52, 0.67, and 0.58, and for the Swiss cohort (19 patients), 0.35, 0.63, 0.49, and 0.95, for FNH, hemangioma, HCC, and metastasis, respectively. Post-hoc explainability analyses were performed to better understand the decision process of the model.
Conclusion: Weakly supervised MIL demonstrated robust performance in classifying FLL using CEUS data during cross-validation and on the held-out test set, without requiring extensive pre-processing. The performance drop in external cohorts, is likely due to small, imbalanced datasets and user- and machine-dependent artefacts. As most AI studies analyzing CEUS videos do not provide external validation of their models, further research is needed before prospective studies can confirm the clinical utility of such algorithms and their potential to assist clinicians in FLL evaluation.

WED-152

An artificial intelligence-based risk prediction model for early-onset hepatocellular carcinoma

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Background and aims: Cancer incidence among younger populations is rising worldwide, with hepatocellular carcinoma (HCC) being the most common type of liver cancer. Despite extensive research on HCC risk prediction, little attention has been paid to early-onset HCC. We aimed to develop and validate an artificial intelligence (AI)-based prediction model of early-onset HCC.
Method: From the Korean nationwide health screening database, a total of 2,863,733 young adults aged 20–39 years who were screened between 2009 and 2010 were included and followed up until December 31, 2021. The primary outcome was HCC incidence. The cohort was randomly split into training, validation, and test sets (8:1:1) to build prediction models.
Results: During a median follow-up of 10.0 years, 1,550 HCC cases were identified. Logistic regression, random forest, multi-layer perceptron, and extreme gradient boosting (XGBoost) models were built and validated using 43 available clinical variables. In the test set, the XGBoost model showed the highest area under the curve (AUC) of 0.861, followed by logistic regression (AUC = 0.857), random forest (AUC = 0.814), and multi-layer perceptron (AUC = 0.781). The top predictive features in the XGBoost model included alanine aminotransferase, fasting serum glucose, gamma-glutamyl transferase, hepatic steatosis, age, creatinine, aspartate aminotransferase, diastolic blood pressure, liver cirrhosis, and diabetes.
Conclusion: We developed and validated an AI-based risk prediction model for early-onset HCC using the XGBoost algorithm. The model incorporated metabolic factors along with established variables like liver cirrhosis. This model may contribute to more active prevention of HCC by providing valuable insights into early-onset HCC risk.

WED-153

A patient charter for hepatocellular carcinoma: a co-created community call for action on equitable access to early diagnosis and multidisciplinary care

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Background and aims: Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and is the sixth most common cancer worldwide. There were approximately 866,136 new cases of liver cancer and 758,725 deaths worldwide in 2022. This abstract introduces the HCC patient charter co-created by patient advocates and healthcare professionals, which outlines seven principles of quality care that people with HCC should expect to receive, wherever they live and irrespective of their socioeconomic status. To introduce the charter, we chose to highlight one of it's seven core principles: 'patients need access to a multidisciplinary team to provide comprehensive care, considering both the liver condition and cancer treatment'.
Method: The charter was developed through multidisciplinary consultations and roundtables with clinicians, patient advocacy groups (PAGS), and healthcare professionals spanning six continents.
Results: The complexity of HCC necessitates a comprehensive approach to care, which is best delivered by a multidisciplinary

team (MDT), consisting of various specialists such as epidemiologists, hepatologists/gastroenterologists, oncologists, radiologists and interventional radiologists, transplant and hepatobiliary surgeons, pathologists, radiotherapists, nurse navigators, psychologists, physiotherapists, nutrition specialists, clinical pharmacologists, palliative care providers[i] and PAGS.
MDTs provide a thorough evaluation of the individual patient's HCC, develop personalized treatment plans[ii] and have been shown to improve patient quality of life. Five year survival rates are significantly higher in the patients who were managed via MDT compared to that of the patients who were not (71.2% vs. 49.4%). Despite international guidelines, such as the Barcelona clinic liver cancer (*BCLC*), European Association for the Study of the Liver, American Association for the Study and Asia Pacific Association for the Study of Liver emphasizing the importance of the multidisciplinary approach, barriers to accessing multidisciplinary care persist. The operational details required to make MDTs effective, such as identifying groups of patients that benefit most, defining the ideal composition of the team and understanding the clinical outcomes, have not been fully established. Resource constraints and insufficient health policies mean that best practice guidelines are not adopted even where they exist, resulting in geographic and socioeconomic disparities in care.
Conclusion: The charter serves as a roadmap for stakeholders to improve the care and outcomes of HCC patients. A key component of this is the implementation of multidisciplinary care. Through implementing a holistic care pathway, healthcare providers can ensure that patients receive the highest standard of care, regardless of their location or socioeconomic status.

WED-154

Artificial intelligence foundation models for histological diagnosis of hepatocellular carcinoma based on 121,344 digitalized whole slide image patches

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Background and aims: Hepatocellular carcinoma (HCC) is known for a high mortality rate. Recent advancements in artificial intelligence, particularly in the development of general-purpose foundation models for computational pathology, enable institutions with the premier medical resources to contribute to disease diagnosis by releasing models pretrained on their private datasets as open-source. We compared the most recent versions of foundation models for the histological diagnosis of HCC.
Method: We assessed four pretrained deep learning models for diagnosing HCC using whole slide images (WSIs). Each WSI was first digitized and annotated by clinical experts. Then, squared image patches of size 1024 were extracted with a sliding-window algorithm. A patch was assigned a label based on its inclusion within a tumor annotation. We finetuned the models on the training and validation sets to incorporate the information from the HCC data. Finally, we evaluated patch-level diagnostic performance of the deep learning models on a test set. The set of models includes a ResNet (convolutional neural network (CNN) with 23.5M parameters, pretrained on 36,666 WSIs), a ViT-S (small vision transformer (ViT) with 21.7M parameters, pretrained on 36,666 WSIs), a UNI (large ViT with 303M parameters, pretrained on 100,426 WSIs), and a Virchow2 (huge ViT with 632M parameters, pretrained on 3,134,922 WSIs).
Results: With 25 patients and 158 WSIs (non-HCC = 95, HCC = 63), we obtained 84,480 training patches from 110 WSIs, 18,432 validation patches from 24 WSIs, and 18,432 test patches from 24 WSIs. On the test set, ResNet achieved an area under curve (AUC) of 0.822 (95% CI: 0.816–0.828), a sensitivity of 0.830 (0.824–0.835), a specificity of 0.868 (0.861–0.874), a positive predictive value (PPV) of 0.805 (0.796–0.814), and a negative predictive value (NPV) of 0.846 (0.839–0.853). ViT-S achieved an AUC of 0.840 (0.836–0.846), a sensitivity of 0.838 (0.833–0.843), a specificity of 0.826 (0.818–0.832), a PPV of 0.775 (0.766–0.784), and an NPV of 0.890 (0.884–0.896). UNI achieved an AUC of 0.869 (0.864–0.874), a sensitivity of 0.873 (0.868–0.878), a specificity of 0.891 (0.883–0.897), a PPV of 0.845 (0.837–0.853), and an NPV of 0.892 (0.887–0.898). Virchow2 achieved an AUC of 0.879 (0.875–0.884), a sensitivity of 0.877 (0.873–0.882), a specificity of 0.868 (0.862–0.875), a PPV of 0.826 (0.818–0.834), and an NPV of 0.918 (0.913–0.924). Virchow2 had the highest AUC, sensitivity, and NPV scores, making it ideal for resource-rich scenarios that prioritize performance. UNI had the best specificity and PPV scores, offering a balance of performance and computational cost.
Conclusion: Foundation models offer great assistance to HCC diagnosis. Larger foundation models pretrained on larger datasets are usually more generalizable, while future models should aim at classifying different tumor characteristics.

WED-155-YI

Validation of hepatocellular carcinoma risk scoring tools in patients with chronic hepatitis B virus and hepatitis C virus infection– results from a large multicentre cohort study

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Background and aims: Hepatocellular carcinoma (HCC) is a recognised complication of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Identifying which patients need close surveillance for cancer is important to maximise the utility of limited resources and minimise the care burden for patients. Risk prediction scores have been developed to stratify patients in both groups, however, the effectiveness of the scores has not been well assessed in mixed ethnicity cohorts. We determined the performance of HCC risk prediction scores in a large, ethnically diverse UK cohort with HBV and HCV.
Method: We analysed the National Institute for Health and Care Research Health Informatics Collaborative (NIHR HIC) cohort derived from electronic health records from a consortium of nine hospital sites in England including 43,203 patients. aMAP (age, sex, albumin-bilirubin, platelets) and PAGE-B (platelet, age, sex) scores were applied to calculate risk of developing HCC in 3-, 5- and 10-years' time. Scores were calculated in patients with HBV or HCV mono-infection at the time of diagnosis. ICD-10 or Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) codes were used to identify HCC. Individuals with death or HCC diagnosed within 6 months of HBV or HCV diagnosis were excluded. The score performance was evaluated by Harrell's C-index and the area under the receiver operating characteristic (AUROC).
Results: 7475 HBV and 8130 HCV mono-infected patients met the inclusion criteria. At diagnosis, median (interquartile range; IQR) age was 42 (33–55) and 49 (39–58) years for HBV and HCV respectively. In the HCV cohort the majority were of White Caucasian (66%), followed by Asian (10%), Black African (2%). There was a mix of ethnicities in the HBV cohort, White Caucasian (26%), Asian (16%), Black-African (14%). A significant association was found between ethnicity and HCC, with higher rates in Asian, Black-Caribbean, and Chinese groups for HBV, and Asian and Black-African groups for HCV ($p < 0.001$). C-index [95%CI] were HBV PAGE-B 0.84 [0.83–0.87]; HBV aMAP 0.82 [0.80–0.85]; HCV aMAP 0.81 [0.80–0.83]. The performance of PAGE-B and aMAP in HBV were not significantly different. AUROC [95%CI] of predicting HCC risk at 3 years, 5 years and 10 years were HBV PAGE-B 0.847 [0.79–0.91], 0.847 [0.79–0.90], 0.832 [0.78–0.88]; HBV aMAP 0.816 [0.75–0.88], 0.793 [0.74–0.85], 0.775 [0.72–0.83]; HCV aMAP 0.811 [0.76–0.86], 0.806 [0.77–0.85], 0.786 [0.75–0.82].
Conclusion: In a multicentre UK cohort, aMAP and PAGE-B scores had comparable predictive value for HCC, supporting their use in ethnically diverse populations. New prediction tools incorporating demographic, clinical and virologic parameters in large longitudinal cohorts may improve the long-term predictive value of risk stratification for HCC in HBV and HCV.

WED-156
Evaluation of elevated tumor markers in the absence of detectable hepatocellular carcinoma during post-curative ablation follow-up

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Background and aims: Hepatocellular carcinoma (HCC) often recurs after curative treatment and requires post-treatment surveillance. While tumor markers are widely used for surveillance, some patients show elevated tumor markers without visible recurrence on imaging. This study aimed to assess the outcomes of HCC patients with persistent tumor marker elevation but no detectable recurrence on imaging following radiofrequency ablation (RFA).
Method: We analyzed 8,660 RFA treatments performed on 1,613 patients with HCC from 1999 to 2015. Among 2,294 cases that exceeded tumor marker cutoff values (alpha-fetoprotein (AFP) > 20 ng/mL for hepatitis C with sustained virological response and >200 ng/mL for others, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) > 15%, des-gamma-carboxy prothrombin (DCP) > 200 mAU/mL), we identified 185 cases of recurrence diagnosed more than 180 days after tumor marker elevation following curative RFA.
Results: The mean interval between tumor marker elevation and HCC recurrence was 336.9 days. At recurrence, tumor markers were elevated as follows: AFP > 20 ng/mL in 125 cases (67.6%), AFP > 200 ng/mL in 64 cases (34.6%), AFP-L3 > 15% in 107 cases (57.8%), and DCP > 200 mAU/mL in 35 cases (18.9%). At recurrence, 124 tumors (67.0%) were less than 20 mm and 163 tumors (88.1%) were less than 30 mm. Recurrence patterns included single intrahepatic lesion in 89 cases (48.1%), 2–3 lesions in 61 cases (33.0%), 4 or more lesions in 24 cases (13.0%), vascular or bile duct invasion in 6 cases (3.2%), and distant metastasis in 5 cases (2.7%). Treatment modalities for recurrence were RFA in 153 cases (82.7%), transarterial chemoembolization in 19 cases (10.3%), resection in 7 cases (3.8%), systemic therapy in 3 cases (1.6%), and best supportive care in 3 cases (1.6%). Local cure was achieved in 138 cases (74.6%).
Conclusion: Even when HCC was not detected on imaging despite elevated tumor markers, many recurrences were subsequently detected and curative treatment was possible with appropriate surveillance. However, it should be noted that cases with multiple intrahepatic recurrences, vascular or bile duct invasion, and distant metastases were observed.

Liver tumours – Experimental and pathophysiology

TOP-109
Treatment of cholangiocarcinoma with Claudin-1 antibodies reprograms the tumor microenvironment to improve survival in an orthotopic mouse model

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Background and aims: Cholangiocarcinoma (CCA) is a highly aggressive adenocarcinoma of the biliary tract system with unsatisfactory therapeutic options. Standard treatment for unresectable or metastatic CCA consisting of cisplatin and gemcitabine combined with checkpoint inhibitors targeting programmed cell death ligand 1

(PD-L1) or programmed cell death 1 (PD-1) offer only very limited objective response rates and survival. Claudin-1 (CLDN1) is a transmembrane protein overexpressed in epithelial cancer cells and a mediator of carcinogenesis, invasion and metastasis. The functional role of CLDN1 for the tumor microenvironment (TME) is largely unknown. Here, we aimed to study the functional role of CLDN1 for the TME and as a therapeutic target using CCA as a model.
Method: CLDN1 expression within the tumor and TME was analyzed by spatial transcriptomics in CCA patient tissues. A hydrodynamic tail vein injection (HDTV) model was applied to generate immunocompetent orthotopic animal models of intrahepatic CCA to study the therapeutic efficacy of anti-CLDN1 monoclonal antibodies (mAbs) as a single agent or in combination with PD-1 mAbs.
Results: CLDN1 was overexpressed in cancer cells and CLDN1 expression was associated with oncogenic signaling and reduced T cell infiltration in patient tissues. In orthotopic mouse models for CCA, CLDN1 gain-of-function studies showed enhanced tumor growth and decreased survival. Treatment with CLDN1 mAbs markedly and significantly reduced tumor burden and intratumoral fibrosis and resulted in increased intratumoral CD3+ and CD8+ T cell infiltration as well as modulation of macrophage localization. Gene expression analyses revealed down-regulation of pathways for fibrogenesis, carcinogenesis and up-regulation of pathways for T cell activation and proliferation. In contrast to PD1 mAb single agent therapy, the combination CLDN1 with PD-1 mAbs markedly and significantly improved overall survival.
Conclusion: CLDN1 plays a functional role in the TME by modulating tumor fibrosis and immune cell infiltration. Treatment with CLDN1 mAbs provides a novel perspective to improve the outcome of CCA by improving the response to CPIs.

TOP-110

Longitudinal analyses of Innate Lymphoid Cells in patients with HCC identifies patterns associated with disease stage and response to therapy with atezolizumab and bevacizumab

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Background and aims: Hepatocellular carcinoma (HCC) is a heterogeneous type of cancer. Patients with HCC differ in their immune cell profiles but there is no evidence this would impact treatment outcome. We investigated innate lymphoid cell (ILC)-pattern in peripheral blood mononuclear cells (PBMCs) of patients with HCC. ILCs are considered the innate counterpart of T cells. ILC composition was monitored at different stages of disease and during therapy with atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF). Frequencies of ILC1 s and natural-killer (NK) cells, ILC2 s with its subgroups of $cKIT^+$ and $cKIT^-$ILC2 s and ILC precursors (ILCPs) along with serum cytokines were measured to characterize patterns which identify response to therapy and correlate with clinical parameters of disease.
Method: PBMCs from 26 patients with advanced stage HCC and 25 patients at the stage of follow-up, who received ablative or surgical treatment and were tumor free at the time of analysis were enrolled. Patients with advanced HCC received therapy with atezolizumab and bevacizumab and were analyzed before treatment and after 3 months.
ILCs in PBMCs were analyzed using flow cytometry. Cytokines were measured in the serum. Clinical parameters were associated with immune cell profiles.
Results: ILC composition in the blood differed comparing tumor free and advanced HCC patients.
In the tumor free cohort, poor liver function and increased level of fibrosis went along with higher ILC2 frequencies. Checkpoint molecules CTLA-4 and PD-1 were increased on ILC1 s and ILC2 s and serum levels of Interleukin (IL)-1, 6, 8, 11, 12, 23, 27, Interferon alpha, TNF alpha, TSLP were lower in tumor free compared to advanced HCC patients, indicating a status of lower systemic inflammation.
Patients with advanced HCC showed lower cytotoxic NK cells but higher helper ILC1 s along with lower ILC2 s. Low ILCPs were a hallmark of advanced disease with poor liver function and high fibrosis scores. During therapy with atezolizumab and bevacizumab, ILC frequency increased with higher frequencies of ILC1 s and ILC2 s but no significant changes in cytotoxic ILC subgroups. Expression of immune checkpoints CTLA-4 and PD-1 increased on all ILCs during therapy. Reduced serum levels of cytokines IL-1 alpha, 4, 12, Interferon alpha, and TSLP but higher levels of IL-2, 6, 10 and IL-18 were measured. Response to therapy at 3 months was associated with a relative change from $CD4^+$ILC1-like cells and $cKIT^+$ILC2 s to $CD8^+$ILC1-like cells and $cKIT^-$ILC2 s.
Conclusion: The profile of ILCs differed significantly in patients with HCC based on the status of the disease. Advanced stage disease was associated with higher inflammatory cytokines, poor cytotoxic capability of ILCs and low expression of immune checkpoints on ILCs. Treatment with atezolizumab and bevacizumab resulted in no significant improvement of cytotoxic subgroups. New immunotherapy strategies need to explore whether targeting the anti-tumor properties of ILCs may improve outcome in early and advanced HCC.

TOP-127-YI

Primary cilia loss promotes neoplastic outgrowth in intrahepatic cholangiocarcinoma through suppression of neutrophilic immune surveillance

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Background and aims: Intrahepatic cholangiocarcinoma (iCCA) are epithelial neoplasms that arise from bile ducts within the liver. Cholangiocytes, which line these ducts, present protruding antennae-like primary cilia into the duct lumen. These sensory organelles regulate normal bile composition and maintain ductular homeostasis. Alterations in primary cilia number have been described in end-stage iCCA, however, whether primary cilia loss is an early event in the pathological process is unknown. As such, understanding whether primary cilia loss is involved in the early neoplastic transformation of biliary cells remains undefined. We aimed to determine: 1. Whether primary cilia are lost prior to the onset of carcinoma in iCCA and 2. How early primary cilia loss sculpts early tumorigenesis.
Method: Using patient iCCA and pre-malignant, diseased tissues we characterised the presence of primary cilia on pre-malignant and malignant biliary cells using immunofluorescence. We then combined transgenic iCCA mouse models in which we concurrently deleted the primary cilia gene *Wdr35* with iCCA-inducing mutations, to study the tumour-promoting effects of primary cilia loss. Using RNA sequencing and organoids derived from these murine models (with or without primary cilia) we characterise the neoplastic transcriptomic changes derived from primary cilia loss and

functionally interrogate how loss of this organelle affects immune cell recruitment to early cancers.
Results: Primary cilia are lost early in iCCA development. Here we show that primary cilia number is decreased in both IPNB and BilIN when compared to normal biliary cells. Experimentally controlled deletion of primary cilia-loss in mutant cells *in vivo* accelerated the formation of ductular neoplasia and significantly altered the immune landscape of these early lesions. Specifically, we found a significant reduction in neutrophil recruitment to iCCAs (across mutations) and demonstrate that this is not due to differential neutrophil priming or cell death. Rather, our data shows that primary cilia loss in mutant biliary cells disrupts their expression and secretion of neutrophil-recruiting chemokines which resulted in the significant reduction of neutrophil migration *in vitro* and a loss of neutrophilic immune infiltration in tumours *in vivo*.
Conclusion: Loss of primary cilia is an early event during the neoplastic transformation of biliary cells. By interfering with the activation of neutrophil recruitment to the liver as part of the normal innate immune response to tumour initiation, loss of primary cilia supports the survival and outgrowth of early neoplastic biliary clones, protecting them from immune clearance and demonstrating why early loss cilia loss is a critical step in cholangiocarcinogenesis.

TOP-128-YI

Efficacy of WNTinib, a novel selective therapeutic for CTNNB1-mutant tumors, in preclinical models of hepatoblastoma

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Background and aims: Hepatoblastoma (HB), the most frequent pediatric form of liver cancer, is a rare disease with a rising annual incidence of 1.8 cases per million children and limited therapeutic options. Standard perioperative platin-based regimens (*e.g.* cisplatin and doxorubicin) are associated with severe and lifelong side effects. The *CTNNB1* mutation is the most prevalent alteration in HB (~90%) and represents a potential therapeutic target. This study aims to *i)* assess the efficacy of WNTinib (an effective Wnt-*CTNNB1* inhibitor in HCC) in HB, and *ii)* explore strategies to enhance WNTinib efficacy in HB.
Method: To evaluate WNTinib efficacy, we performed 3 distinct animal models, including subcutaneous implantation of patient-derived xenograft (PDX) HB-tumors (n = 6), or 5 × 10^6 immortalized (HepG2) and PDX-derived (TT001) HB cells in NSG mice (n = 14/arm). Animals were treated with WNTinib (30 mg/kg, 5 days per week) or placebo until the end of the study, with tumor growth monitored throughout. To identify strategies enhancing WNTinib performance, we performed a kinome-wide CRISPR screen in which TT001 cells were treated with WNTinib (3 uM) for 3 weeks, and subsequently exposed to 3,052 unique single-guide RNAs targeting 763 human kinase genes. Candidate genes sensitizing cells to WNTinib are being validated *in vitro*.
Results: In the PDX animal model WNTinib delayed tumor growth in 4/5 *CTNNB1* mutant PDX models and demonstrated significantly better overall survival (OS) ($p < 0.05$) when compared to the control arm. In the HepG2 and TT001 models, WNTinib significantly reduced tumor growth ($p = 0.03$ and $p = 0.032$, respectively) and extended OS (log-rank $p = 0.008$ and $p = 0.03$, respectively) compared to the placebo. The CRISPR screen identified the top significantly depleted DYRK1A, MAPK1, and TESK2, suggesting their potential role as enhancers of WNTinib's activity in HB. Interestingly, DYRK1A inhibition has been shown to modulate WNT pathway activation in other contexts. The mechanisms underlying potential crosstalk between DYRK1A inhibitors and WNTinib in HB are currently being investigated. In our preliminary data, WNTinib and Dyrk1A-IN-1 inhibitor demonstrated strong synergy at low concentrations -based on the obtained combination index of ≤0.01- in 6 different HB cell lines, highlighting their potential as a promising dual treatment strategy for HB.
Conclusion: We have demonstrated that WNTinib effectively delays tumor progression and increases the overall survival in HB experimental models and identified DYRK1A kinase as a potential target to boost the efficacy of WNTinib activity in HB.

TOP-129-YI

Perineural invasion drives hilar cholangiocarcinoma progression via epithelial-mesenchymal transition augmented by cancer-associated Schwann cell-derived nerve growth factor inducible (VGF)

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Background and aims: Perineural invasion (PNI) is a frequently observed pathological feature in hilar cholangiocarcinoma (hCCA), and it is associated with poor prognosis and aggressive behavior. However, the underlying mechanisms and potential therapeutic strategies for addressing PNI remain elusive.
Method: This study retrospectively recruited 324 eligible hCCA patients to assess the prognostic significance and clinic-pathological correlation of PNI. A novel spatial proteomics approach integrating laser capture microdissection with high-resolution mass spectrometry was utilized to decipher the molecular alterations in hCCA cells and nerve fibers within PNI regions. Tumor-Schwann cell (SCs) co-culture model, patient-derived organoids, and several *in vivo* models were employed to explore the impact of the identified target on hCCA progression and to investigate potential therapeutic strategies.
Results: In this large cohort study of hCCA, PNI was detected in 59.3% (192/324) of patients and was identified as an independent risk factor associated with adverse prognosis (harzard ratio = 1.73 [1.22–2.45], $p = 0.015$), lymph node metastasis, and distant metastasis. The comparative spatial proteomics analysis of PNI regions (N = 13) versus non-PNI regions (N = 11) unveiled an up-regulation of the neurotrophic factor VGF in neural fibers as well as epithelial-mesenchymal transition (EMT) in hCCA cells. Multiplex immunofluorescence staining validated the specific overexpression of VGF in SCs within intra-tumoral nerve fibers. Further spatial distance analysis revealed an association between SC-derived VGF and EMT in hCCA cells within PNI regions. *In vitro* experiments demonstrated that both recombinant VGF protein and SCs-derived conditional media both could promote the proliferation, invasion, and EMT in hCCA cells. Furthermore, in the subcutaneous tumor implantation mouse model and sciatic nerve tumor injection mouse model, co-implantation of hCCA cells with SCs boosted the proliferation, circulating tumor cell dissemination, and nerve invasion of hCCA,

while SCs clearance, EMT inhibition, or VGF blockade could reverse the promoted progression.
Conclusion: This study establishes PNI as an independent pathological risk factor in hCCA and provides insights into the underlying molecular mechanisms, implicating SCs-derived VGF to promote EMT in hCCA cells. These findings support considering PNI as a pathological criterion and emphasize the clinical therapeutic prospects of clearing SCs, inhibiting EMT, and blocking VGF in the management of hCCA.

THURSDAY 08 MAY

THU-063
Engineered oncolytic vesicular stomatitis virus expressing HBsAg and IL-15 enhances immune activation and tumor killing in hepatitis B-positive hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal cancers worldwide, with chronic hepatitis B virus (HBV) infection being a major risk factor. Despite its high incidence, effective treatment options for HBV-positive HCC remain limited. This study aims to develop a novel therapeutic strategy for HBV-positive HCC by combining oncolytic virotherapy, therapeutic vaccination, and immune modulation.
Method: We engineered a recombinant vesicular stomatitis virus (rVSVM51R) to express hepatitis B surface antigen (HBsAg) and a superagonist form of interleukin-15 (IL15) fused with the IL15Rα sushi domain (rVSVM51R-S-mIL15-Ra). The therapeutic efficacy of this multifunctional oncolytic virus was evaluated in HBV-positive subcutaneous hepatoma and primary HCC mouse models. Single-cell RNA sequencing was used to analyze tumor-infiltrating immune cells, and cell depletion experiments identified key immune cell populations contributing to tumor inhibition. The humanized version of the virus (rVSVM51R-S-hIL15-Ra) was tested in a humanized mouse model to confirm its translational potential.
Results: rVSVM51R-S-mIL15-Ra demonstrated superior antitumor activity compared to rVSVM51R-mIL15-Ra or rVSVM51R-S, enhancing immune activation and promoting tumor cell destruction. Single-cell RNA sequencing revealed that rVSVM51R-S-mIL15-Ra increased infiltration of antigen-presenting macrophages, Th1 and memory CD4+ T cells, and effector CD8+ T cells into the tumor microenvironment, resulting in enhanced tumor killing. Cell depletion experiments confirmed the essential roles of macrophages, CD4+ T cells, and CD8+ T cells in tumor inhibition. Importantly, rVSVM51R-S-hIL15-Ra exhibited significant therapeutic efficacy in humanized mouse models, demonstrating its potential for clinical application.
Conclusion: This study presents a multifunctional oncolytic virus capable of effectively targeting HBV-positive HCC by inducing tumor cell destruction, activating anti-HBsAg immunity, and modulating the tumor microenvironment. This novel approach holds promise not only for HBV-positive HCC but also for other tumor types, offering a potential new avenue for cancer immunotherapy.

THU-064
GPC3-based mRNA cancer vaccine for hepatocellular carcinoma immunotherapy

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Background and aims: Messenger RNA (mRNA) vaccine has emerged as a promising strategy for cancer therapy. While personalized mRNA vaccine based on tumor-specific antigen (TSA) has obtained attention for its strong specificity and therapeutic potential, the high cost and complexity limit broader clinical application. In contrast, tumour-associated antigen (TAA)-based vaccine may offer a potentially simpler and more accessible approach, addressing key challenges associated with personalized therapies. In this study, we aim to develop a universal mRNA cancer vaccine targeting tumour-associated antigen Glypican-3 (GPC3) for hepatocellular carcinoma (HCC).
Method: We designed a GPC3-based mRNA vaccine for HCC and evaluated the therapeutic efficacy and safety of the cancer vaccine. We employed single-cell sequencing, spatial transcriptomics and mass cytometry to characterize the tumour microenvironment (TME) in pre-clinical model following combination therapy and to elucidate the mechanism.
Results: Our novel vaccine showed effective antigen production and elicited potent anti-tumour immune responses. It markedly suppressed HCC progression, particularly when utilized in combination with immune adjuvant. This demonstrated the feasibility of developing cancer vaccine based on TAA. Mechanistically, the mRNA-GPC3 cancer vaccine reprogrammed the tumour microenvironment in HCC and significantly enhanced the interaction between cDC1 and $CD8^+$ T cells.
Conclusion: The GPC3-based mRNA cancer vaccine showed considerable therapeutic efficacy in HCC. The combination with an immune adjuvant disrupted immune tolerance in HCC, presenting a promising translational treatment strategy for HCC. This study also indicated the viability of TAA-based cancer vaccine and the potential adaptability to other solid tumours, providing a versatile platform for cancer immunotherapy.

THU-065
Targeting CDC7 enhances anti-PD-1 immunotherapy in hepatocellular carcinoma

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Background and aims: Improving the effectiveness of immune checkpoint blockade for patients with hepatocellular carcinoma (HCC) remains challenging. The aim of this study is to identify the role of cell division cycle 7 (CDC7) in resistance to anti-PD-1 therapy in HCC.
Method: Orthotopic and subcutaneous HCC tumors and hydrodynamic tail vein injection models were used, as well as the subcutaneous B16F10 and MC38 tumors. RNA-sequencing was performed to identify CDC7's downstream effectors.
Results: CDC7 was overexpressed in HCC tissues and correlated with inferior prognosis and responses to anti–PD-1 treatments in HCC patients. We confirmed the oncogenic role of CDC7 in promoting HCC cell growth and metastasis. Genetic depletion or pharmacological inhibition of CDC7 elicits an increased influx of T cells into tumors, reduces tumor burden and prolongs the survival in HCC mouse models, while overexpressing CDC7 generates the opposite effects. CDC7 promotes tumor-associated macrophages infiltration and M2 polarization. In addition, CDC7 negatively manipulates PD-L1 expression on HCC cells via mTOR signaling. Lastly, blocking CDC7 functions augments antitumor immunity and enhances the effectiveness of anti-PD-1 therapy without causing additional toxicity in HCC mouse models, as well as in syngeneic B16F10 tumor models.
Conclusion: Our findings unveil a previously unrecognized role for CDC7 in regulating HCC antitumor immunity, potentially advancing HCC immunotherapy.

THU-075

A naturally derived monoterpene potentiates sorafenib's anticancer efficacy in drug-induced-hepatocellular carcinoma animal model

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Background and aims: Sorafenib (SB) is a multikinase inhibitor and is currently one of the first-line treatments for advanced hepatocellular carcinoma (HCC). However, its clinical benefit often went along with extensive side effects and the development of drug resistance, reducing the possibility of its long-term use. In a view to widen its therapeutic possibilities, combination therapy with other agents is thus being pursued. Our previous studies identified a monoterpene, safranal (SF); one of the major bioactive constituents of saffron, as a promising inhibitor of HCC progression. These data justify the identification of whether synergy, such as between SB and SF, exists toward a desired outcome of HCC treatment.
Method: In this study, we investigated the therapeutic use of SF or the combination of SB with the cirrhosis rat model of HCC and assessed the efficacy of SB and SF in inhibiting tumor growth. In addition to developing an animal model, RNA-seq Libraries were constructed and analyzed, differential gene expression was assessed, gene ontology enrichment, pathway and network analyses were employed and both immunohistochemical and immunoblotting techniques were utilized.
Results: In the cirrhotic rat model of HCC, treatment with SF-SB combination increased the anticancer potential of SB. The study presents an inexpensive natural bioactive agent, SF, to extend therapeutic potency in SB. Transcriptome analysis eventually identified 45 genes associated with suppression of HCC and included cell proliferation, response to oxidative stress, apoptosis, and regulation of the cell cycle. The combination downregulated NF-κB-p65, COX-2, and β-catenin, pointing out the use of this combination as one of the low-cost oncological therapies. Further studies must be done to establish safe dosages and clinical applications.
Conclusion: NF-κB, β-catenin, COX-2, TNF-α, cyclin B1, and MMP-9 pathways have been suggested to be implicated in the development of liver cancer and promote tumor growth, angiogenesis, inflammation, and inhibit apoptosis. Combined treatment with SF and SB decreases Bcl-2 levels and increases pro-apoptotic proteins such as Bax, caspase-8, caspase-9, and caspase-3, resulting in apoptosis. The combined treatment reduces proliferative markers (Ki-67, PCNA, cyclin B1) and inflammatory markers (NF-κB, β-catenin, MMP-9, COX-2), demonstrating anti-proliferative, anti-inflammatory, and apoptotic effects in HCC models.

THU-076-YI

RIPK3 is a metabolic regulator impacting mitochondrial dysfunction, endoplasmic reticulum stress and tumour development during murine chemical-induced hepatocarcinogenesis

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Background and aims: Receptor-interacting protein kinase 3 (RIPK3)-dependent signalling is triggered under chronic liver injury in humans. We have previously shown that blocking RIPK3 arrested steatotic liver disease progression and ameliorated hepatic metabolic dysfunction in mice. Still, the precise metabolic role of RIPK3 during hepatocarcinogenesis remains elusive.
Method: Two-week-old male C57BL/6 wild-type mice (WT) or *Ripk3*-deficient ($Ripk3^{-/-}$) pups were injected with diethylnitrosamine (DEN; 25 mg/kg i.p.). At 42 weeks macroscopic tumours were counted and measured for phenotypic characterization. Gene expression and protein production were evaluated through qRT-PCR and immunoblotting, respectively. Liver samples were processed for immunophenotyping by flow cytometry.
Results: Ablation of *Ripk3* abrogated tumour frequency and tumour size in DEN-exposed mice, compared with WT counterparts. In line with our previous reports, peroxisome proliferator-activated receptor-gamma coactivator-1alpha (*Pgc-1α*), implicated in mitochondrial biogenesis, was markedly increased in $Ripk3^{-/-}$ mice, compared with WT counterparts, in all experimental conditions. In turn, the expression of mitochondrial fission 1 (*Fis1*) and dynamin-related protein 1 (*Drp1*) were decreased in tumour nodules from $Ripk3^{-/-}$ mice, consistent with improved mitochondrial quality. Mitochondrial dysfunction is known to be closely related to endoplasmic reticulum (ER) stress, while mitochondria-ER interplay is critical for cell fate and inflammation. In this regard, the absence of *Ripk3* downregulated the three major unfolded protein response pathways in the livers of DEN-exposed mice, as assessed by reduced levels of total activating transcription factor 6 (ATF6), X-box binding protein 1 (XBP1 s) and ATF4, as well as both protein kinase R-like ER kinase (PERK) and eukaryotic Initiation Factor 2 (EIF2α) phosphorylation. Further, *Ripk3* deficiency reduced the expression of the downstream inflammasome markers caspase-1 and interleukin-1β, together with reduced macrophage infiltration in DEN livers. Finally, blocking RIPK3 did not impact the hepatic infiltration of CD4+T or CD8+T cells. Still, the levels of programmed death-1 (*Pd-1*) and its ligand *Pd-l1* were reduced in tumour nodules from mice lacking *Ripk*3.
Conclusion: *Ripk3* deficiency reduced hepatic tumour burden in a murine model of chemical-induced hepatocarcinogenesis. Our results indicate that RIPK3 impacts mitochondrial and ER homeostasis, likely contributing to metabolic dysfunction and inflammation in liver carcinogenesis. Moreover, *Ripk3* deletion influenced the PD-L1/PD-1 axis, dampening T cell exhaustion within the tumour microenvironment.
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THU-077-YI

E7386 enhances lenvatinib's antitumor efficacy and upregulates ATF4 signalling in preclinical models and human hepatocellular carcinoma

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Background and aims: Lenvatinib monotherapy is an approved first-line therapy for advanced hepatocellular carcinoma (aHCC). ~30% of aHCC show aberrant activation of beta-catenin and is associated with

immune evasion and limited immunotherapy responses. However, it remains an undruggable target. Here, we studied the antitumor and antiangiogenic activity of combining E7386 (an oral CREB-binding protein (CBP)/beta-catenin protein-protein interaction inhibitor) with lenvatinib and elucidated an additional mechanism of action of E7386 that boosts antitumor response.
Method: We generated a genetically engineered *CTNNB1*-mutant (encoding for beta-catenin) murine HCC model and randomized the animals to receive vehicle, E7386, lenvatinib, or the combination (n = 22–23 per arm). We evaluated survival and analyzed the tumors transcriptomically (single-sample gene set enrichment analysis) and at the protein level (immunohistochemistry and western blotting), along with five patient-derived organoids (PDOs), four HCC cell lines, and seven paired pre-/post-treatment human HCC specimens receiving E7386 in combination with lenvatinib (NCT04008797).
Results: *In vivo*, E7386 + lenvatinib significantly prolonged mouse survival in comparison with either monotherapy ($p < 0.05$). Cell lines and PDOs corroborated that sensitivity to E7386 depends on processes beyond CBP/beta-catenin interaction blockade. Mechanistically, transcriptomic analysis revealed that E7386 dysregulated multiple pathways governed by CBP partners. One of the top dysregulated pathways *in vivo* and *in vitro* represented the activation of Activating Transcription Factor 4 (ATF4) assessed by *ATF4* gene expression and enrichment of pathway-related gene signatures. Among seven paired patient samples obtained, upregulation of ATF4 signatures was confirmed in four patients, three of which exhibited maximum tumor shrinkage (MTS) larger than 30%. *In vivo* and *in vitro*, E7386 triggered ATF4-mediated integrated stress response (ISR) governed by the GCN2/EIF2alfa/ATF4 pathway, altering the expression of targeted pathways related with protein synthesis, cell cycle and angiogenesis, as suggested by transcriptomic analysis. In addition, E7386 concomitantly potentiated the antiangiogenic effects of lenvatinib *in vivo*, assessed by deconvoluting transcriptomic data and immunostaining, resulting in reduced CD31+ cells and endothelial cell content, and increased hypoxia.
Conclusion: The combination of E7386 and lenvatinib enhanced survival in mice and achieved anti-tumor responses in patients. Mechanistically, E7386 induced ATF4-dependent ISR, thereby potentially altering protein synthesis, reducing cyclin levels and limiting cell cycle progression. E7386 potentiated the antiangiogenic effects of lenvatinib, resulting in reduced angiogenesis, contributing to extended survival in mice and enhanced antitumor activity compared with either monotherapy.

THU-078
Artificial intelligence-driven prediction of biology-related poor outcome and presence of vascular invasion in hepatocellular carcinoma

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Background and aims: The median overall survival (OS) for patients with resectable hepatocellular carcinoma (HCC) is 5 years, but ~70% experience tumor recurrence. Advances in digital pathology and artificial intelligence (AI) are driving progress toward personalized clinical management. Here we aimed to develop an AI model capable of molecularly classifying HCC and the presence of microvascular invasion (mVI), providing information on the molecular biology associated with poor outcomes.
Method: A transformer-based deep-learning (DL) algorithm was developed using digitized hematoxylin and eosin (H&E) slides from an in-house cohort of 431 surgically resected HCC patients (training cohort). In the training cohort, 5-fold cross-validation was applied and the model was then deployed on two test sets: TCGA-LIHC (TCGA) (n = 363) and advanced-stage HCC (aHCC) (n = 64).
Results: In the TCGA cohort, patients with HCC molecular subclasses of proliferation (*S1* "stromal"; *S2* "stemness-angiogenesis") had a median survival of 3.8 years (5-year OS: 45%) vs non-proliferation subclass (*S3* "differentiated") patients, who had good outcome with a median survival of 5.8 years (5-year OS: 54%; $p < 0.005$). In the internal cross-validation, the DL-model showed significant prediction of molecular subclasses, achieving median area under the curve (AUC) values of 0.75 ± 0.11 for *S1*, 0.75 ± 0.07 for *S2*, and 0.79 ± 0.10 for *S3*. Consistently, the model's performance was reproduced in the test sets with AUCs of 0.72–0.80 on TCGA and 0.76–0.81 on aHCC. Patients from the TCGA classified into the *S3* non-proliferation subclass by the model had a median survival of 5.8 years (5-year OS: 52%), while patients classified into the *S1*/*S2* proliferation subclass had a median survival of 3.5 years (5-year OS: 44%; $p < 0.05$). In the same line, aHCC patients from the second test set stratified by the DL-model into the *S3* proliferation subclass showed an improved 3-year OS of 89% (95% CI: 71–100%) vs *S1*/*S2* proliferation subclass patients (42% [95% CI: 25–71%]; $p = 0.02$). In TCGA, 25% of the patients presented mVI. The prediction of mVI by the DL-model achieved a median AUC of 0.70 ± 0.08 in the internal cross-validation and 0.62 ± 0.07 in TCGA. Presence of mVI predicted by AI was associated with worse median OS (4.9 years vs 7.6 years for absence of mVI; $p < 0.005$) and an immunosuppressive microenvironment ($p < 0.001$).
Conclusion: The AI-based model presents a strong predictive capability for identifying HCC patients with favorable biology-related outcomes (*S3* molecular subclass) and mVI. The use of AI to predict molecular and pathological prognostic factors from routinely available H&E slides offers a personalized approach for assessing tumor biology.

THU-079
Beta klotho as a regulator of liver cancer cell proliferation and liver cancer development

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Background and aims: Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers and is ranked as the fourth leading cause of cancer morbidity worldwide. Abnormal fibroblast growth factor (FGF) signaling, mediated by FGF receptors (FGFR), has been identified as a driver of liver cancer in 20–30% of cases. However, selective FGFR inhibitors show only limited efficacy in patients with liver cancer, suggesting the involvement of other genes that control liver cancer progression. Recently, we identified KLB, a coreceptor involved in FGF signaling, as a regulator of cell proliferation in Hep3B cells, an FGF19-positive HCC cell line. However, how KLB regulates proliferation in these cells remains unclear. In this study, we aim to

investigate the molecular mechanism through which KLB regulates hepatocyte proliferation.
Method: KLB-deficient Hep3B cells were generated by lentiviral shRNA-mediated knockdown. Subsequently, the effect of KLB deficiency on hepatocyte growth, proliferation, and apoptosis was compared to wildtype cells. To identify the underlying mechanism of KLB-dependent regulation of liver cancer cell proliferation, transcriptomic and proteomic analyses of wildtype and KLB-deficient Hep3B cells were performed.
Results: Through analysis of the cancer dependency atlas (DepMap), we identified KLB as the top essential gene controlling Hep3B viability. Experimental validation of this finding through lentiviral knockdown of KLB in Hep3B cell revealed a 50% reduction of cell viability, which was explained by a 35% reduction in cellular proliferative capacity. Similar to previous studies, specific inhibition of FGFR4 using BLU9931 did not affect cell proliferation. However, pan-FGFR inhibition decreased cell proliferation to a similar extent as lentiviral knockdown of KLB, indicating the involvement of either FGFR1–3. Pathway enrichment analysis revealed that loss of KLB dysregulated many cancer-related pathways, including Hippo and Wnt signaling, cytokine-cytokine receptor interaction, and proteoglycans of cancer.
Conclusion: By inducing a lentiviral shRNA-mediated knockdown of KLB in Hep3B cells, we observed a decrease in cell proliferation upon a loss of KLB, suggesting that KLB can regulate liver cancer cell proliferation. Moreover, we identified that loss of KLB in Hep3B cells resulted in a dysregulation of cancer-related pathways, indicating a role for KLB in liver cancer cell development.

THU-080

Platelet-derived extracellular vesicles (PEVs) in hepatocellular carcinoma. Emerging diagnostic biomarkers

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Background and aims: Hepatocellular carcinoma is a primary liver cancer where platelets have been proposed as key mediators of carcinogenesis. Platelet activation induces the release of extracellular vesicles (PEVs). The study aims to determine the use of PEVs as a potential circulating biomarker of HCC.
Method: Two hundred thirty-five patients living with liver disorders were included: 53.6% (126/235) were MASLD (control group), 18.7% (44/235) cirrhotic patients followed for 5 years and 27.7% (65/235) had HCC. Plasma-heparin samples collected at the entry of the study were used to characterize PEVs by size, (0.2–1 µm Megamix Plus SC protocol, BD) and the expression of CD42b (glycoprotein Ib) and phosphatidylserine (the binding partner of annexin V) cell surface. Levels of PEVs Annexin V CD42b+ were quantified in plasma-heparin samples by flow cytometry. In a pilot study levels of PEVs were measured before and after HCC treatment. PEVs were isolated by FACs and the transcriptome profile was analyzed by the GeneChip™ miRNA 4.0 Array.
Results: The main sex 66.4% were male and average age 60 ± 11 years. Alpha-fetoprotein, GGT and AST serum level were increased significantly in HCC in comparison with non-HCC cirrhotic patients ($p = 0.016$, $p = 0.007$ and $p < 0.001$). In patients with HCC development a significant increase of PEVs was found (F4-HCC: 1785 ± 229; F4: 656 ± 156; Control: 525 ± 95 U/µl; $p < 0.0001$ and $p < 0.0001$ respectively), despite no significant differences in serum total platelets ($p = 0.33$). Diagnostic accuracy of PEVs-CD42b was addressed by AUROC: 0.80 (0.70–0.89; $p < 0.001$) with 70% sensitivity, 81.5% specificity; PPV 79% (Cut off: 463.75 U/µl). In multivariate analysis age, sex, AFP and PEVs-CD42b (OR: 1.001 (1.000–1.002; $p = 0.009$) were independently associated with HCC diagnosis. In addition, PEVs levels were also significantly increased in BCLC-A-HCC stage patients compared to the cirrhotic group ($p < 0.001$). In a subgroup of patients undergoing curative treatment ($n = 6$; 5 transplants and 1 resection) and 6 non-responders treated with sorafenib, PEVs levels decreased after treatment in the cured group, this trend was not observed in the non-responder group. We found significant differences in the transcriptomic profile of PEVs from BCLC-A HCC compared to cirrhotic patients; 9 microRNAs were upregulated (fold change >2, p value >0.01) and 10 were down regulated.
Conclusion: Circulating PEVs levels are raised in patients with HCC despite no changes in platelet levels. In clinical settings, PEVs showed potential as non-invasive biomarker for HCC diagnosis and treatment response. The preliminary data indicate a differential miRNA profile within platelet-derived EVs, but further studies are necessary to elucidate their potential contribution to HCC.

THU-081

Association of T cell epitope spreading with the clinical efficacy of HBV-TCR T cell therapy for HBV-related HCC

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Background and aims: The clinical success of therapies with T cells engineered with a Chimeric Antigen Receptor (CAR) or a T Cell Receptor (TCR) has been remarkable in hematological cancers but limited in solid cancers. By studying the immunological features of patients with HBV-related HCC treated with mRNA-TCR-engineered T cells, we observed that complete or partial response to the TCR-T cell treatment occurring in some patients was associated with the triggering of an inflammatory reaction, and it was not proportional to the quantity and persistence of TCR-T cells infused into the patients. We hypothesize that the efficacy of TCR-T cell therapy against HBV-related HCC can be associated not with their persistence but with an ability to alter the HCC microenvironment and induce novel antitumor T cells.
Method: Two patients with objective partial reduction of the HBV-HCC were studied during the course of multiple infusions of escalating doses of mRNA electroporated HBV-TCR T cells (maximal dose $3–10 \times 10^6$ CD8+TCR+ T cells/kg). Frequency of engineered and naturally induced HBV-specific T cells were quantified at multiple time points using two different methods (ELISPOT and whole blood cytokine release assay).
Results: Volumetric reduction of HCC metastasis (Pt1) and AFP values (Pt2) were associated with inflammatory events (CXCL-10 elevation/increased frequency of activated T cells) but were not proportional nor temporally related to TCR-T cell infusion. T cells specific for different HBV proteins were undetectable at the start of treatment but become detectable intermittently after the initial escalation phase of the treatment (<42 days after first infusion). Newly induced T cells were specific for HBV antigens not recognized by the adoptively transferred HBV-TCR T cells.
Conclusion: We provided preliminary evidences that clinical efficacy of TCR-T cell therapy in patients with HBV-related HCC is not directly proportional to the quantity and persistence of infused TCR-T cells but to their ability to induce inflammation and trigger a T cell response against novel T cell epitopes through a possible process of T cell epitope spreading.

THU-084

Comprehensive characterization of the peripheral immune landscape through single-cell transcriptomics in hepatocellular carcinoma patients undergoing immunotherapy

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Background and aims: Immunotherapy combinations have enhanced prognosis for hepatocellular carcinoma (HCC) patients eligible for systemic therapy, with about 20% achieving durable radiological responses. However, the factors influencing response or resistance remain unclear, hindering patient selection and treatment customization. In this study, we focused on first-line treatment with atezolizumab (anti-PDL1) and bevacizumab (anti-VEGF) (atez/bev).
Method: cfDNA (Cell-free DNA) levels were quantified and the C228T mutation in TERT promoter was analyzed in 11 HCC patients treated with atez/bev. Peripheral CD45+ cells were sorted and labeled with a panel of 30 immune markers (AbSeq Immune Discovery Panel). Cells were isolated individually using the Rhapsody system and 400 genes were amplified. Cell annotation was performed using Celldex and the Monaco reference dataset.
Results: The majority of patients (72.7%) of patients were male (8/11) with a median age of 64 years. The most prevalent underlying cause of liver disease was hepatitis C virus infection (54.5%). The median follow-up period was 19 months. During follow-up, two patients (18.2%) exhibited a complete radiological response (CR), five patients (45.4%) demonstrated a partial radiological response (PR), and four patients (36.4%) exhibited disease progression (PD) as the best radiological response, assessed according to the mRECIST criteria. Patients who exhibited a response (CR/PR), demonstrated lower baseline levels of circulating cell-free DNA (cfDNA), with a mean of 3.95 ± 1.96 ng/µl compared to 5.80 ± 1.69 ng/µl in patients with PD. No statistically significant differences were observed in TERT C228 T mutation levels between patients who achieved CR/PR (14.06 ± 6.04) and those who exhibited PD (13.60 ± 12.15). The analysis of cell populations in peripheral blood revealed the presence of 17 distinct clusters of cells in the cohort under study. Patients with PD as the best radiological response exhibited a baseline level of 0.56% [0.37–0.83] of plasmablasts, compared with 0.19% [0.13–0.55] in patients with CR+RP (p = 0.03). Patients who achieved CR or PR exhibited alterations in the Th1/Th17 lymphocyte population between the baseline measurement (4.3% [1.19–5.29]) and the three-month follow-up (2.9% [0.79–3.3]) (p = 0.03).
Conclusion: In this preliminary analysis, significant differences in specific immune cell populations were identified utilizing single-cell technology. This approach may serve as a valuable tool for identifying patients with distinct prognostic outcomes under atezolizumab and bevacizumab (atez/bev) treatment. Molecular investigations aiming to elucidate gene and protein expression profiles are currently ongoing.

THU-085-YI

SMG7 as a potential driver of chronic liver disease progression to hepatocellular carcinoma

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Background and aims: SMG7 factor has a main role in the nonsense-mediated mRNA decay (NMD) pathway, which eliminates mRNAs with common errors, such as the presence of a premature termination codon (PTC), avoiding their translation. In addition, SMG7 promotes the survival of cells after genotoxic stress by inducing the ATR-Chk1 pathway. The continuous exposition of lipotoxic free fatty acids (FFA) in chronic liver disease (CLD) leads to cellular stress and liver damage. In fact, many NMD targets are implicated in cellular stress response. Therefore, this work aimed at studying the involvement of NMD, and specially SMG7, in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic-dysfunction associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC).
Method: Expression (mRNA) of 22 NMD components was analyzed in two retrospective HCC cohorts (cohort 1 [n = 89 HCC and non-tumor paired adjacent tissues (NTAT)] by microfluidic-based qPCR array and cohort 2 [n = 31 HCC and n = 31 NTAT] by RNA-seq), and validated in six external cohorts with healthy, MASLD, MASH, HCC, and/or NTAT samples. Human (THLE2) and mouse primary hepatocytes (MPH) were treated with FFAs (oleate and palmitate). Pharmacological (NMDI14, which blocks SMG7-UPF1 interaction) and genetic modulation of SMG7 were carried out in two HCC-derived cell lines (Hep3B and SNU-387) to explore the functional effects on proliferation, migration, colony and tumorospheres formation. Additionally, NMD target genes expression (mRNA to pre-mRNA ratio) was measured.
Results: SMG7 is consistently overexpressed in samples of MASH, HCC, and MASH-derived HCC from different internal and external cohorts. Besides, the expression of SMG7 (mRNA) was induced by palmitate in THLE2 and MPH and its overexpression in HCC cell lines promotes proliferation, and colony and tumorospheres formation. The silencing of SMG7 decreased the proliferation and migration of SNU-387, while in Hep3B does not have major functional effects, possibly due to the compensatory increase in UPF1, another key NMD factor. In fact, the co-silencing of SMG7 and UPF1 reduced tumor aggressiveness in both HCC-cell lines. Accordingly, the treatment with NMDI14 (blocking the SMG7-UPF1 interaction) reduced the aggressiveness of the HCC cell lines, without affecting the viability of MPH. Mechanistically, there were no changes in the expression of NMD target genes when SMG7 was modulated, suggesting the implication of novel alternative pathways.
Conclusion: NMD, and especially the SMG7 factor, could play a relevant role in the MASLD-HCC progression, therefore, paving the way towards the identification of biomarkers and/or therapeutic targets in these pathologies. Fundings: ISCIII (FI21/00141, PI23/00652, DTS22/00057, MV23/00068; co-funded by the European Union), MINECO (FPU21/04833), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/CIBERehd.

THU-086

Translational approaches to evaluating novel antifibrotic and anticancer drugs for hepatocellular carcinoma: strategies for prevention and treatment

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Background and aims: Most hepatocellular carcinoma (HCC) cases develop in the context of severe liver fibrosis and cirrhosis, driven by chronic liver inflammation. A key hallmark of this process is the accumulation of hyaluronic acid (HA), a major component of the extracellular matrix. This study aimed to evaluate the potential of two potent HA synthesis inhibitors as a preventive strategy to impede hepatocarcinogenesis in HCC.
Method: HA synthesis genes *HAS2* and *HAS3* in human HCC clinical specimens were analyzed using qRT-PCR from 23 paired tumor and non-tumoral adjacent tissues collected from HCC resection. HA inhibition in vivo was performed in preclinical model of chronic inflammation using adult male transgenic HCC mouse model (HCC-TG) together with its wildtype counterpart (WT) using either non-glycosylated (4-MU) and novelly synthesized glycosylated-4-methylumbelliferone (4-MUR), the later targets only (pre)neoplastic cells. Following oral treatment with two concentrations of 12.5 and 25 mg/kg/day for 3 months, macroscopical and histological parameters of the livers, levels of serum transaminases, and in-depth molecular analysis of genes related to fibrosis, HA synthesis, and inflammation were assessed by qRT-PCR and Western blot.
Results: From human HCC specimens, *HAS2* was upregulated in adjacent non-tumoral compared to HCC ($p < 0.001$) while *HAS3* showed the opposite ($p < 0.05$). During and following in vivo treatment in mice, body and liver weight measurement indicated that both 4-MU and 4-MUR were safe. 4-MUR administration did not increase the levels of alanine transaminase and lactate dehydrogenases in HCC-TG mice. Histological analysis showed that compared to controls, both 4-MU and 4-MUR improved liver histology by reduction of inflammation and fibrosis grades ($p < 0.001$ compared to controls). Further, molecular analysis on 139 mouse liver tissues showed that both compounds dysregulated genes related to HA synthesis (*Has2, Has3, Hyal1, Hyal2*), HA receptor (*Cd44*), fibrosis (*Acta, Fsp1*) and inflammation (*Cxcl1, Il-6, Il1b*, and *TNFα*). The extent of fibrotic-associated genes down-regulations was more noticed for 4-MUR.
Conclusion: This study demonstrated that blocking HA synthesis using both 4-MU and 4-MUR effectively reduced liver damage and inhibited the process of hepatocarcinogenesis, likely through their specific targeting mechanism.

THU-087
TIGAR SUMOylation: a key modulator of metabolic balance in hepatocellular carcinoma

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Background and aims: Tumors, including hepatocellular carcinoma (HCC), undergo extensive metabolic reprogramming to sustain their growth and survival. This study explores a novel, non-tumor-suppressive function of p53 in the metabolic reprogramming of HCC via one of its target genes, *TP53-Induced Glycolysis and Apoptosis Regulator* (TIGAR). While TIGAR is known for its protumorigenic role—shunting glucose from energy production toward nucleotide synthesis and DNA repair—the regulatory mechanisms driving its activation remain poorly understood. Recently, SUMOylation, a pivotal post-translational modification (PTM), has been implicated in liver cancer progression, potentially shedding light on TIGAR's activation.
Method: A comprehensive SUMO interactome analysis was performed using GST-tagged SUMO Binding Entities (SUBEs) for protein pulldown in multiple human hepatoma cell lines (HuH7, PLC, HepG2, and SNU449).
Results: TIGAR displayed a significantly elevated level of SUMOylation, particularly in the SNU449 cell line, which subsequently became the primary focus. Bioinformatic tools were employed to predict SUMOylation-prone sites on the TIGAR protein. Using these predictions, we developed stable cell lines expressing both wildtype and mutant TIGAR variants. The introduction of mutations led to a marked reduction in TIGAR SUMOylation levels. Cells expressing the mutant TIGAR exhibited diminished proliferation, migration, invasion, and spheroid formation. Furthermore, loss of TIGAR SUMOylation disrupted the pentose phosphate pathway, as evidenced by an increased NADP/NADPH ratio and a reduced GSH/GSSG ratio, resulting in heightened oxidative stress.
Conclusion: This study identifies SUMOylation as a novel regulatory mechanism for TIGAR, offering a promising therapeutic target in liver cancer. By disrupting TIGAR SUMOylation, we highlight a potential strategy to induce oxidative stress and inhibit tumor growth. Given TIGAR's dual roles in cancer and normal cellular function, we propose that inhibiting TIGAR SUMOylation, alone or in combination with existing therapies, may serve as an effective approach for HCC treatment. This underscores the broader significance of PTMs as therapeutic targets in oncology.

THU-088
MicroRNA-372-3p impairs fatty acid metabolism in hepatocellular carcinoma cells by targeting CPT1A and ACSL4

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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide; however, treatments remain ineffective for many patients. Understanding molecular mechanisms that promote HCC could yield a new therapeutic option. Recent studies suggest emerging roles of microRNAs in HCC biology, including microRNA-372-3p (miR-372-3p), which has been implicated in the pathogenesis of various cancers. Nevertheless, the role of miR-372-3p in HCC remains controversial. In this study, we employed a transcriptomic approach to dissect the molecular function of miR-372-3p in HCC cells.
Method: We generated control and miR-372-3p-overexpressing (372-OE) HCC cells from three independent lines and assessed their proliferation, migration, invasion, and colony formation. To identify the molecular function of miR-372-3p in HCC, we employed RNA-seq analysis of control and 372-OE HCC cells, followed by gene set enrichment analysis (GSEA). To investigate fatty acid metabolism, we

stained control and 372-OE HCC cells for their lipid droplets and determined levels of triglycerides and fatty acid oxidation (FAO). We used confocal and transmitted electron microscopy to examine the interactions of lipid droplets with mitochondria and lysosomes. Finally, we used the bioinformatic approach to identify potential targets of miR-372-3p in lipid metabolism and validated their direct interaction with dual luciferase assays.

Results: We showed that miR-372-3p levels were suppressed in HCC cell lines compared with normal hepatocyte cell lines. Overexpression of miR-372-3p impaired proliferation, migration, invasion, and colony formation of HCC cells, suggesting its tumor suppressing function. Transcriptomic analysis of 372-OE HCC cells revealed enrichment of downregulated genes in fatty acid metabolism, including *CPT1A*, *CPT2*, and *ACSL4*, which are known to facilitate FAO. Consistent with our transcriptomic analysis, we found that miR-372-3p promoted accumulation of lipid droplets and high levels of triglycerides while inhibiting FAO in HCC cells. Moreover, 372-OE HCC cells showed impairment in utilizing lipids in the absence of glucose. We further showed that the interactions of lipid droplets with mitochondria and lysosomes were significantly compromised in 372-OE HCC cells, consistent with decreasing FAO. Mechanistically, we computationally identified three potential direct targets of miR-372-3p in FAO and demonstrated the direct interaction between miR-372-3p and the 3' untranslated regions of *CPT1A* and *ACSL4* transcripts by dual luciferase assays.

Conclusion: miR-372-3p impairs lipid metabolism in HCC cells by suppressing expression of FAO genes and thus could serve as a new therapeutic target to control cancer growth.

THU-089-YI

Tumor microenvironment differences in liver cancer are lineage-dependent when controlled for oncogenic pathway activation

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Background and aims: Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, following hepatocellular carcinoma (HCC). ICCA and HCC resemble morphologically distinct liver epithelial cell compartments and exhibit different genetic alterations. They also display a unique tumor microenvironment (TME). Unlike HCC, iCCA is characterized by a stroma-rich TME that affects therapeutic responses to chemotherapy and immunotherapy. However, the molecular mechanisms driving stromal formation in iCCA remain largely undefined. This study aims to investigate the molecular mechanisms driving the stromal phenotype in iCCA while controlling for oncogenic pathway activation.

Method: We established a syngeneic mouse model using organoids derived from murine cholangiocytes and hepatocytes. Both were genetically engineered to carry *Trp53* deletion and $Kras^{G12D}$ mutation (chol-PK and hep-PK, respectively) to control liver tumor formation for both cell lineage and genetic alterations. After orthotopic implantation ($n \geq 9$ per group), liver tumors were systematically analyzed using multiplexed ion beam imaging (MIBI) with a 36-plex panel to map TME spatial distribution ($n \geq 4$ per group). Cell lineages were annotated semi-automatically with the self-organizing map, an unsupervised machine-learning algorithm. Transcriptome and secretome analyses of the organoids were performed to identify cell-intrinsic factors linked to stromal enrichment.

Results: Upon orthotopic implantation, chol-PK and hep-PK organoids formed tumors with 100% and 78% penetrance, respectively, reflecting human iCCA and HCC. Chol-PK tumors were stroma-dominant, with immune cells concentrated at the tumor border. In contrast, hep-PK tumors had a denser cancer cell architecture and more extensive immune infiltration. MIBI revealed distinct spatial patterns of myofibroblasts, T cells, and myeloid cells between tumor types. Transcriptome analysis revealed 186 shared genes ≥ 2-fold up-/downregulated (padj < 0.01) in both organoid lines upon *Trp53* deletion and Kras activation, but 2057 genes were uniquely altered in chol-orgs (≥2-fold, padj < 0.01). The 1011 uniquely upregulated genes in chol-PK were enriched in pathways related to stromal cell modulation, such as focal adhesion (padj < 0.00025).

Conclusion: Our novel, cell lineage-controlled liver cancer model effectively demonstrates relevant differences in TME architecture reminiscent of human iCCA and HCC despite activating the same oncogenic pathways. Lineage-dependent expression changes upon transformation may explain the distinct stromal responses observed in these two cancer entities.

THU-090

Glutaminolysis-driven iron accumulation in the liver: a mechanism for aging through Lysosomal dysfunction

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Background and aims: Cellular senescence in the liver can be triggered by various factors, including the accumulation of hepatotoxic compounds such as ammonium and iron. Furthermore, metabolic alterations can enhance the hepatic susceptibility to aging. Glutaminase isoform 1 (GLS1) plays a crucial role in ammonium metabolism, converting glutamine to glutamate and ammonium in mitochondria. Our objective is to investigate the involvement of GLS1 and its functional consequences in liver cell senescence.

Method: We employed mouse models and primary hepatocyte cultures for our study. We also analysed aged individuals and obese patients.

Results: Our research indicates that aging individuals experience increased glutaminolysis and hepatic iron accumulation. We found that hepatocyte glutaminase (GLS1) overexpression promotes

hepatic iron accumulation and accelerates aging in vivo. Mechanistically, both in vivo and in vitro experiments demonstrate that toxic ammonia accumulation disrupts the lysosomal acidification capacity, impairing critical processes such as mitophagy and iron metabolism, thereby making hepatocytes more susceptible to ferroptotic stress. Furthermore, the use of an ammonia scavenger and an iron chelator mitigates metabolic dysfunction-associated steatohepatitis (MASH) and ameliorates age-related hallmarks in vitro by restoring lysosomal acidification capacity and enhancing mitochondrial function.
Conclusion: These findings identify a novel mechanism influencing hepatic susceptibility to aging and suggest that GLS1 may serve as a potential target for modulating mitochondrial function by reducing iron and ammonium levels in the context of cellular senescence. Additionally, these results support the potential of metabolite chelators as promising therapeutic options for aging.

THU-092
Modulation of the tumor microenvironment: targeted silencing of AATF suppresses TGF-β signaling via lncRNA MIR100HG in hepatocellular carcinoma
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Background and aims: Hepatocellular carcinoma (HCC) is a fatal chronic liver disease with limited therapeutic options. Novel approaches targeting its molecular drivers could be effective in blocking the pathological signaling. Previously, we have shown the pivotal role of apoptosis antagonizing transcription factor (AATF) in promoting angiogenesis in HCC. However, the effect of targeting AATF in the tumor microenvironment (TME) and its effect on HCC development and progression remains unexplored. Here we aim to assess liver-specific silencing of AATF in TME and its effect on tumor growth in an orthotopic xenograft model of HCC.
Methods: Orthotopic xenograft models of HCC were generated by implanting human HCC cells, QGY-7703, into the livers of athymic nude mice. Liver-specific AATF silencing was accomplished via tail vein injection of an adeno-associated viral vector 8 (AAV8) containing siRNA sequences targeting AATF. Tumor progression was monitored over a 4-week period before euthanizing the mice. Whole transcriptomics analysis and functional validation were carried out using liver tissues of control and siAATF mice, and the data were mapped against human and mouse genomes separately to differentiate species-specific expression.
Results: The targeted silencing of AATF in the liver of the orthotopic HCC mouse model showed a notable decrease in tumor growth in comparison to the control mice. The RNA seq transcriptomic analysis showed a significant alteration in the TME (mouse) upon AATF silencing, as evidenced by decreased inflammation, immune response, epithelial-mesenchymal transition, extracellular matrix formation, and angiogenesis. Of note, in the tumor (human), pathways related to the cell cycle, cellular stress response, and metabolism were downregulated in siAATF mice compared to the controls. Furthermore, the integrative analysis of the human-mouse genome showed the transforming growth factor-beta (TGF-β) signaling pathway to be responsible for the tumor-TME interactions. The co-expression analysis of long non-coding RNA (lncRNA) and messenger RNA (mRNA) showed a positive correlation to the downregulated TME-related processes in siAATF mice. Consistently, six hub lncRNAs involved in extracellular matrix remodeling were found to be downregulated in siAATF mice compared to controls. Further analysis and functional validation revealed that silencing of AATF modulated the tumor microenvironment by suppressing the TGF-β signaling pathway via the lncRNA MIR100HG in HCC.
Conclusion: Thus, the study offers compelling molecular evidence supporting AATF's role in TME remodeling, suggesting its potential as a therapeutic target in HCC.

THU-095
Single-cell spatial proteomic landscape of intrahepatic cholangiocarcinoma immune microenvironment reveals immune evasion via FSTL1negative macrophage
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Background and aims: Intrahepatic cholangiocarcinoma (ICC), an aggressive biliary malignancy, is usually diagnosed at advanced or metastatic stages, resulting in poor prognosis with five-year survival rate less than 5%, significantly lower than many other cancers. The incidence of ICC has risen steadily, yet effective treatments remain scarce. Understanding the ICC immune landscape while preserving the tumor microenvironment (TME) architecture could reveal potential targets for innovative therapies to improve patient outcomes.
Method: An imaging mass cytometry (IMC) panel was designed to analyze 36 biomarkers across 36 tissue regions from 12 each ICC patients, including tumor tissue, adjacent tumor and non-tumor tissue, and normal tissue. This approach produced single-cell resolution histology images, enabling cell-type clustering and assessment of spatial distribution and functional changes with subsequent in vivo and in vitro experiments validating results above.
Results: A comprehensive analysis of the ICC immune microenvironment was performed. In the tumor region, immune cell numbers decreased, while an unusual significant positive interaction between M1-phenotype macrophages and tumor cells were observed. At the tumor margin, an accumulation of M2 macrophages, CD4+ T cells, CD8+ T cells, Treg cells, and neutrophils was identified. M2 macrophages showed positive correlations with Kupffer cells and negative correlations with fibroblasts and endothelial cells, while neutrophils exhibited significant positive correlations with Treg cells. To further investigate, macrophages were re-clustered into seven subsets (C1–C7). Among M1 macrophages, only the FSTL1-negative Mac C6 subset demonstrated a positive correlation with tumor cells, suggesting its role in altering the tumor microenvironment, while Mac C1 and Mac C2 subsets were negatively correlated. Additionally, 8 cellular neighborhoods were defined, including an immune "barrier zone" at the tumor margin, primarily composed of neutrophils and Treg cells, which restricted the infiltration of tumor-killing immune cells. The Mac C6 subset was closely associated with this immune barrier. Functional validation using macrophage with characteristic proteins of the Mac C6 confirmed these findings through co-culture with tumor cells and immune cells.
Conclusion: Our study reveals for the first time a distinct immune landscape in ICC, highlighting the role of Mac C6 macrophage subset in immune regulation, promoting immune evasion and immune barrier. Targeting Mac C6 or disrupting the immune barrier may enhance anti-tumor immunity, offering new therapeutic strategies for ICC.

THU-096
FSP1 inhibitor icFSP1 enhances lenvatinib sensitivity for hepatocellular carcinoma treatment by promoting ferroptosis through the FSP1/MIR4435-2HG pathway
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Background and aims: The tyrosine kinase inhibitor Lenvatinib treats advanced hepatocellular carcinoma (HCC). However, resistance hinders its therapeutic effect. Here, icFSP1, a ferroptosis suppressor protein 1 (FSP1) inhibitor, significantly enhances the anti-tumour effect of Lenvatinib in HCC both in vitro and in vivo. This study aimed to explore the effect of icFSP1 on lenvatinib sensitivity and understand its mechanism.
Method: The half-life of icFSP1 and lenvatinib and the synergy between the two drugs were observed in two hepatocellular carcinoma cell lines. The upstream target genes of FSP1 were traced in TCGA, FerrDb, and other databases, and the lncRNA MIR4435-2HG was positively correlated with FSP1. MIR44435-2HG was verified to be associated with ferroptosis in two different hepatocellular carcinoma cell lines using different assessments of ferroptosis markers. Next, apoptosis, proliferation, migration, and invasion assays further validated the regulatory mechanisms of MIR4435-2HG knockdown or overexpression and icFSP1 on tumorigenesis and development and sensitivity to lenvatinib in cells. Finally, the effects of MIR4435-2HG and icFSP1 on sensitivity to lenvatinib were verified in BALB/c-nu mice, and the changes in cells of mouse tumor tissues were verified by HE staining, and the proliferation and lipid peroxidation of mouse tumor tissues were verified by ki67 and 4-HNE staining.
Results: icFSP1 could inhibit tumor growth and enhance the sensitivity of lenvatinib for hepatocellular carcinoma treatment. MIR4435-2HG was closely associated with ferroptosis in hepatocellular carcinoma cells. Meanwhile, rescue assays yielded that MIR4435-2HG/FSP1 is a positive feedback pathway, and MIR4435-2HG plays a positive promoting role in hepatocellular carcinoma development. Finally, we found that the combination of MIR4435-2HG and icFSP1 modulated the sensitivity of in vitro and in vivo treated hepatocellular carcinomas to lenvatinib.
Conclusion: We identified a drug and molecular mechanism that enhances the sensitivity of lenvatinib for hepatocellular carcinoma treatment to transform lenvatinib resistance.

THU-097

A syngeneic and orthotopic HCC mouse model demonstrating the high efficacy of combination therapies targeting the ECM and immune microenvironment

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Background and aims: The stromal composition of hepatocellular carcinoma (HCC) typically features a thin basement membrane-like ECM at its center, surrounded by a dense extracellular matrix (ECM) enriched with cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), which promote tumor progression. We explored novel therapeutic approaches targeting components of the HCC tumor microenvironment (TME) using a syngeneic and orthotopic HCC model in immunocompetent mice.
Method: Dt81Hepa1-6/βgeo HCC cells (1×10^5) were injected into the spleens of male C57BL/6 mice leading to a homogeneous colonization of the livers with HCC foci. At day 17 after inoculation, 5–8 mice per group received a) 0.075 mg/kg of the mTOR inhibitor rapamycin (Rapa) as monotherapy via daily intraperitoneal (i.p.) injection; b) 2 mg/kg i.p. of an antisense oligonucleotide (ASO) to the macrophage polarization modulator INT (ImmuneNTech)-12 twice a week; c) the combination of both agents. PBS only injected HCC-bearing mice served as controls (Ctrl). Five weeks post-surgery mice were sacrificed and the livers analyzed.
Results: Both monotherapies, Rapa and INT-12 ASO, induced a highly significant HCC reduction, as reflected by hepatic beta-galactosidase activity and reduction in liver weight and liver to body weight ratio compared to Ctrl. The combination of Rapa and INT-12 ASO was slightly superior to the monotherapies. Histological assessment via Sirius Red staining demonstrated a significant reduction of hepatic collagen content in treated livers vs Ctrl (1.5% vs 5% collagen area), indicating a strong anti-fibrotic effect. Quantitative immunohistochemistry showed a significant reduction in CD68+ macrophages across all treatment groups, most prominently with combination therapy. All treatments markedly reduced FoxP3+ regulatory T cells. qPCR revealed unconventional patterns in M1/M2 macrophage markers, suggesting a strong early inflammatory response in this HCC model. Treatment safety was confirmed by unchanged liver enzymes and creatinine.
Conclusion: Our highly reproducible orthotopic and syngeneic model of HCC in immunocompetent mice allows the rapid testing of novel anti-cancer combination therapies targeting the HCC TME. Our TME-targeting monotherapies, and particularly their combination, effectively prevented HCC progression. Beyond their direct anti-tumor effects, these therapies show anti-fibrotic activity as evidenced by reduced collagen levels.

THU-098

miR-30e-3p/CXCL3 axis predicts early tumor escape in hepatocellular carcinoma patients undergoing sorafenib treatment

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Background and aims: Curative treatment options for hepatocellular carcinoma (HCC) remain largely limited to a minority of patients diagnosed at early disease stages. Immunotherapy and Tyrosine Kinase Inhibitors (sorafenib and lenvatinib) represent the first-line treatments in advanced cases. Although immunotherapy has revolutionized HCC treatment, only a limited number of patients achieves a prolonged response. The identification of biomarkers that stratify patients to tailored treatments or predict early tumor escape remains an unsolved clinical need. MicroRNAs and chemokines have crucial roles in HCC progression and drug resistance. We previously reported high miR-30e-3p levels in non-responder patients undergoing sorafenib treatment. Here, we aimed at identifying novel miR-30e-3p targets involved in sorafenib response, which could also serve as predictive biomarkers for treatment outcomes.
Method: miR-30e-3p and CXCL3 levels were measured by qPCR analysis in serum and tissue of HCC patients and DEN-induced HCC rat model. CXCL3 targeting by miR-30e-3p was assessed by functional studies (qPCR, Western Blot, ELISA) and dual-luciferase reporter assay in transiently transfected and stably infected HCC cell lines. CXCL3 levels were evaluated by ELISA assay in supernatant of HCC cell lines and serum of sorafenib-treated HCC patients and correlated with treatment response. Statistical analyses were performed to investigate correlations with clinicopathological features.

Results: CXCL3 was found to be upregulated in human and rat HCCs, showing a direct correlation with CXCR2 receptor and an inverse one with miR-30e-3p. Functional studies and dual-luciferase reporter assay demonstrated CXCL3 targeting by miR-30e-3p in HCC cell lines. In DEN-HCC rat model, higher CXCL3 tissue levels were associated with sorafenib resistance, showing a negative correlation with apoptotic markers and tumor suppressor genes and a positive one with tumor size. In HCCs, higher CXCL3 mRNA levels associated with microvascular invasion, while higher CXCL3 and miR-30e-3p levels at two-months follow-up were observed in serum samples of non-responder patients. Additionally, CXCL3 protein levels inversely correlated with days of sorafenib treatment and positively correlated with neutrophils count, whereas miR-30e-3p positively correlated with serum levels of HCC marker alfa-fetoprotein (AFP). CXCL3 and miR-30e-3p showed a promising predictive potential in ROC curve analysis.
Conclusion: CXCL3 is a novel miR-30e-3p target in HCC and predicts sorafenib resistance. If validated in larger cohorts, CXCL3 and miR-30e-3p represent promising circulating biomarkers for early detection of tumor escape in advanced HCCs undergoing sorafenib treatment.

THU-099
Atorvastatin and gene expression signatures in hepatocarcinogenesis

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Background and aims: Hepatocellular carcinoma (HCC) represents a significant global health burden as the fourth leading cause of cancer-related deaths. While statins have shown promise in HCC prevention, their molecular mechanisms remain poorly understood. We investigated the effect of atorvastatin (AT) on gene expression profiles and hepatocarcinogenesis in a hexachlorobenzene (HCB)-induced HCC model.
Method: Male Wistar rats were divided into four groups: control, AT (5 mg/kg), HCB (100 mg/kg), and AT+HCB. After 30 days of treatment, we analyzed hepatosomatic index, liver histology, and performed RNA sequencing to evaluate transcriptomic changes. Gene Set Enrichment Analysis and KEGG pathway analysis were used to identify key molecular pathways. Protein expression of selected targets was confirmed by immunohistochemistry.
Results: HCB treatment significantly increased hepatosomatic index (28%, $p < 0.01$) and induced preneoplastic lesions, which were prevented by AT co-administration. RNA sequencing revealed HCB activated multiple oncogenic pathways, including RHO GTPase cycle, TGF-β, and receptor tyrosine kinase signaling, with 84.8% concordance with established cancer pathway genes. AT treatment upregulated protective PPAR signaling, autophagy, and cellular stress response pathways while downregulating oncogenic pathways activated by HCB. AT significantly reduced the expression of key oncogenic proteins including TGF-β1, p53, and c-Myc in HCB-treated liver tissue.
Conclusion: Atorvastatin effectively prevents HCB-induced hepatocarcinogenesis through multiple mechanisms, including modulation of key oncogenic pathways and promotion of protective cellular responses. These findings provide new insights into the molecular mechanisms of statin-mediated HCC prevention and identify potential therapeutic targets for future interventions.

THU-100
Functional properties of unannotated, small RNA clusters during hepatocarcinogenesis

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Background and aims: Despite the revolution in personalised cancer care, primary liver cancer lacks early detection biomarkers and actionable mechanisms of carcinogenesis are poorly understood. We previously isolated blood extracellular vesicles (EVs) from patients and identified clusters of unannotated, small non-coding RNA (smRCs) with the ability to accurately detect early-stage HCC (von Felden et al. Gut 2022). Herein, we aim at delineating the functional role of our candidate smRCs during hepatocarcinogenesis.
Methods: Cell-of-origin analysis was performed by spatial transcriptomics (RNAscope™) on primary HCC tissue. Lentiviral CRISPR/Cas9-mediated genome editing was used to generate clonal smRC1 knockout Huh7 cells and validated by RTqPCR. We performed functional assays: proliferation curve, cell viability MTT colorimetric assay, morphogenesis assay on Matrigel® layer, colony formation assay and cell migration on Transwell® supports. Epithelial-to-mesenchymal-transition (EMT) specific markers were quantified by Western blot and immunocytochemistry. RNA sequencing was conducted on smRC-KO and wildtype control clones followed by differential gene expression analysis (DESeq2 package).
Results: We confirmed the expression of smRCs in tumour tissues and intratumoural stromal cells via spatial transcriptomic analysis. We established an in vitro model based on the lentiviral.
CRISPR/Cas9 system to reduce the expression of smRC1 in HCC cells. Functional assays suggest a role for smRC1 in the tumour cell biology, with a significant reduction of proliferation at 48 hours (70% of control), viability (75% of control), morphogenesis (5% of control), clonogenic ability (30% of control) and migration (10% of control) in the knockout clones compared to the smRC1-expressing clones. Moreover, smRC1 expression was associated with EMT, with increased Vimentin and decreased E-Cadherin levels. RNA sequencing analysis revealed an >8-fold upregulation of genes related to apoptosis (DYNLT3, NOXA), mitochondrial function (APOOL, CHM) and EGFR-pathway (EREG) (all adjusted $p < 0.01$). Further assays aiming to investigate the apoptotic process, mitochondrial functionality, EGFR-pathway activation and drug sensitivity are pending in order to validate these findings.
Conclusion: In conclusion, we demostrated a functional role for our previously identified small, non-coding RNA transcripts derived from unannotated genomic regions. Successful execution might reveal potential novel therapeutic strategies for primary cancer prevention.

THU-101-YI
Selective targeting of class I histone deacetylases with new derivatives of ursodeoxycholic acid as a novel treatment strategy for bile duct cancer

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Background and aims: Cholangiocarcinoma (CCA) includes a heterogeneous group of biliary tumors characterized by poor prognosis. Available systemic therapies for patients with advanced CCA are merely palliative, attesting the need to find novel effective approaches. Altered expression and/or function of certain epigenetic regulators such as histone deacetylases (HDACs) has been closely related to the development and progression of different types of cancer, including CCA. We have previously developed a new family of HDAC6 selective inhibitors derived from ursodeoxycholic acid (UDCA) that showed preferential enterohepatic biodistribution after oral administration (Caballero-Camino, FJ, *et al. Hepatology* 2021). Here, we hypothesize that selectively targeting the deregulated HDAC isoforms in CCA with novel UDCA-derived HDAC inhibitors could be a valuable epigenetic-based therapeutic strategy for CCA.
Method: The expression levels of the different HDACs were analyzed in tumor tissue samples from 4 international cohorts of patients with CCA. Advanced computational methods were applied to design and synthesize UDCA-derived drug candidates. Therapeutic potential of the lead compound was further characterized in experimental models of naïve and chemoresistant CCA, including human tumor spheroids and murine CCA organoids.
Results: Class I HDACs –1, 2 and 8– were found overexpressed in human CCA tumors from 4 cohorts of patients with CCA compared to control tissues. Computationally-aided rational design yielded 9 UDCA-derived drug candidates for selective targeting class I HDACs. Among them, the lead compound (Epi-UDCA) was selected based on class I HDAC inhibitory potency and selectivity on enzymatic assays. In CCA cell lines, Epi-UDCA displayed marked antiproliferative capacity at low doses (2 μM) and strong apoptotic induction at higher doses (10 μM). Epi-UDCA halted the growth of 3D human CCA spheroids and murine tumor organoids, promoting cancer cell death. Importantly, low doses of Epi-UDCA (2 μM) halted the invasion capacity of human CCA cells in extracellular matrix (ECM)-coated transwell migration assays. Proteomic analysis of CCA cells exposed to Epi-UDCA (2 μM) revealed significant changes in the expression of 396 proteins directly involved in important cancer-related processes such as cell cycle progression, angiogenesis, ferroptosis, and transcriptional regulation by tumor suppressor protein p53, among others. Finally, Epi-UDCA displayed strong antitumoral capacity against cisplatin-resistant CCA cells and spheroids, while combined administration of Epi-UDCA with cisplatin re-sensitized these cells to chemotherapy.
Conclusion: The unique properties of Epi-UDCA, a novel UDCA-derived class I selective HDAC inhibitor, provide this drug with promising therapeutic potential for the treatment of naïve and cisplatin-resistant cancers, including CCA.

THU-103-YI
Impact of PNPLA3 and TM6SF2 single nucleotide polymorphisms in metabolic dysfunction-associated steatohepatitis-linked hepatocellular carcinoma development in 3D extracellular matrix models

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Background and aims: The PNPLA3 and TM6SF2 single nucleotide polymorphism (SNP) mutations are strongly implicated in increased susceptibility to Metabolic Dysfunction-Associated Steatohepatitis (MASH), accelerated liver fibrosis, and a heightened risk of Hepatocellular Carcinoma (HCC), underscoring their critical role in the pathogenesis of liver disease. Despite this, in vitro studies utilising hepatocytes and hepatic stellate cells (HSCs) have largely overlooked the impact of these mutations. This study aims to investigate the cellular behaviour associated with PNPLA3 and TM6SF2 SNPs using genotyped-paired human HCC cell lines and primary HSCs cultured within bioengineered 3D liver models, including human-derived extracellular matrix (ECM) scaffolds and ECM hydrogels.
Method: Human primary HSC and HCC cell lines were genotyped for SNPs PNPLA3 (rs738409) and TM6SF2 (rs58542926) and matched as: $PNPLA3^{WT}/TM6SF2^{WT}$ and $PNPLA3^{HOM}/TM6SF2^{WT}$. Cells were grown as mono- and co-cultures in healthy and cirrhotic decellularised 3D scaffolds and ECM hydrogels for 13 days and were treated with a MASH cocktail for 72 hrs. Cell behaviour was assessed using H&E, Live/Dead staining, qPCR and spectral flow cytometry.
Results: Co-cultures genotyped for $PNPLA3^{HOM}/TM6SF2^{WT}$ exhibited significantly higher profibrogenic markers, including mRNA for YAP and ACTA2, compared to $PNPLA3^{WT}/TM6SF2^{WT}$ cells. Flow cytometry and qPCR demonstrated a significant increase in TGFB1 expression in $PNPLA3^{HOM}/TM6SF2^{WT}$ mono- and co-cultures compared to $PNPLA3^{WT}/TM6SF2^{WT}$ cells grown in cirrhotic ECM scaffolds. Notably, flow cytometry analysis further demonstrated increased expression of Fibroblast Activating Protein (FAP) on $PNPLA3^{HOM}/TM6SF2^{WT}$ HSC in co-culture compared to $PNPLA3^{WT}/TM6SF2^{WT}$ HSC within healthy ECM (55.4% versus 40.6%) and cirrhotic ECM (36.6% versus 25.4%). Co-cultures within both healthy and cirrhotic scaffolds demonstrated increased PD-L1 expression relative to single cultures, indicating immune-modulatory effects. Furthermore, in human-derived liver 3D ECM hydrogels, MASH induced $PNPLA3^{HOM}/TM6SF2^{WT}$ co-cultures presented and enhanced increase of ACTA2 expression in both healthy and cirrhotic ECM conditions compared to $PNPLA3^{WT}/TM6SF2^{WT}$. These findings highlight the profound impact of PNPLA3 and TM6SF2 mutations on fibrotic and immunological responses in liver disease models.
Conclusion: This study demonstrates the utility of novel 3D models using human-derived healthy and cirrhotic liver ECM scaffolds and hydrogels to explore the impact of PNPLA3 and TM6SF2 genotypes on HSC and HCC behaviour, shedding light on their roles in MASH progression. These models offer significant potential for enhancing the reliability of future drug clinical trials by providing more physiologically relevant platforms to evaluate therapeutic responses and identify genotype-specific therapeutics.

THU-104-YI
A large-scale genetic analysis of hepatocellular carcinoma reveals novel mutational patterns and ancestry-linked mutations

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Background and aims: In recent years, the integration of next-generation sequencing (NGS) into routine clinical practice has revolutionized personalized cancer treatment. Hepatocellular carcinoma (HCC), the fifth most common cancer worldwide, has seen notable advancements in systemic treatments. However, despite the growing use of molecular and immunotherapies, no reliable

biomarkers exist to guide patient selection for specific therapies. To advance the development of targeted treatments in genetically defined subgroups of HCC, an understanding of the spectrum of genetic alterations (GAs) is essential. Here, we present what is, to our knowledge, the largest genomic analysis of real-world cohorts of HCC and combined HCC-cholangiocarcinoma (cHCC-CCA) patients, utilizing an extensive diagnostic panel to provide detailed insights into the full range of genomic alterations in these tumors.

Method: A retrospective analysis was conducted on 2,372 patients with HCC and 151 with cHCC-CCA using data from the FoundationCORE database. Tumor samples underwent genomic profiling with the FoundationOne platform, which assessed short variants, fusion-rearrangements, and copy number alterations in over 300 tumor-associated genes. Tumor mutational burden (TMB) and genetic ancestry status were determined for most of the cohort. Gene associations were identified using Fisher's exact test, with a significance threshold of $p < 0.05$.

Results: We present a comprehensive and representative analysis of the genomic landscape of HCC, highlighting mutational spectra across genetic ancestries, including African, American, European, East Asian, and South Asian populations. The most frequent GAs in HCC included *TERT* (59.3%), *TP53* (36.9%), *CTNNB1* (34.1%), *MYC* (14.1%), and *ARID1A* (12.3%). Female patients exhibited higher frequencies of GAs in *RB1*, *PTEN*, *CDKN2B*, and *BAP1*. Patients with East Asian ancestry had fewer *TERT*, *CTNNB1*, and *BAP1* GAs but showed enrichment for *TP53*, *MUTYH*, and *TET2* GAs. In contrast, patients of African ancestry had increased *TP53* and *TSC2* GAs but were otherwise similar to those with Western ancestries. Compared to HCC, cHCC-CCA exhibited higher frequencies of *IDH1/2* (11.2%) and *FGFR* (6.0%) GAs. Additionally, we will provide a detailed overview of potentially actionable GAs across both cohorts.

Conclusion: A comprehensive understanding of the most prevalent GAs is crucial for advancing molecular therapeutic and biomarker development in HCC. Our large-scale genomic analysis reveals subgroup-specific and ancestry-linked mutational signatures and defines the extensive landscape of GAs in HCC, offering valuable insights for the design of clinical trials targeting these alterations. Additionally, we provide novel insights into the genomic landscape of the rare cHCC-CCA subtype and defining the frequency of targetable GAs.

THU-105

Liver-derived mesenchymal stem cells promote epithelial-mesenchymal transition in a hepatocellular carcinoma spheroid coculture model

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Background and aims: Mesenchymal stem cells (MSC) play a highly debated role in cancer. Potent anti- and pro-tumour properties have been shown *in vitro* and *in vivo* depending on the type of tumour studied and the origin and priming of the MSC used. Here, we investigate the interaction between liver-derived MSC and hepatocellular carcinoma (HCC), with a focus on cancer cell proliferation, invasiveness and gene expression. We postulate that their shared hepatic origin can lead to unique insights on the potential implication of MSC in carcinogenesis.

Method: We established a 3D coculture spheroid model by combining Human Adult Liver Progenitor Cells (HALPC), a population of liver-derived mesenchymal stem cells described by our team, and one of three human hepatocellular carcinoma cell lines (HuH7, HepG2, and Hep3B). Cancer cell proliferation was studied through spheroid growth follow-up, chemiluminescent measurement of ATP, and Ki67 immunostaining using light sheet fluorescent microscopy. Cancer cell invasiveness was investigated using transwell and spheroid invasion assays. RNA sequencing was conducted on HALPC and cancer cells from control and coculture spheroids separated by fluorescence-activated cell sorting.

Results: HCC 3D coculture with HALPC resulted in a dose-dependent inhibition of spheroid growth. At 25 days post-formation, control spheroids were up to 70 times larger in volume than 50:50 coculture spheroids. This correlated with lower total ATP contents in coculture spheroids at several time points, indicative of lower amounts of cells per spheroids. The inhibition of cancer cell proliferation was then confirmed by a reduction of up to 66% in Ki67-positive cells in coculture conditions ($p = 4.6 \times 10^{-5}$), using light sheet microscopy. Invasion studies demonstrated the induction of an invasive phenotype in the cancer cell lines when co-cultured with HALPC. Comprehensive transcriptomic analysis showed massive changes in expression levels, with 2002 and 3601 up- or downregulated genes in HALPC and cancer cells, respectively ($| logFC | > 1$; p adj. < 0.05). In cancer cells, gene set enrichment analysis revealed dysregulation of several cancer hallmarks gene sets, with significant positive enrichment of the epithelial-mesenchymal transition (EMT) gene set (Normalized Enrichment score = + 2.7; p adj. = 1.1×10^{-18}).

Conclusion: We showed in a 3D coculture model that liver-derived MSC decreased the proliferation and induced the invasiveness of several human HCC cell lines. This was associated with the induction of an EMT phenotype at the transcriptomic level. These findings provide evidence for a potential role of organ resident MSC in HCC progression via EMT. Ongoing work will confirm the acquisition of the EMT phenotype at the protein level and validate the obtained results *in vivo*, using an orthotopic xenogeneic bioluminescent mouse model currently being established in our laboratory.

THU-106

Macrophage-targeted biodegradable polymer nanocarriers loaded with a cytokine pathway activator effectively suppress orthotopic HCC growth in immune-competent mice

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Background and aims: Tolerogenic myeloid cells, tumor-associated macrophages (TAMs) are promising targets for immunological cancer therapies. However, systemic administration therapies addressing these cells often leads to side effects, including autoimmunity. The treatment of hepatocellular carcinoma (HCC), which is rich in TAMs, with checkpoint inhibitors has shown limited efficacy, including combination therapies. Therefore, specific reprogramming of TAMs from a T-cell-suppressive to a T-cell-activating state is an attractive novel therapeutic strategy. TAM modulation with small molecular immunomodulators has been hampered by poor water solubility or systemic toxicity. We therefore employed our prominently liver macrophage targeting, biodegradable polymer nanoparticles (NP; Kaps L et al, PNAS 2022) to deliver macrophage repolarizing small molecules to the liver and to HCC. NP were loaded with the cytokine-pathway modulator INT(ImmuneNTech)-16 and tested in our syngeneic orthotopic and immunocompetent mouse model of HCC.

Method: Multifocal hepatocellular carcinoma (HCC) was induced in C57BL/6 mice via intrasplenic injection of Dt81 HCC cells, leading to liver colonization and the development of advanced multifocal HCC within 3–5 weeks. Beginning in week 3 and continuing through week 5, mice were treated intravenously twice weekly with either unloaded nanoparticles (NPs), NPs loaded with INT-16 (at doses of 0.5 or 1.5 mg/kg), free INT-16, or vehicle control. Liver/body weight,

tumor load and tumor counts were determined. Liver histology was assessed using H&E staining and quantitative immunohistochemistry for CD3, CD8, CD68, YM1, iNOS, and Granzyme B. Hepatic proinflammatory transcripts and immune cell subtypes were quantified by qPCR and flow cytometry.
Results: The NP+INT-16 high-dose group achieved a highly significant antitumor effect, resulting in near-complete tumor regression, while all other therapies were largely ineffective. TAMs and immune suppressive cytokines were suppressed, whereas cytotoxic CD8+ T cells were significantly increased. The NP-mediated delivery of INT-16 significantly reduced the toxicity typically associated with systemic administration of the free drug.
Conclusion: NP+INT-16 monotherapy efficiently repolarized the suppressive tumor microenvironment towards anti-tumor immunity, resulting in a highly significant reduction of HCC growth. This approach can be translated to a phase 1b clinical development, coupled with new serological assays to assess immune activation in the tumor microenvironment.

THU-111
Cryptochrome proteins as key regulators in circadian rhythm-enhanced photodynamic therapy for cholangiocarcinoma

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Background and aims: Cholangiocarcinoma (CCA) is an aggressive malignancy with limited treatment options. Photodynamic therapy (PDT) holds potential but is hindered by tumor-specific mechanisms and circadian rhythms. Cryptochrome proteins (CRY1/CRY2), key circadian regulators, influence metabolism and DNA repair, potentially reducing PDT efficacy. KL001, a CRY stabilizer, modulates these processes. This study examines KL001's role in enhancing PDT, evaluates circadian rhythm effects on PDT, and validates findings through chronotherapy.
Method: TCGA and GEO datasets were analyzed for CRY1/CRY2 expression and prognostic impact. DEG, WGCNA, and GO/KEGG enrichment identified pathways influencing PDT response. HUCC-T1 cells were treated with PBS, KL001, Ce6 (PDT photosensitizer), or KL001 + Ce6 under light irradiation (650 nm, 10 J/cm²). Proliferation, migration, and colony formation were assessed via CCK-8, Transwell, and colony assays. RNA-seq identified molecular pathways affected by KL001 and PDT. In vivo PDT chronotherapy in xenograft models compared circadian-aligned versus standard treatment.
Results: CRY1/CRY2 were overexpressed in CCA and correlated with poor prognosis. Pathway analysis linked CRY proteins to DNA repair and metabolism. KL001 + PDT synergistically inhibited cell proliferation (38% increase, $p < 0.01$), migration (45% reduction, $p < 0.01$), and colony formation (60% reduction, $p < 0.01$). RNA-seq showed modulation of DNA repair genes (e.g., RAD51, BRCA1) and metabolic pathways, with increased oxidative stress and cell death. Chronotherapy improved PDT efficacy, reducing tumor volume by 58% ($p < 0.01$) and extending survival.
Conclusion: KL001 enhances PDT by targeting DNA repair and metabolic pathways. Circadian-aligned PDT further amplifies therapeutic effects, demonstrating the importance of circadian biology in optimizing CCA treatment. These findings support integrating chronotherapy into PDT protocols for improved outcomes.

THU-112
Proinflammatory cytokines drive peripheral Foxp3high Tregs into tumor sites: a reliable and accessible prognostic biomarker for HCC patients

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Background and aims: Regulatory T cells (Tregs) play a critical role in hepatocellular carcinoma (HCC) progression, but systemic Treg depletion risks autoimmunity. Despite known Treg heterogeneity, no consensus exists on their functional subtypes. This study aimed to classify Treg subpopulations using single-cell CITE-seq and validate their clinical and prognostic relevance in HCC patients.
Method: Single-cell CITE-seq was conducted on 51,067 $CD4^+$ T cells from eight HCC patients, analyzing samples from tumor, non-tumor, and peripheral blood. Validation involved 96 HCC patients and 53 healthy donors through flow cytometry, functional assays, and clinical data integration.
Results: Trajectory and TCR analyses identified a $Foxp3^{high}$ Treg subset in peripheral blood that preferentially migrates to tumor sites, acquiring a terminally differentiated, activated phenotype. Tumor-infiltrating $Foxp3^{high}$ Tregs exhibited elevated LAYN and tissue-resident memory (TRM) signatures and enhanced Foxp3 expression driven by proinflammatory cytokines in the tumor microenvironment. The CCL5/CCR5 axis mediated their recruitment from peripheral blood to tumors. A significant correlation was found between peripheral and intratumoral $Foxp3^{high}$ Tregs, supporting their potential as biomarkers. A predictive model using peripheral $Foxp3^{high}$ Tregs/$CD4^+$ T cells >3.5% was developed, demonstrating robust prognostic performance for overall survival and early recurrence, with AUROCs exceeding 0.75 in both training and validation cohorts.
Conclusion: Peripheral $Foxp3^{high}$ Tregs migrate to tumors via the CCR5-CCL5 axis and mature under proinflammatory cytokines influence. Their proportion in blood correlates with tumor presence, making them a promising biomarker for predicting HCC outcomes.

THU-113-YI
Distinct roles of SOS1 and SOS2 in lipid metabolism and tumorigenesis: implications for therapeutic targeting in cancer and metabolic disorders

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Background and aims: Mutations in RAS genes are implicated in approximately 30% of human cancers. RAS guanine nucleotide exchange factors (GEFs), SOS1 and SOS2, are broadly expressed across tissues and play key roles in metabolism, tissue homeostasis, and carcinogenesis, with emerging connections to obesity and lipid metabolism, both significant cancer risk factors. This study aims to investigate the regulatory roles of SOS1/2 in adipose and liver, focusing on their involvement in adipogenesis, High-Fat Diet (HFD)-induced changes, and hepatocellular carcinoma (HCC) progression.
Method: Conditional Cre-ER2 mice were used to study SOS1 and SOS2. Adipogenesis was analyzed in stromal vascular fractions (SVF), and mouse embryonic fibroblast (MEF) cells. SVF and MEF cells were

treated with 4-hydroxytamoxifen (4OHT) and then exposed to adipogenic induction media. Adipogenic capacity was measured using BODIPY staining and imaging at the Incucyte. In steatosis studies, SOS1 was depleted before the HFD began (pre-HFD); and after feeding them for 45 days with HFD, (post-HFD). Lipid content in the liver was measured in both cases, along with glucose tolerance testing. For diethylnitrosamine (DEN)-induced hepatocellular carcinoma studies, SOS1 was depleted one month after DEN treatment (DT1M), and after six months into DEN treatment (DT6M). Tumor number and burden, histological analyses, molecular analyses, bulk RNA-seq, and whole-exome sequencing (WES) were conducted. For therapeutic evaluation, the SOS1-RAS inhibitor BI-3406 was tested alone and in combination with sorafenib.
Results: SOS1 depletion significantly impaired lipid droplet accumulation in MEFs and SVFs, while SOS2-deficient cells maintained normal adipocyte differentiation and lipid storage. SOS1-depleted cells exhibited increased oxidative stress and mitochondrial dysfunction, impairing lipid metabolism. In vivo, SOS1 depletion reduced liver lipid accumulation in both pre-and post-HFD models. In HCC models, early SOS1 depletion (DT1M) greatly reduced tumor burden and number. Late depletion (DT6M) showed variable outcomes. SOS2 deletion consistently led to the highest tumor burden across experimental groups. Treatment with BI-3406 alone showed limited efficacy. However, combining BI-3406 with sorafenib reduced tumor number and burden.
Conclusion: SOS1 emerges as a potential therapeutic target due to its ability to reduce lipid accumulation, thereby protecting the liver from steatosis. Moreover, HCC experiments highlight a protective role of SOS1 during early tumorigenesis. In contrast, SOS2 is associated with increased tumor burden. While RAS::SOS1 inhibition alone shows limited efficacy, its combination with sorafenib yields promising results, paving the way for more effective therapeutic strategies.

THU-114
Liposomal doxorubicin and atezolizumab promote EMT regression by acting on the tumor microenvironment: preclinical in vitro and in vivo studies

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Background and aims: Hepatocellular carcinoma (HCC) is a highly aggressive liver cancer whose onset and progression is driven by immune-escape. HCC is characterized by the upregulation of the checkpoint inhibitor PD-L1, that helps immune evasion. The combination of the PD-L1 inhibitor atezolizumab and bevacizumab is the gold standard for advanced HCC treatment. Nevertheless, HCC management remains a significant challenge, highlighting the need for novel therapeutic approaches.
The aim of this study is to investigate the anticancer and immunomodulatory role of atezolizumab-targeted liposomal doxorubicin (Stealth Immunoliposomes, SIL), using as control its untargeted counterpart (Stealth Liposomes, SL) in vitro and in vivo models of HCC.
Method: The effect of SL and SIL was evaluated on HepG2 and Huh7 cells treated with TNF-alpha to obtain a model of EMT, by analyzing the expression of PD-L1, and the EMT markers by ICC and qPCR. The role of the two formulations on Akt-1 and p65 protein and gene expression was also assessed. In vivo efficacy was assessed in a syngeneic mouse model of HCC, obtained by injecting subcutaneously Hepa1-6 cells in C57BL/6J immunocompetent mice. The mice were then treated with vehicle (control), SIL, SL, Atezolizumab, or SL+Atezolizumab. Treatments were administered intraperitoneally (5 mg/kg every 3 days for 6 doses). Tumor volumes were measured and collected at sacrifice to evaluate Cytotoxic T Lymphocytes, M1 and M2 macrophages by flow cytometry.
Results: In the EMT in vitro model, SIL reduced PD-L1 protein ($p < 0.001$) and gene expression ($p < 0.05$), and increased E-cadherin ($p < 0.05$), decreased Vimentin ($p < 0.001$), and Beta-catenin ($p < 0.05$) protein expression. An increasing effect on p65 protein expression was observed after SIL treatment only in the EMT model obtained with Huh7 cells ($p < 0.05$), suggesting that the modulation of NFkBeta pathway occurs differently in the two cell lines. SIL decreased protein and gene expression of Akt-1 in both HepG2 ($p < 0.0001$ and $p < 0.01$ respectively) and Huh7 ($p < 0.0001$ and $p < 0.001$ respectively) cells, indicating that this formulation reduced EMT by acting on the Akt-1 pathway. In vivo, mice treated with Atezolizumab + SL was the most effective treatment in reducing tumor growth ($p < 0.05$ vs controls and atezolizumab-treated mice). Flow cytometry analysis revealed higher number of Cytotoxic T cells and M1/M2 ratio in the tumor microenvironment of these mice ($p < 0.05$ vs controls).
Conclusion: In vitro, SIL treatment, beside exerting an immunomodulatory role in the tumor microenvironment, reduces tumor cell invasiveness by acting on the EMT. Atezolizumab + SL treatment reduces cancer growth in vivo, increases macrophage polarization towards an antitumoral phenotype and the immune response against cancer cells, suggesting that the combination of immunotherapy and chemotherapy might be a suitable strategy in HCC management.

THU-115-YI
Targeting UBE2I-mediated protein hyper-SUMOylation halts cholangiocarcinoma progression and rewires the tumor-stroma crosstalk

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Background and aims: Cholangiocarcinoma (CCA) includes a diverse range of biliary malignant tumors characterized by dismal prognosis. Alterations in post-translational modifications contribute to abnormal protein dynamics, cellular disturbances, and disease. In this study, we investigated the role of SUMOylation in CCA progression and its potential as a therapeutic target.

Method: Using a combination of human CCA cells and primary tumours, we analysed the levels and function of protein SUMOylation, identifying deregulated SUMOylated proteins by immunoprecipitation and mass spectrometry analysis. The response to genetic (*UBE2I*-knockdown) or pharmacological (ML792 and SAMe) inhibition of SUMOylation was assessed *in vitro* and in two *in vivo* models of CCA. Co-culture experiments between wild-type or UBE2I-knockdown cancer cells and CCA-derived cancer-associated fibroblasts (CAFs) and human endothelial cells were carried out to unveil the impact of SUMOylation in the crosstalk between CCA cells and the TME.
Results: Analysis of human CCA cells and primary tumors revealed increased expression and activity of the SUMOylation machinery, correlating with unfavorable clinical outcomes. Critically, we found that the majority of SUMOylated proteins deregulated in CCA, identified after immunoprecipitation and mass spectrometry analysis, are implicated in cell proliferation, survival, or cellular homeostasis. The response to genetic (UBE2I-knockdown) or pharmacological (ML792 and SAMe) inhibition of SUMOylation was assessed in vitro and in two in vivo models of CCA. Depleting SUMOylation effectively halted tumorigenesis in subcutaneous and oncogene-driven models of CCA in vivo. Furthermore, the genetic and pharmacological inhibition of SUMOylation reduced CCA cell proliferation and hindered colony formation and spheroid growth in vitro. Co-culture experiments between wild-type or UBE2I-knockdown cancer cells and CCA-derived cancer-associated fibroblasts (CAFs) and human endothelial cells were then carried out to unveil the relevance of SUMOylation in the crosstalk between CCA cells and the tumor microenvironment (TME). Importantly, experimental depletion of SUMOylation encompasses a profound impact on the establishment of the TME as it arrests the growth of CAFs and vascular cells.
Conclusion: Aberrant protein SUMOylation contributes to CCA progression by promoting cell survival and proliferation and contributes to the conformation of the TME. Impairing SUMOylation halts CCA growth and, thus, may represent a potential novel therapeutic strategy for patients with CCA for whom current targeted therapies are limited.

THU-116

Novel chemotherapy selectively induces double-strand DNA breaks and death in naïve and Cisplatin-resistant cholangiocarcinoma tumours

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Background and aims: Cholangiocarcinoma (CCA) comprises a heterogeneous group of biliary malignant tumours characterized by dismal prognosis. Current first-line chemotherapy, including Cisplatin and Gemcitabine, provides limited survival benefits due to the development of chemoresistance. Cisplatin induces single-strand DNA breaks, activating DNA repair mechanisms that diminish its effectiveness. In this study, we present the design, chemical synthesis, and therapeutic evaluation of a new generation of chemotherapeutic agents with unique polyelectrophilic properties, capable of inducing high frequency of double-strand DNA breaks, thereby inhibiting DNA repair and promoting cancer cell death.
Method: We designed, chemically synthesized, and therapeutically evaluated two novel chemotherapeutic agents, Aurkine 16 and Aurkine 18. Their binding and damage to DNA were characterized by Atomic Force Microscopy (AFM), Transmission Electron Microscopy (TEM), comet assay, and electrophoretic mobility of the pUC18 plasmid. Their antitumour effects were tested in human naïve and cisplatin-resistant CCA cells, cancer-associated fibroblasts (CAFs), and healthy cholangiocytes as controls, as well as in xenograft models of CCA.
Results: Aurkines effectively induced double-strand DNA breaks, leading to increased DNA damage and elevated levels of reactive oxygen species, resulting in greater cytotoxicity compared to Cisplatin in CCA cells. Unlike Cisplatin, Aurkines did not activate key proteins involved in single-strand DNA repair, such as ATR and CHK1 phosphorylation. Importantly, these compounds also triggered apoptosis in Cisplatin-resistant CCA cells and CAFs while exhibiting no harmful effects in healthy cholangiocytes, demonstrating malignant selectivity. Additionally, Aurkines demonstrated cytotoxicity in other Cisplatin-resistant cancers, such as breast and ovarian cancer. This selective action against malignant cells was attributed to differences in histone deacetylase (HDAC)-dependent DNA packaging between normal and cancer cells. *In vivo*, Aurkines effectively halt naïve and Cisplatin-resistant CCA tumour growth without adverse effects. Transport studies revealed that Aurkines were selectively taken up by transport proteins OCT1, OCT3, CTR1, and OATP1A2, whereas Cisplatin only modestly utilizes CTR1.
Conclusion: Aurkines represent promising therapeutic candidates for both naïve and Cisplatin-resistant cancers due to their unique polyelectrophilic properties and selective targeting of cancer DNA.

THU-121

Claudin-1 modulates cell plasticity, carcinogenic signaling and proliferation in patient-derived cholangiocarcinoma organoids in vivo

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Background and aims: Cholangiocarcinoma (CCA) is a hepatobiliary adenocarcinoma with poor prognosis and unsatisfactory treatment options. Claudin-1 (CLDN1) is a transmembrane protein expressed in

tight junctions and exposed on the cell surface in liver fibrosis and cancer. We have previously shown that targeting exposed CLDN1 using highly specific CLDN1 monoclonal antibodies (mAbs) robustly inhibited tumor growth across CCA CDX and PDX mouse models. Here, we aimed to study the mechanisms by which CLDN1 drives cholangiocarcinogenesis using patient-derived CCA tissues and organoid models.

Method: Transcriptional regulation of CLDN1 expression was studied using a large panel of known key regulators of CCA progression in patient-tissues combined with pharmacological intervention and loss-of-function studies using CLDN1-specific mAbs and RNAi in patient-derived organoids and cell-based models. In vivo proof-of-concept studies using humanized CLDN1 mAbs were performed in a patient-derived organoid xenograft model.

Results: CLDN1 protein was overexpressed in cancer cells of patient CCA tumor tissues. Spatial transcriptomics revealed CLDN1 co-localization of well described CCA driver pathways. CLDN1 expression significantly increased in CCA patient-derived organoids upon the activation of TNFα/NF-kB or Wnt/β-catenin pathway signaling, both highly implicated in in CCA progression. Perturbation studies using CLDN1 mAbs in patient CCA organoids showed a marked modulation of the organoid phenotype with a robust decrease in viability. Targeting cancer cell CLDN1 using highly specific mAbs markedly inhibited tumor growth in a CCA patient-derived organoid xenograft mouse model. In line with morphological changes, transcriptomic profiling of CLDN1 mAb-treated organoids revealed a pronounced effect on cell architecture and proliferation, a downregulation of the expression of gene sets encoding for oncogenic signaling, hypoxia, metabolism, EMT and stemness. Mechanistically, targeting exposed CLDN1 using CLDN1 mAbs suppressed key CCA signaling pathways, including Notch1, SRC-FAK, Hippo-YAP and STAT3 signaling across patient-derived models. Genetic loss-of-function studies confirmed the functional impact of the pathways and findings for CLDN1 as a CCA driver and therapeutic target.

Conclusion: Transcriptional regulation and perturbation studies in patient-relevant models unravel a key functional role of CLDN1 as a signal transducer of multiple pro-tumorigenic signaling cascades which regulate CCA cell plasticity and fate, stemness and EMT. Robust CLDN1 overexpression in patient CCA combined with completed in vivo proof-of-concept studies provide an opportunity for the clinical development of CLDN1-specific mAbs to improve the dismal outcome of CCA patients.

THU-122

Can fractal descriptors distinguish vascular organization within the tumor microenvironment?

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Background and aims: The architecture of tumor vasculature is known to impact response to therapy, especially in the field of anti-angiogenic drugs. This is particularly well-illustrated in hepatocellular carcinoma (HCC) arising in the context of cirrhosis, where anti-angiogenic therapies, either alone or in combination, have become a standard of care. Accordingly, providing a comprehensive landscape of tumor vasculature would be critical for predicting treatment response and adapting treatment strategies effectively. Our objective is to quantify vascular architecture and assess the presence of significant variations across distinct tissue environments, including tumoral and non-tumoral regions, as well as tissues with vascular invasion (VI+) and without vascular invasion (VI-).

Method: In this study, we characterized the vascular architecture of HCC using two complementary mathematical concepts: the fractal dimension D_f and the Hurst index H. We analyzed 29 histological samples of HCCs, immunostained for vessels using CD31 and segmented, and quantified via the classical boxcounting method D_f and via lagtime-distribution calculus H within the central tumoral zones, the peritumoral regions, and in distant non-tumoral liver tissue.

Results: Our analysis revealed distinct differences in fractal dimension between non-tumoral ($D_f^{non\text{-}tumoral} = 1.73 \pm 0.02$), peritumoral ($D_f^{peritumoral} = 1.57 \pm 0.03$), and tumoral tissues ($D_f^{tumoral} = 1.3 \pm 0.02$) ($p < 0.001$), and similar differences in the Hurst index ($H_{tumoral} = 0.32 \pm 0.008$ and $H_{non\text{-}tumoral} = 0.16 \pm 0.02$). Furthermore, the presence ($D_f^{tumoral\ VI-} = 1.27 \pm 0.02$) or absence ($D_f^{tumoral\ VI+} = 1.3 \pm 0.04$) of tumoral vascular invasion did not alter the fractal dimension of the vasculature, neither intra-tumoral nor peri-tumoral ($p = 0.68$).

Conclusion: In conclusion, our findings show that vascular architecture quantified via its fractal dimension is clearly different between the central regions of HCCs, its peritumoral zone, and liver parenchyma. Furthermore, we show that the presence/absence of vascular invasion is not impacting vascular fractality. These promising results provide motivation to further investigate non-invasive approaches that are able to quantify fractality whereby adding valuable diagnostic information.

THU-123-YI

YAP activity in cancer-associated fibroblasts is relevant for immune escape in cholangiocarcinoma

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Background and aims: The transcriptional co-activator Yes-associated protein (YAP) is the main component of the Hippo pathway, playing an essential role in cholangiocarcinoma (CCA). YAP activity has emerged as relevant mediator of activation of resident fibroblasts into cancer-associated fibroblasts (CAFs) and important for tumor endothelial cells (TECs). This project aims to investigate the molecular role of YAP in CCA-resident CAFs and TECs.

Method: We established multiple organoid-based, syngeneic CCA models by intrahepatic implantation of murine cholangiocyte organoids, genetically engineered to obtain activating $Kras^{G12D}$ and deletary *Trp53* mutations, and combined with 1 out of 3 different co-alterations: deletion of *Smad4* (PKS), *Arid1a* (PKA), and *Msh2* (PKM). Intratumoral YAP activity was assessed in a Cyr61-GFP reporter mouse line. $Yap^{flox/flox}$ Tomato-reporter mice were crossed with $Col1a2^{CreERT2}$ and $Cdh5^{CreERT2}$ mice to generate fibroblast- and endothelial cell-specific, Tamoxifen-inducible Yap KO mice ($Yap^{\Delta CAF}$ and $Yap^{\Delta TEC}$), respectively. Tumors were collected 7 days after knock out for imaging and single-cell RNA sequencing analysis.

Results: All three organoid lines led to CCA formation upon intrahepatic implantation ($n \geq 5$ per group). PKS organoids exhibited the highest penetrance at 91%. The percentage of eGFP+ fibroblasts in CCAs in Cyr61-eGFP reporter mice was 8%, 26%, and 14% for PKA, PKS, and PKM, respectively ($p < 0.01$). Yap activity in endothelial cells was not measurable in this reporter system. Importantly, no differences in

CCA morphology and TME composition could be observed in $Yap^{\Delta TEC}$ mice 7 days after KO. Conversely, CCA in $Yap^{\Delta CAF}$ mice showed signs of tumor shrinkage after KO (tumor volume 51 mm^3 [KO] vs. 152 mm^3 [Ctrl], $p < 0.05$). Immunohistological analysis revealed increased infiltration of T cells in $Yap^{\Delta CAF}$ CCAs ($p < 0.01$). Notably, intratumoral CD8+ T cell percentage increased 3.4-fold ($p < 0.01$), while no significant differences were observed in the populations of LY6G/6C+, F4/80+, B220+, or NK1.1+ cells. Single-cell RNA-sequencing analysis is ongoing to explore the tumor microenvironment in $Yap^{KO\text{-}CAF}$ models.

Conclusion: The findings demonstrate that YAP activity in CAFs supports immune escape of CCAs via inhibition of CD8+ T cell infiltration and imply therapeutic potential. Further investigation into underlying molecular mechanisms is therefore warranted.

THU-124

3,4-dihydroxyphenylpropionic acid deficiency in chronic hepatitis B promotes hepatocellular carcinoma

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Background and aims: Despite therapy with potent antiviral agents, chronic hepatitis B (CHB) patients remain at high risk of hepatocellular carcinoma (HCC). While metabolites have been rediscovered as active drivers of biological processes, the specific metabolites modulating HCC risk in CHB patients is largely unknown.

Method: We recruited 3368 CHB patients who were under nucleos(t)ide analogues treatment and achieved hepatitis B virus (HBV) DNA undetectable. Plasma samples have been collected when patients were enrolled in this cohort. During a median follow-up of 43.5 months, a total of 76 incident HCC cases were ascertained. Using a nested case-control design, 76 HCC cases and 76 controls without HCC development were selected by propensity score matching. Targeted metabolomics analysis was employed to examine metabolite compositions of baseline plasma. The role of 3,4-dihydroxyphenylpropionic acid (3,4-DHPPA) in hepatoma tumorigenesis was investigated both *in vitro* and *in vivo* studies.

Results: Baseline characteristics were comparable between the two groups, except for higher alanine aminotransferase (ALT) levels in cases (median, 24.5 vs 32.0 U/L). Metabolomics analysis annotated 190 compounds. Of them, 103 and 87 were increased and reduced in baseline plasma of CHB patients with HCC development, respectively. Notably, 3,4-DHPPA was significantly reduced in baseline plasma of patients with HCC development. Kaplan-Meier survival analyses showed that 4-year cumulative incidence of HCC decreased significantly in patients with higher 3,4-DHPPA levels at baseline. After adjusting age, sex, bilirubin, albumin, platelet and ALT elevation, individuals with higher 3,4-DHPPA exhibited a decreased risk of HCC. 3,4-DHPPA preferentially inhibit proliferation of HCC cells *in vitro*. Notably, in primary HCC mouse models induced with oncogenes or chemicals, 3,4-DHPPA significantly prevented HCC development.

Conclusion: The deficiency of circulating 3,4-DHPPA possibly contributes to HCC development in CHB patients with viral control. These insights hint at novel strategies to further reduce HCC risk in the antiviral era.

THU-125

Activation of coagulation system and platelet aggregation in patients with primary sclerosing cholangitis and cholangiocarcinoma

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Background and aims: Venous thromboembolism in cancer patients remains a major health problem. In cholangiocarcinoma (CCA), the role of the tumor cells in the abnormal activation of the coagulation cascade and platelet aggregation has been poorly studied. A well-established risk factor of CCA is primary sclerosing cholangitis (PSC), where a hypercoagulation state was previously reported. Starting from these observations, in this study we aimed at assessing the expression of components of coagulation and fibrinolysis pathways along with the platelet function in PSC and CCA.

Method: Formalin-fixed, paraffin-embedded archival tissues from liver biopsy or surgical resection for PSC, intrahepatic CCA (iCCA), and implanted grafts (controls) (n = 10 in all) were stained by immunohistochemistry or immunofluorescence (IF) for the following: tissue factor (TF), factor (F) X, FXI, FXIIIA, von Willebrand factor (vWF), fibrinogen and endothelial protein C receptor (EPCR). Fibrin deposition within the portal vein radicle lumen (portal vein microthrombosis, PVMT) was assessed by Martius Scarlet Blue staining. Additionally, IF for TF and FX was performed in patient-derived organoids (OG) from PSC and iCCA (both n = 10). Quantitative evaluation of extracellular vesicles (EVs) isolated from conditioned medium of PSC-OG and iCCA-OG was quantified by cytometric analysis (FACS) by means of specific markers (Calcein-AM, EpCam-PE and Annexin V). Finally, FACS evaluated the effects of EVs on platelet aggregation using CD41, CD62P and Annexin V.

Results: Aberrant expression of coagulation factors was found in iCCA and PSC, but not in controls. TF and FX, but not FXI, were upregulated in cholangiocytes and stromal cells, more prominently in iCCA than in PSC. Fibrinogen was diffuse throughout the stroma, with marked fibrin deposition in the stroma, of both iCCA and PSC, where FXIIIA was expressed by both cholangiocytes and macrophages. Moreover, PVMT was observed in both PSC (n = 4/10) and iCCA (n = 2/10), particularly in samples showing the highest expression of TF. Endothelial cell (EC) expression of EPCR was significantly weaker in tumor than in PSC and controls, while vWF expression was increased in ECs of PSC and iCCA. Upregulated expression of TF and FX were

confirmed in PSC-OG and iCCA-OG. Additionally, EVs derived from either PSC-OG or iCCA-OG strongly induced platelet activation.
Conclusion: PSC and iCCA showed a phenotype of activated procoagulation and impaired fibrinolysis, regardless of the development of PVMT. Patient-derived organoids provide a novel *in-vitro* model to study effects on platelet activation, possibly mediated by EVs. Future studies are needed to understand if the perturbation of blood coagulation/fibrinolytic pathways may provide targets for therapeutic intervention to hamper progression of PSC and CCA, which are both short of effective treatments.

THU-126

So hot, yet so cold: bacterial lipopolysaccharides hinder tumor adaptive immunity by producing inflammatory and suppressive innate immunity in non- or poorly-infiltrated hepatocellular carcinoma

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Background and aims: Immunologically silent (cold) liver tumors, with little or no infiltration, account for two-thirds of hepatocellular carcinomas (HCCs) and represent a major challenge for immune-based cancer therapies. Little is known about the molecular and cellular mechanisms involved in T-cell exclusion.
Method: We rigorously selected a set of low-infiltration human HCCs from patients managed at the Hepatobiliary Centre of Paul-Brousse Hospital (Villejuif), generated extensive molecular, transcriptomic (applying a workflow based on unsupervised machine learning algorithms) and immunophenotypic data using flow cytometry and tissue staining, as well as thorough clinicopathological data. This comprehensive and diverse dataset has been further integrated to better understand the molecular and cellular responses driving such a tumor ecosystem, and to discover new regulatory networks involved in the immune evasion of HCC.
Results: We show that cold human HCCs contain large amounts of bacterial lipopolysaccharides (LPS) from Gram-negative bacteria (a typical Pathogen-associated molecular pattern "PAMP"), associated with LPS/Toll-like receptor 4 (TLR4) signalling-mediated inflammatory response, recruitment of myeloid immunosuppression and increased expression of immune checkpoint molecules, that would prevent T cell infiltration into the TME. To substantiate the role of LPS-induced immunoinflammatory response in human cold HCC, we used a model of non-T-cell-infiltrated HCC in mice transgenic for the MYC oncogene, in which different TLR4 agonists (LPS formulated in liposomes from different Gram-negative bacterial strains) were administered. The exogenous LPS was confirmed to accumulate in the liver. We show that the level of tumor infiltration by myeloid-derived suppressor cells (MDSCs) expressing immune checkpoint molecules upon LPS challenge is highly dependent on the inflammatory potency (high, medium or low) of the LPS and, consequently, on the signalling pathway committed. The lower the LPS-dependent inflammatory response, the more myeloid immunosuppression is significantly reduced. Conversely, the more intense the inflammatory response, the more intense the recruitment of MDSCs.
Conclusion: Non/poorly infiltrated HCCs form a heterogeneous set of tumors in which different mechanisms of immune escape may exist/coexist, including a mechanism involving an inflammatory response mediated by LPS-TLR4 signaling in the recruitment of immunosuppressive myeloid cells and, ultimately, in the T-cell exclusion. This study highlights the contribution of tumor-extrinsic mechanisms originating from the gut microbiota to the failure of tumor immunity in HCC.

SATURDAY 10 MAY

SAT-063

Engineering NK cell immunotherapy to optimise liver tumour homing and block PD-L1-mediated inhibition of T cells

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Background and aims: NK cells are being developed for adoptive cell therapy of cancer and chronic viral infections, such as hepatocellular carcinoma (HCC) and hepatitis B (HBV), with the advantages of intrinsic tumour-killing capacity, lack of MHC restriction and low toxicity. Cytokine activation (IL2/12/15/18) is widely used to promote memory-like NK cells with enhanced anti-tumour functionality. However, we recently showed that cytokine activation induces PD-L1 on human and murine NK cells, resulting in inhibition of HBV-specific T cells (*Diniz, SciTranslMed 2022*).
Method: The aims of this study were therefore to engineer primary NK cells to be retained within Hepatocellular carcinoma (HCC), exerting anti-tumour function without impeding the activity of neighbouring anti-tumour T cells through PD-L1. *To do this we genetically manipulated NK cells to express the chemokine receptor CXCR6 (which retains liver-resident NK cells) and to secrete anti-PD-L1 antibodies to counteract their checkpoint inhibition of T cells.*
Results: Using VSV-G pseudotyped lentivirus we achieved successful transduction of primary human NK cells confirmed by the significant induction of CXCR6 expression. Higher numbers of $CXCR6^{+}$NK-cells were recovered from matrigel containing CXCL16 (the ligand for CXCR6) or HepG2 supernatant compared to untransduced NK-cells, indicating that the encoded CXCR6 receptor was functional. Production and secretion of anti-PD-L1 was confirmed by its capacity to block PD-L1 on NK or hepatoma cells *in vitro*, preventing staining of this ligand by flow cytometry. Their secretion of anti-PD-L1 antibodies converted cytokine-activated transduced NK cells into predominant 'helpers', able to boost $CD8^{+}$T cell responses to HBV peptide stimulation or hepatoma cells.
Conclusion: In summary, we genetically engineered cytokine-activated NK cells to have enhanced homing/retention within liver tumours and to mediate anti-tumour activity whilst releasing their helper function to boost antigen-specific T cells. This approach should promote the dual anti-tumour functionality of NK cells and T cells, to work in tandem rather than in opposition, against HCC.

SAT-064

Expression and role of trefoil factor 3 (TFF3) in hepatoblastoma

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Background and aims: Trefoil factor (TFF3) is a small peptide secreted by epithelial mucous producing cells involved in the protective and reparative response triggered by epithelial injury. TFF3 is overexpressed in different solid tumors and contributes to carcinogenesis. We have evaluated TFF3 expression and its pro-tumorigenic role in hepatoblastoma (HB), the most common pediatric liver cancer.

Method: TFF3 expression was examined in three HB transcriptomic datasets (GSE75271, GSE81928 y GSE104766), in HB tissues (immunohistochemistry) and in the mouse HB model induced by mutant YAP/b-CAT hydrodynamic plasmid injection. TFF3 gene expression regulation and function were tested in human HB cell lines in which its expression was manipulated. The effect of TFF3 expression of HB growth in vivo was evaluated in a subcutaneous xenograft model in nude mice.

Results: TFF3 mRNA and protein were overexpressed in human HB tissues and in the lesions developed in the mouse YAP/b-CAT HB model. Normal liver tissues did not express TFF3. Overexpression of TFF3 in HepG2 cells potently induced cell proliferation, anchorage-independent growth and increased resistance to cisplatin treatment. TFF3 stable transfection promoted the downregulation of genes associated with liver differentiation, and induced that of inhibitors of hepatocellular differentiation, as well as genes associated with glucose uptake and glycolysis. SeaHorse experiments revealed that TFF3 markedly enhances glycolysis. *TFF3* expression was potently upregulated in hypoxia. Its overexpression enhanced that of genes involved in glycolysis under hypoxic conditions, as well as hypoxia-triggered cell growth. TFF3 expression enhanced the growth of HepG2 cells xenografted in nude mice.

Conclusion: *TFF3* is significantly overexpressed in clinical and experimental HB tumors, being almost undetectable in normal liver parenchyma. Activation of YAP and b-CAT pathways, predominant in HB, may trigger TFF3 expression in hepatocytes. In HB cells, TFF3 expression promotes the manifestation of neoplastic traits. TFF3 may be an important determinant in the adaptation of HB cells to hypoxia. Pharmacological targeting of TFF3 expression or activity may be leveraged to increase HB response to cisplatin.

SAT-075

Prediction of hepatocellular carcinoma using AI-driven MRI radiomics: development of the AI-HCC prediction model

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Background and aims: Early detection of hepatocellular carcinoma (HCC) is essential to improve patient survival for which annual HCC screening is recommended. Compared to ultrasound, MRI has improved early detection of HCC, but its use is limited by increased costs and reduced availability. Identification of patients at risk of HCC would target MRI screening and preventive measures to those patients most in need. The aim of this study is to develop an AI-based support system for the accurate prediction of future HCC development in patients with liver cirrhosis.

Method: A retrospective analysis was conducted on sequential MRI data from patients with liver cirrhosis who underwent HCC surveillance through annual MRI screening. In 2018, HCC surveillance changed in the study institution from an ultrasound-based to MRI-based surveillance regimen. MR images were analyzed by ensemble machine learning modeling (XGBoost), as an initial feasibility study. Consequently, a deep learning model (AI-HCC) was developed, utilizing ConvNeXt-based CNN for processing 3D MRI scans. The AI-HCC model was then combined with Transformer encoders to capture temporal dependencies across sequential MRI observations. Clinical data of all study patients were collected, including general demographic, disease-specific, HCC and survival data.

Results: MRI data of 243 patients (88 females, 36%) with liver cirrhosis were analyzed, of which 37 patients developed HCC. The majority of patients with HCC suffered from MASH (n = 15, 40.5%) or alcoholic liver disease (ALD, n = 8, 22%). Patients had long-term follow-up by MRI, with an average of 2.8 ± 1.9 MRI assessments per patient, and a mean follow-up duration of 23.2 ± 23 months. The AI-HCC prediction model was tested using a variety of MRI sequences in order to develop the final AI-HCC prediction model. The predictive power of the final AI-HCC model showed excellent predictive performance, achieving an AUC-ROC of 0.95, 0.94, and 0.98 for the 12-month, 24-month, and 36-month HCC prediction horizons, respectively. For patients with MASH, the model achieved an AUC-ROC of 0.956 ± 0.021, which was significantly higher than seen in

patients with alcoholic liver disease (AUC-ROC: 0.850 ± 0.045, p < 0.05), at the same prediction horizon.
Conclusion: Our study reports the development of an accurate AI-HCC prediction model, with high predictive power (AUC-ROC >0.94) for the prediction of hepatocellular carcinoma development in patients with liver cirrhosis. Predictive properties of the AI-HCC model were similar across three years leading up to HCC, illustrating the potential for early HCC risk stratification. The AI-HCC prediction model has great potential to target MRI screening to those at high risk for HCC, while avoiding unnecessary HCC surveillance in low-risk patients, thereby changing the HCC surveillance landscape.

SAT-076
Therapeutic potential of Human antigen R inhibition in chronic liver disease and hepatocellular carcinoma
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Background and aims: The RNA-binding protein HuR (Human antigen R) importantly regulates the stability and translation of a wide range of transcripts involved in metabolism, inflammation, and cancer (e.g., TNFα, MYC). While several studies have highlighted the tumor-promoting function of HuR in hepatocellular carcinoma (HCC), emerging evidence indicates that HuR inhibition may promote Metabolic Dysfunction-Associated Steatohepatitis (MASH). Therefore, the role of HuR in these diseases remains unclear and the therapeutic potential of HuR inhibition in these diseases remains to be demonstrated. In this study, we have characterized the impact of HuR inhibition on both HCC and MASH development.
Method: HuR expression was measured in liver tissues from patients and mouse models of hepatic steatosis, MASH, HCC, and intrahepatic cholangiocarcinoma (ICC). The potential of HuR inhibition was evaluated by genetic (siRNA, AAV8) or pharmacologic approaches (HuR inhibitors: CMLD-2 and MS-444) in a panel of hepatic cancer cell lines, primary hepatocytes and mouse models of MASH (mice fed a choline-deficient amino acid-defined high-fat diet: CDAHFD). A proteomic analysis in hepatic cancer cells was performed to characterize the impact of HuR inhibition on cancer-related processes and identify potential targets.
Results: HuR is overexpressed in HCC and ICC as compared to non-tumoral tissues. Histological analyses revealed that some patients exhibit a strict nuclear localization pattern, while others display nuclear and cytoplasmic localization. HuR inhibitors markedly reduced hepatic cancer cell proliferation, viability and migration. For MS-444, but not for CMLD-2 or HuR silencing, cells accumulated in prophase, thus suggesting some HuR-independent effects. A proteomic analysis confirmed that HuR inhibitors alter a network of oncogenes and tumor suppressors, including known HuR targets (e.g., ATG5), associated with a poor prognosis. However, HuR inhibition promotes hepatic steatosis in primary hepatocytes and in mice fed a CDAHFD, through the downregulation of ApoB.
Conclusion: HuR is an important tumor promoter in HCC and HuR inhibitors display interesting anti-cancerous properties in hepatic cancer cells. However, HuR inhibition also exacerbates hepatic lipid metabolism and thus promotes MASH development, thus suggesting cautions regarding the use of HuR inhibitors in clinical practice.

SAT-077
OGT and c-Myc promote non-canonical activation of gene expression by EZH2 in hepatocellular carcinoma
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Background and aims: Hepatocellular carcinoma (HCC) is the most frequent form of liver cancer. The histone methyltransferase (HMT) EZH2 is frequently upregulated in HCC tissues and its expression correlates with HCC aggressivity and poor prognosis. As the catalytic subunit of PRC2, the canonical activity of EZH2 is to trimethylate H3K27 to mediate gene repression. In cancer, EZH2 can have non canonical roles including activation of gene expression in a PRC2- and/or HMT-independent manner. EZH2 is regulated by post-translational modifications, including O-GlcNAcylation by OGT, an enzyme that is also upregulated in HCC. We showed that OGT co-localizes with EZH2 at the promoter of a set of genes involved in cancer-associated pathways in human hepatoma cells.
Method: Here, we used chromatin immunoprecipitation followed by sequencing (ChIP-seq), RNA-sequencing (RNA-seq), computational analysis and functional studies to assess the role of OGT in the epigenetic and transcriptional regulation of cancer-associated genes by EZH2 in HCC.
Results: Our data indicate that OGT is more frequently associated with activation of gene expression by EZH2 than with EZH2-mediated gene repression. In line with our gene ontology and pathway analysis of EZH2/OGT co-activated genes that showed an enrichment of genes related to cell cycle and cancer pathways, including Myc targets, the majority of promoters with EZH2 and OGT co-recruitment also exhibit c-Myc binding.
Conclusion: Collectively, our data uncover that OGT and c-Myc promote non-canonical functions of EZH2 in transformed liver cells and provide important insights for epigenetic strategies as potential future anti-HCC therapies.

SAT-078
Immunoregulation and T cell paralysis mediated by MDSC induction in hepatocellular carcinoma following rVSV-NDV therapy
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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality and is characterized by a profoundly immunosuppressive tumor microenvironment limiting effective immune responses. The therapeutical potential of a recombinant chimeric virus, rVSV-NDV, has been demonstrated to mediate therapeutic effects in preclinical models of HCC. This study evaluates the interplay between oncolytic virus therapy and tumor-induced immune suppression, focusing on identifying strategies to overcome immunotherapy resistance.
Method: Using an orthotopic model of HCC in mice, the therapeutic potential of the recombinant virus rVSV-NDV was evaluated. The immune infiltration into the tumor was analyzed using flow cytometry. Confocal microscopy examined the spatial relationship of $CD8^+$ T cell and MDSCs. *In vitro* assays were conducted to investigate the role of HCC tumor cells in driving monocyte differentiation into MDSCs and their suppression of T cell activity via methylglyoxal transfer. Single-cell RNA sequencing (scRNA-seq) was used to analyze MDSC populations and transitional states in murine HCC models.
Results: Treatment with rVSV-NDV resulted in the infiltration of monocytes and effector CD8+ T cells into the liver and tumor. However, infiltrating monocytes differentiated into myeloid-derived suppressor cells (MDSCs), which coincided with $CD8^+$ T cell infiltration and potentially neutralize their cytotoxic effects.

Confocal microscopy revealed that CD8$^+$ T cell–MDSC interactions were localized to the tumor border, thereby highlighting spatial dynamics of immune suppression. *In vitro*, HCC cells were shown to drive monocyte-to-MDSC differentiation, resulting in T cell suppression via methylglyoxal transfer. scRNA-seq analyses identified a distinct MDSC population and suggested an intermediate state between mononuclear phagocytes and MDSCs, indicating a transitional process.
Conclusion: This study elucidates the mechanism of MDSC-mediated immune suppression and the role in neutralizing T cell activity within the immunosuppressive microenvironment of HCC. The findings reveal a complex interaction between oncolytic viral therapy and tumor-induced immune resistance, providing insights that could guide the development of more effective immunotherapies for HCC. Further research is ongoing to elucidate the processes driving mononuclear phagocyte differentiation into MDSCs and identify potential therapeutic targets.

SAT-079
Metabolic and functional characterization of CD8+ T-cell subpopulations in hepatocellular carcinoma: implications of tumor microenvironment on T-cell dysfunction
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Background and aims: CD8 T-cells are crucial in adaptive immune response, against viral infections and tumors. The tumor immune microenvironment (TIME) can disrupt immunological pathways. In Hepatocellular Carcinoma (HCC), CD8 T-cell functional defects correlate with disease stage and clinical outcomes, but the molecular bases of their dysfunction are not fully understood. Recent studies reveal the importance of specific CD8+ T-cell subpopulations in the tumor microenvironment, highlighting that within tumor-infiltrating lymphocytes (TILs), CD103+CD39+ cells are enriched for tumor-reactive T cells in solid tumors. Additionally, in liver and tumor tissues two distinct CD8+ T-cell populations can be found with opposing clinical implications: Terminally exhausted (TEX) and Tissue resident memory (TRM) cells. A high TRM/TEX ratio predicts better patient outcomes, while tumor-reactive T cells show the greatest functional improvement after anti-PD-1 therapy. These findings underscore the complementary roles of TRM and TEX cells in immune responses during checkpoint therapy. Our study aims to comprehensively characterize metabolic and functional differences between tumor-infiltrating and liver-infiltrating CD8+ T-cell subpopulations.
Method: We performed phenotypic expression of surface markers (CD103, CD39 and PD1) that can define different CD8 subsets: Tissue resident memory (TRM), Tumor reactive and Terminally exhausted cells (TEX). By analyzing metabolic status, DNA damage response, and cytokine production, we seek to elucidate TIME's impact on T-cell functionality.
Results: The tumor microenvironment was enriched of TEX cells (CD39+ CD103- PD1+) and CD39+/CD103+ Tumor-reactive-cells. Exposure to TIME led to dysfunction, with a higher percentage of PD1+/Tim3+ Tumor-reactive cells. TRM cells (CD103+CD39-PD1+) in the liver were less exhausted (CD103+CD39-PD1lo) than their tumor counterparts (CD103+CD39-PD1hi and CD103+CD39-PD1+Tim3+). Metabolic analyses revealed that tumor-infiltrating subpopulations had lower glucose uptake and higher mitochondrial membrane depolarization, indicating significant metabolic strain, and higher histone H2AX phosphorylation, indicating more DNA damage. TEX showed highest H2AX phosphorylation, while TRM the lowest. In tumor-infiltrating CD8+ T-cells, mitochondrial membrane depolarization correlated positively with p-H2AX+ cells and negatively with glucose uptake. Functional analysis revealed an overall lack of functionality in tumor-infiltrating TEX cells. Finally, an enrichment of TEX cells was observed in patients with larger tumor nodules size, while Tumor-reactive and TRM cells were reduced in the same group of patients.
Conclusion: The TIME imposes significant metabolic and DNA damage stress on CD8+ T-cell subpopulations, leading to functional impairments. Therapeutic strategies targeting these metabolic challenges are essential for enhancing anti-tumor immunity.

SAT-080-YI
The NLRP3 inflammasome and its downstream target Il1R, but not IL18R drive hepatocarcinogenesis
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Background and aims: Hepatocellular carcinoma (HCC) is the most common form of liver cancer and often arises in the chronically inflamed liver, which can lead to liver injury and the malignant transformation of hepatocytes. The NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome is a key regulator of sterile inflammation in liver disease, but its role in hepatocyte malignant transformation remains incompletely understood. Activation of the NLRP3 inflammasome by pathogen- or damage-associated molecular patterns (PAMPs/DAMPs) initiates the secretion of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18). This study aimed to investigate the role of NLRP3 and its downstream targets (IL-1β and IL-18) in inflammation- and primary sclerosing cholangitis (PSC)-related hepatocarcinogenesis.
Method: NLRP3 expression was analyzed in liver tissue samples obtained from hepatocellular carcinoma (HCC) patients (n = 6) and non-cancerous controls (n = 5). In mice, HCC was induced using the N-nitrosodiethylamine/carbon tetrachloride (DEN/CCl_4) model in wild-type (WT), *Nlrp3*$^{-/-}$, *Il1r*$^{-/-}$ and *Il18r*$^{-/-}$ mice. PSC-related hepatocarcinogenesis was modeled by crossing *Nlrp3*$^{-/-}$ mice with multidrug resistance gene 2 knockout mice (*Mdr2*$^{-/-}$/*Nlrp3*$^{-/-}$), which were analyzed at 64 weeks of age. Tumor development, immune cell infiltration, and proliferation were assessed in both models.
Results: Analysis of human HCC tissue demonstrated a significant upregulation of NLRP3 expression compared to non-tumor controls. In both murine tumor models (DEN/CCl_4 and genetic modified *Mdr2*$^{-/-}$) NLRP3 deletion significantly reduced tumor burden and inflammation. Reduced inflammation was evidenced by decreased staining for Kupffer cells and activated hepatic stellate cells. Additionally, NLRP3 deletion reduced hepatocyte proliferation, as confirmed by Western blot and immunostaining. To further dissect the downstream pathways, tumor development was assessed in *Il1r*$^{-/-}$ and *Il18r*$^{-/-}$ mice. Interestingly, *Il1r*$^{-/-}$ but not *Il18r*$^{-/-}$ mice exhibited reduced tumor burden, inflammation, Kupffer cell and hepatic stellate cell activation. The deletion of *Nlrp3* or *Il1r*, but not *Il18r*, led to increased CD8$^+$ T cells infiltration and elevated *Interferon-γ*

(*Ifnγ*) expression. RNA-Seq analysis supported these findings by revealing upregulation of T-cell activation pathways in tumor tissues from NLRP3-deficient mice compared to WT controls. Thus, the deletion of NLRP3 or IL1R, but not of IL18R showed protective effects for HCC development.
Conclusion: NLRP3 is overexpressed in human HCC tissue and promotes hepatocarcinogenesis in murine models. Deletion of NLRP3 or IL1R, but not IL18R, reduces HCC development, highlighting their roles as key drivers of tumorigenesis. These findings suggest that potential therapeutic strategies for HCC may include targeting the NLRP3 inflammasome or IL-1 signalling.

SAT-081

Development and performance of AI in supporting the diagnosis of liver tumors using B-mode ultrasound

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Background and aims: Early diagnosis of liver tumours is crucial for timely intervention in liver cancer. Abdominal ultrasound (US) is recommended as a screening tool for hepatocellular carcinoma (HCC). However, diagnostic performance in US examinations depends on the operator's expertise. We developed an artificial intelligence (AI) to assist the diagnosis of four types of lesions—HCC, metastatic tumors (META), haemangiomas (HEM), and cysts—enabling beginners to achieve expert-level diagnostic performance. The efficacy of AI was evaluated through clinical trials.
Method: B-mode US images of liver mass labelled with diagnoses from other modalities were collected from 11 institutions. Using the 104,908 still US images, the AI was trained; the detection module used YOLOv5 with DeepSORT, while the classification module used VGG-19. In the clinical trials, B-mode US videos, collected in clinical practice, were used. Human readers diagnosed the lesions with and without AI assistance and results were compared. Two tests were conducted, with results standardized using Z-scores for analysis.
For detection, the first trial used 59 cases (36 solitary, 14 multiple, 9 non-lesion images), and the second trial involved 60 cases (40 solitary, 12 multiple, 8 non-lesion images). For classification, the first trial included 50 cases (15 HCCs, 13 METAs, 18 HEMs, 4 cysts), and the second trial used 50 cases (15 HCCs, 15 METAs, 15 HEMs, 5 cysts). Thirty-six readers participated, comprising 16 experts (certified specialists) and 20 beginners.
Results: The performance of AI with cross-validation were as follows; recall = 0.929, precision = 0.906, and F1 score = 0.917 for detection, the accuracy = 0.890 for 4-disease classification, and accuracy = 0.937, sensitivity = 0.897, and specificity = 0.957 in malignant discrimination. In the clinical trials, recall and F1 score improved significantly under AI assistance (both $p < 0.0001$), while precision showed a trend toward improvement ($p = 0.2377$). Subgroup analysis revealed significant improvements in recall in the expert's group ($p = 0.0002$). In the beginner's group, significant improvements were observed in recall, precision, and F1 score ($p < 0.0001$, $p = 0.0192$, $p < 0.0001$, respectively). In 4-disease and malignant discrimination, accuracy improved significantly under AI assistance (both $p < 0.0001$). Subgroup analysis confirmed significant improvements in both tasks for experts and beginners ($p < 0.0001$ for both groups in 4-disease classification, $p = 0.0184$ for experts and $p < 0.0001$ for beginners in malignant discrimination,). Diagnostic accuracy, sensitivity, specificity, and Matthews correlation coefficient improved across all lesion types under the AI-support.
Conclusion: The developed AI demonstrated significant diagnostic support for both beginners and experts, underscoring its potential as a valuable tool for enhancing the diagnosis of liver mass in US practice. This AI shows a promising step toward societal implementation of AI-powered US diagnostics.

SAT-082-YI

The metabolic heterogeneity induced by different genetic mutations in hepatocellular carcinoma leads to a particular response to feeding a lipid-enriched diet

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Background and aims: Hepatocellular carcinoma (HCC) represents 75% to 85% of primary liver cancers. The heterogeneity among HCC patients, due at least in part to metabolic reprogramming, makes it difficult to find more specific treatments. This highlights the need to distinguish between different HCC subtypes. Our previous research has demonstrated the pivotal role of E2F transcription factors in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD) and related metabolic dysregulation. The objectives here were: 1) to study the metabolic heterogeneity of two HCC subtypes (more and less dedifferentiated) and the influence of a high-fat diet on their development and progression; and 2) to analyze the role of E2F transcription factors in the metabolic reprogramming associated with each HCC subtype.
Method: the two HCC subtypes were developed in C57BL/6J mice fed a chow (CD) or high-fat diet (HFD) by the *Sleeping Beauty* technique. One of the HCC subtypes was highly dedifferentiated, overexpressing *MYC* and β-catenin oncogenes (*mHCC1*), while the other was highly differentiated overexpressing β-catenin and repressing the tumor suppressor *PTEN* (*mHCC3*). Weight was monitored weekly and a glucose tolerance test was performed. Tumor number and size, white adipose tissue (WAT) lipolysis, serum and hepatic lipid levels were determined. In addition, E2F1 and E2F2 factors were quantified by western blotting and a proteomic study was performed on tumor (T) and healthy (CT) tissues. The TCGA cohort was also analyzed using the cBioPortal tool.
Results: The *mHCC1* model showed a higher tumor formation rate and a pronounced response to HFD while the *mHCC3* model didńt. Tumor development did not lead to changes in either body weight or serum glucose management, regardless of the animal model or diet. The accelerated tumor growth observed in the *mHCC1*-HFD model was associated with a reduction in the tumor storage of triglycerides (TG) and diglycerides (DG), and an increase in serum fatty acids (FA), cholesterol and TG. According to the proteome profile, this phenotype was associated to changes in biological pathways affecting TG degradation, FA oxidation and lipoprotein clearance. This phenotype was not observed in the *mHCC1*-CD model or when *mHCC3* was developed under a CD or HFD diet, where a marked increase in the accumulation of tumor lipids (cholesteryl ester, DG and TG) was found. The upregulation of β-catenin in both mouse models fed a CD or a HFD was related with a decrease in tumor E2F1 levels, consistent with the decrease observed in HCC in patients with β-catenin mutations.

Conclusion: The combination of genetic mutations linked to highly dedifferentiated HCC subtypes leads to the metabolic heterogeneity that promotes progression of HCC. Treatments aimed at preventing TG degradation, FA oxidation and lipoprotein clearance should be evaluated.

SAT-083-YI

Clinical potential and non-canonical roles of the cytosolic aspartyl-tRNA synthetase (DARS1) in hepatocellular carcinoma

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Background and aims: Aminoacyl-tRNA synthetases (ARSs) catalyze the transfer of amino acids to tRNAs for protein synthesis. Here, we explore the potential of the cytosolic aspartyl-tRNA synthetase (DARS1) as diagnostic biomarker and therapeutic target, as its molecular implication in hepatocellular carcinoma (HCC).
Method: DARS1 levels were analyzed in cytosolic/nuclear protein fractions of HCC patients ($n = 42$ patients) and seven *in silico* cohorts (mRNA/protein). DARS1 levels were detected in plasma samples of two cohorts (Discovery: 8 HCC vs. 8 controls; Validation: 32 HCC vs. 15 MASLD vs. 14 cirrhosis vs. 21 controls). Functional assays were performed in three liver cancer-derived cell lines (HepG2, Hep3B, SNU-387) after DARS1 modulation (silencing, overexpression, pharmacological inhibition). DARS1-overexpressing Hep3B cells were used for *in vivo* orthotopic tumor formation. Immunoprecipitation of DARS1 and quantitative proteomics were performed in cytosolic/nuclear Hep3B fractions.
Results: DARS1 abundance was increased in HCC tissues (mRNA/protein), and in plasma samples of HCC patients [Area Under Curve (AUC) HCC *vs.* controls: 0.8376; HCC *vs.* MASLD: 0.9016; HCC *vs.* cirrhosis: 0.8095]. DARS1 levels were higher in aggressive tumors (i.e. invasive, dedifferentiated) and in patients with adrenal/lung metastasis. Consistently, *DARS1* silencing and pharmacological inhibition reduced, while *DARS1* overexpression increased, functional parameters of aggressiveness *in vitro*. In fact, orthotopic tumors formed by *DARS1*-overexpressing Hep3B cells had increased establishment capacity and growth *in vivo*. Mechanistically, DARS1 protein levels were higher in nuclear, but not cytosolic, samples of HCC. An immunoprecipitation assay revealed 182 cytosolic and 132 nuclear DARS1 interactors, three of the latter being members of the Spt-Ada-Gcn5 acetyltransferase (SAGA) complex, which regulates MYC acetylation and stability. This non-canonical interaction was confirmed by *in silico* docking of DARS1/SAGA crystal structures. Additionally, *DARS1* silencing reduced MYC protein levels and phosphorylation, and the expression of MYC targets was reduced in RNA-seq data of *DARS1*-silenced HepG2 cells. Consistently, *DARS1* silencing reduced drug-induced senescence (Gemcitabine, Etoposide, Cisplatin), suggesting a link between DARS1-SAGA interaction and MYC-regulated senescence.
Conclusion: The aspartyl-tRNA synthetase (DARS1) is overexpressed in HCC tissues and is a potential biomarker in liquid biopsy. DARS1 targeting could represent a therapeutic strategy for HCC though a mechanism that might involve its non-canonical nuclear interaction with the SAGA complex and the modulation of MYC activity. Fundings: ISCIII (ERDF/ESF, "Investing in your future"; PI20/01301, PI23/00652), MINECO (FPU20/03957), JdA (PEMP-0036-2020, BIO-0139), FSEEN and CIBERobn/ehd.

SAT-084

Microscale detection of selenium in liver tissue using laser ablation-inductively coupled plasma time-of-flight mass spectrometry

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Background and aims: Selenium (Se) is an essential trace element absorbed into the body from the soil through food consumption. In biological systems, selenium plays a crucial role in defense against oxidative stress as an integral part of the active centers of antioxidative enzymes such as glutathione peroxidases. The distribution of selenium in the body follows a complex hierarchy among organs and selenoenzymes and may be altered in the presence of cancer. Chronic selenium deficiency has been linked to the development of hepatocellular carcinoma. As a trace element, selenium concentrations in biological samples are low, necessitating the use of macroscopic tissue amounts for bulk quantification. Laser ablation (LA) combined with inductively coupled plasma time-of-flight mass spectrometry (ICP-TOFMS) is a state-of-the-art micro-analytical technique. In LA-ICP-TOFMS, a focused laser beam rasters across the sample, with each laser pulse ablating material that is transported to the mass spectrometer. Each laser shot corresponds to a pixel in the resulting elemental map, enabling high-resolution spatial analysis. The unique capability of ICP-TOFMS to simultaneously measure the full mass spectrum allows for the detection endogenous elements such as phosphorus (P) and iron (Fe) alongside with Selenium. Recent advancements in hardware, software, and methodology have further improved the technique's spatial resolution, sensitivity, and data acquisition speed, making it a powerful tool for studying trace elements in biological tissues with unprecedented detail and efficiency. This study aimed to evaluate the feasibility of detecting selenium in the liver using the novel LA-ICP-TOFMS technique.
Method: We employed a chemically induced hepatocellular carcinoma (HCC) model in Wistar rats, with and without selenium supplementation in their drinking water. Tissue sections with 5 µm thickness were prepared from formalin-fixed paraffin-embedded (FFPE) liver samples and subsequently analyzed by LA-ICP-TOFMS.
Results: The LA-ICP-TOFMS results showed that through concurrent detection of endogenous of elements such as iron (Fe) and phosphorus (P), imaging of Selenium in liver tissue was possible. Measurement conditions were optimized to allow the detection of hepatic selenium at a resolution of 2.5 µm, corresponding to subcellular scale. Selenium detection in the liver was achieved in both Se-supplemented and non-supplemented animals.
Conclusion: For the first time, we report microscale measurements of selenium distribution in the liver using the recent technological advancements of LA-ICP-TOFMS. This novel technique offers promising applications in understanding the relationship between selenium and liver tumor development at the single-cell resolution, contributing to a broader understanding of selenium's role in cancer prevention.

SAT-085-YI

The role of CNNM4 in the progression of cholangiocarcinoma: implications for ferroptosis and therapeutic potential

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Background and aims: Cholangiocarcinoma (CCA) is a heterogeneous neoplasm of the biliary epithelium that easily infiltrates, metastasizes and recurs. Magnesium disbalance is a hallmark of CCA, being the magnesium transporter CNNM4 a key driver of various hepatic diseases. This study aims to unravel the role of CNNM4 in the initiation and progression of CCA.
Method: CNNM4 protein and gene expression were assessed *in vitro*, *in vivo* and in patients with CCA. Silencing of *CNNM4* was effectively achieved by using siRNA or shRNA in CCA cell lines and GalNAc-conjugated siRNA in a transposon-based CCA mice model. The impact of CNNM4 on tumor cell proliferation, migration and invasion to the lungs was evaluated using the chicken chorioallantoic membrane model. Proteomic analysis was employed to elucidate the underlying molecular mechanisms.
Results: CNNM4 was upregulated in CCA samples from eight independent patient cohorts, comparing resected CCA samples (both iCCA and eCCA) with controls. Overexpression of CNNM4 was also confirmed in AKT/NICD, AKT/YapS127A and AKT/Fbxw7ΔF mouse models, as well as in human iCCA and eCCA cell lines, which also exhibited reduced intracellular Mg2+ levels, demonstrating a role for CNNM4 in Mg2+ extrusion in CCA. Functional studies showed that CNNM4 deficiency attenuated cell growth, chemoresistance, migration, invasion, tumorigenesis, cancer stem cell properties and the Warburg effect both *in vitro* and *in vivo*. Interestingly, proteomic analysis identified nuclear protein 1 (NUPR-1), an inhibitor of ferroptosis, as critical for the observed effects in CCA cells when CNNM4 levels are reduced. Knockdown of CNNM4 led to a significant reduction in NUPR-1 levels and increased iron accumulation and lipid peroxidation *in vitro* and *in vivo*. Furthermore, both the iron chelator deferiprone and overexpression of NUPR-1 were able to reverse the reduced proliferation induced by CNNM4 silencing, highlighting the specificity of ferroptosis in CNNM4-associated effects.
Conclusion: This study demonstrates that increased CNNM4 expression drives CCA progression and malignancy and that its inhibition may be an effective therapeutic strategy to limit proliferation and metastasis in CCA patients.

SAT-086

Tumour-infiltrating regulatory T cells engage Nrf2 signalling to support their metabolic adaptation in hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, represents the third leading cause of cancer-related mortality worldwide. Within HCC tumours, regulatory T cells (Tregs), a specialized subset of CD4+ T cells, accumulate in substantial numbers. This accumulation inversely correlates with patient survival rates, indicating their crucial role in suppressing anti-tumour immune responses. Despite their clinical significance, the molecular mechanisms enabling Treg adaptation and persistence within the HCC microenvironment remain poorly understood. Our previous research demonstrated that in cirrhosis, a condition underlying the majority of HCC cases, Tregs exhibit functional impairment and increased susceptibility to apoptosis. This dysfunction stems from a compromised antioxidant response pathway associated with dysregulated nuclear factor erythroid 2-related factor 2 (Nrf2) signalling. Building upon these findings, we hypothesised that intratumoral Tregs engage Nrf2 signalling for their adaptation within the HCC microenvironment, thereby promoting their metabolic fitness and expansion.
Method: Integrating cutting-edge omics technologies with advanced in vivo models, we investigated the metabolic regulation of intratumoral Tregs through three distinct approaches: characterisation of Nrf2-dependent signalling networks governing human intratumoral Treg metabolism; assessment of tumour microenvironment-derived metabolic signals, specifically lactate, on Treg metabolic programming; and evaluation of targeted Nrf2 pathway modulation through both pharmacological and genetic approaches in an established HCC mouse model.
Results: Our analysis revealed that Tregs in non-tumoral liver tissue exhibit metabolic quiescence and increased susceptibility to apoptosis. However, upon exposure to the lactate-enriched tumour microenvironment, Tregs demonstrate enhanced Nrf2 activation, which coordinates metabolic reprogramming essential for their survival and immunosuppressive capacity. Genetic deletion of Nfe2l2 (encoding Nrf2) in Tregs significantly reduced intratumoral Treg infiltration and attenuated tumour progression in vivo. Notably, pharmacological Nrf2 inhibition favourably modulated the ratio of effector to regulatory immune cells within the tumour microenvironment while preserving systemic immune homeostasis.
Conclusion: Our findings establish Nrf2 as a critical immune checkpoint regulator that governs Treg metabolic adaptation within the tumour microenvironment. This discovery reveals a promising therapeutic strategy for HCC treatment through selective modulation of Nrf2 signalling, potentially enabling the reversal of tumour-associated immunosuppression and enhancement of anti-tumour immune responses.

SAT-087

MiR-485-3p as a predictor of therapeutic response and its role of the PIAS3/STAT3/VEGF signal in Atezolizumab plus Bevacizumab therapy for hepatocellular carcinoma

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Background and aims: In atezolizumab/bevacizumab (atezo/bev) therapy for unresectable hepatocellular carcinoma (uHCC), the tumor immune environment is regulated through vascular endothelial growth factor (VEGF) inhibition to maximize immune checkpoint blockade; however, evidence for VEGF as a biomarker is limited. This study aimed to investigate serum VEGF and associated microRNAs (miRNAs) as rapid biomarkers and their regulatory mechanisms in atezo/bev therapy.
Method: Fifty-four patients with uHCC who were treated with atezo/bev therapy were enrolled and assigned into objective response (OR) and non-OR groups according to the best therapeutic response in 12 weeks using the modified response evaluation criteria in solid tumors. Serum VEGF levels and associated miRNA expression were compared. Furthermore, the effect of cell transfection with specific miRNA was investigated.
Results: There was no significant difference in the pretreatment serum VEGF levels between the groups; however, the 3-week/pretreatment ratio of serum VEGF levels was significantly lower in the OR group than in the non-OR group. The pretreatment serum levels of 10 miRNAs, especially miR-485-3p involved in VEGF expression, were higher in the OR group than in the non-OR group and were further elevated after 1–7 days and 3 weeks. miR-485-3p suppressed HuH-7 migration, enhanced the expression of protein inhibitor of activated (PIA) signal transducer and activator of transcription 3 (STAT3) (PIAS3), and suppressed the expression of phosphorylated STAT3/VEGF.
Conclusion: Serum miR-485-3p is a more sensitive biomarker than VEGF for the early prediction of therapeutic response in atezo/bev therapy for uHCC.

SAT-088

Integrated multi-omics profiling of pan heat shock proteins in hepatocellular carcinoma identifies CCT3 and CCT7 as druggable oncogenes in hepatocytes

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Background and aims: Hepatocellular carcinoma (HCC) is associated with poor prognosis due to limited targeted therapies, necessitating the identification of novel therapeutic targets. Heat shock proteins (HSPs) are recognized as carcinogen regulators; however, their function in HCC remains unclear. This study aims to screen and characterize pan HSP expression in HCC at the multi-omic level and to enhance our understanding of disease pathogenesis.
Method: We created a comprehensive atlas of 132 human HSPs and assessed their expression in HCC patients using a bulk RNA-sequencing analysis. We utilized weighted gene co-expression network analysis (WGCNA), and intramodular connectivity to discover key HSPs in HCC. We validated key HSPs with three independent single-cell RNA-seq (scRNA-seq) datasets (two from

HCC, one from healthy subjects) in combination with high-dimensional WGCNA and proteomics datasets. Furthermore, we performed a comprehensive bioinformatic analysis and integrated a multi-omic network of key HSPs at bulk, single-cell, and proteome levels. Subsequently, we conducted *in-vitro* assays with HCC cell lines, employing RT-PCR, western blotting, and gene silencing by RNA interference to assess their impact on proliferation, apoptosis, and cell cycle. Finally, we screened clinically approved anticancer therapeutic compounds against the key HSPs by using molecular docking and molecular dynamics simulations.
Results: Gene set enrichment analysis revealed proteostasis and HSPs are upregulated in HCC. Further, WGCNA identified thirteen hub HSPs contributing to cancer-related pathways. The scRNA-seq analysis in combination with high-dimensional WGCNA, revealed two key HSP genes, *CCT3*, and *CCT7* as highly upregulated in hepatocyte cells. Comprehensive bioinformatic analysis with publicly available transcriptome and proteomic datasets confirmed elevated expression of CCT3 and CCT7 in HCC at gene and protein levels, highlighting their role in poor prognosis. Multi-omic network of these HSPs revealed that they regulate crucial cancer-related pathways. *In-vitro* silencing of CCT3 and CCT7 in HCC cell lines induced cell cycle arrest and apoptosis via caspase-3, PARP, and Bcl-xL pathways, suggesting their proto-oncogenic role. Finally, drug repurposing by molecular docking and molecular dynamics of 286 clinically approved anti-cancer drugs showed that talazoparib and irinotecan could be potential inhibitors of CCT3 and CCT7, respectively.
Conclusion: This study provides the first multi-omics characterization of pan-HSP expression in HCC, uncovering CCT3 and CCT7 as oncogenic drivers and novel druggable targets.

SAT-089-YI

mRNA-based vaccination for tumor neoantigens to induce a therapeutic T cell response in HCC

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Background and aims: Hepatocellular carcinoma (HCC) develops through a stepwise mutational process that gives rise to neoantigens (NA), which are aberrant proteins restricted to tumor cells. NA can be exploited to elicit a T cell-mediated immune response by priming T cells with mRNA vaccines encoding these specific targets. While this approach has demonstrated success in clinical trials for patients with metastatic melanoma, data on its efficacy in HCC remains unavailable (Ott, Wu, Nature, 2017; Lang, Sahin, Nature reviews drug discovery, 2021).
Method: RNA-Seq. of Dt81Hepa1-6 HCC cells were performed to detect NA derived from single nucleotide variants (SNV), splice variants (SV), fusion genes (FG) as well as insertion and deletion (InDel) using a bioinformatic algorithm. The top ten most promising NA of each mutation class were selected from all ranked NA candidates based on VaxRank, MHC class I/II binding and expression. MHC class I and PD-L1 expression was quantified in the Dt81Hepa1-6 cells via flow cytometry. Sequence-specific immunogenicity of NA-coding decatopes was evaluated via IFN-γ ELISpot. C57BL/6JRj mice (8-10 w, ♂) were intrasplenically injected with Dt81Hepa1-6 cells to develop macroscopic HCC lesion during 28 days. For in vivo therapy, HCC mice were injected (i.v.) with lipoplexes (LPX) loaded with NA coding mRNA (LPX:NAmRNA, according to 16 mg/kg NAmRNA) at day 7, 14 and 21 post tumor inoculation. Vaccination-derived effects were analyzed at day 28.
Results: Dt81Hepa1-6 cells displayed a complex mutanome with high expression of HCC key genes (e.g., *Afp, Spats, Mcm6, Mcm3, Nt5dc2*) as well as MHCI and PD-L1 which provided a suitable platform for NA vaccination approaches against HCC. We identified highly immunogenic NA while SNV, SV, FG and InDel-derived candidates induced strong sequence-specific $CD8^+$ and $CD4^+$ T cell responses to Dt81Hepa1-6 cells as assessed by ELISpot. Mice vaccinated with LPX:NAmRNA showed reduced hepatic tumor burden compared to LPX controls (serum AFP: −53%, liver weight: −27%, histological quantification: −46%), while the treatment was well-tolerated as indicated by normal behavior of the mice and laboratory safety parameter profiles for liver, kidney and hemolysis. T cell infiltration was significantly increased in the liver (+63%, $^{****}p < 0.0001$) in the spleen (+18%, $^{****}p < 0.0001$) and in the blood (+55%, $^{****}p < 0.0001$) in treated mice versus controls. Among T cells, $CD8^+$ were the dominant subgroup while being substantially increased in the liver (+24%) in the spleen (+38%) and in the blood (+25%).
Conclusion: Vaccination with immunogenic NA-based mRNA LPX resulted in a convincing T-cell mediated anti-tumor response in HCC mice, paving the way for further in vivo studies with optimized vaccines.

SAT-090

MFAP-5 siRNA nanohydrogels for antiangiogenic stromal-targeting HCC therapy

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Background and aims: Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer and the third leading cause for cancer-related death worldwide. Cancer-associated fibroblasts (CAF) were previously identified as target cells in the tumor-microenvironment (TME), highly releasing microfibril-associated protein 5 (MFAP-5), a proangiogenic protein supporting HCC tumor growth (Schneider P. et al., Adv. Mat., 2024.).
Method: Biodegradable nanohydrogels (NG) with strong liver tropism were used as carriers for anti-MFAP-5 small interfering RNA (siRNA). C57BL/6JRj mice (8–10w, ♂) were gavaged with increasing doses of CCl_4 over a period of 6 weeks. After induction of liver fibrosis, mice were intrasplenically injected with Dt81Hepa1-6 HCC cells to develop macroscopic HCC lesion during 28 days. After intravenous injection, biodistribution of co-florescent labeled NG loaded with Cy5.5-siRNA (F-NG:siCy5.5) was assessed by In Vivo Imaging System (IVIS) on organ level and also on cellular level in single cell suspension of enzymatically digested livers by flow cytometric analysis. For tumor therapy, mice were intravenously injected with three doses of anti-MFAP-5 siRNA (siMFAP5) loaded NG (NG:siMFAP5, according to 1 or 2 mg/kg siRNA) in week 4 after tumor inoculation. Translational studies were conducted to reveal insights in molecular pathways of MFAP-5 interference in human and murine cells and the presence of MFAP-5 in patient-derived resectates of primary liver tumors.
Results: F-NG:siCy5.5 co-localized in the liver of HCC mice and were efficiently taken up by CAF> dendritic cells> macrophages in the liver. NG:siMFAP-5 induced a convincing anti-tumor effect by knockdown of MFAP-5 (−52% on mRNA level and −87% on protein level in CAF) compared to untreated control (n = 5). Treated mice showed a dose dependent reduced hepatic tumor burden as reflected by the surrogates reduced liver weight (−63%), morphometric quantification of tumor load in liver sections (−32%) and serum AFP levels (−48%). RNA-Seq. analysis of whole liver tissue (NG:siMFAP-5 vs. control, n = 3) revealed downregulated angiogenesis pathways via NOTCH signaling interference, which could be confirmed on protein level by RNA-scope staining of liver sections for Hes1 as marker for

NOTCH activation. MFAP-5 was highly expressed in surgical tumor resectates of patients with HCC and cholangiocarcinoma (CCC). A correlation of NOTCH activation (Hes1) and upregulated markers for angiogenesis (CD34, CD105) as well as tumor growth (Ki/67, AFP) could also be observed in human and murine cell lines (HepG2, HUVEC, Dt81Hepa1-6, 2H-11) following MFAP-5 incubation.
Conclusion: Biodegradable NG:siMFAP-5 induced a convincing anti-tumor effect by inhibition of NOTCH mediated angiogenesis in a clinical relevant murine HCC model. The translational relevance of MFAP-5 could be demonstrated in human cell lines and patient-derived resectates for HCC and CCC.

SAT-091-YI
Using patient-led genetics to identify new therapeutic targets in metastatic cholangiocarcinoma
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Background and aims: Cholangiocarcinoma (CCA) includes a diverse range of biliary malignant tumors characterized by dismal prognosis. Tumors are commonly diagnosed when patients present locally-advanced or metastatic disease, limiting the access to potentially curative surgery. The genetic heterogeneity of CCAs has been reported, indicating that the most common gain-of-function mutations in *K-RAS* and *IDH1*, and *FGFR2*-translocations only occur in 16%, 10% and 15% of patients, respectively. These activating mutations are found in a complex genomic landscape where large number of genes are mutated at low frequencies. The role of these heterogeneously mutated genes in CCA progression is unknown and whether these accessory mutations modify the effect of more common mutations to promote tumor metastasis remains to be studied. Here, we investigate the genetics behind CCA dissemination, describing how cell intrinsic changes impact on cancer cell behavior and shape the tumor microenvironment making it more permissive to metastasis.
Method: Analysing whole genome/exome sequencing data from 277 patients diagnosed with intrahepatic CCA we identified a patient-led list of CCA mutations. We then developed an *in vivo* screen where we expressed gain of function *K-Ras*^{G12D} with a CRISPR/Cas9 gRNA library targeting genes mutated in the patient data. Immunohistochemistry analysis was performed to characterize the primary and metastatic tumors and their microenvironments. Using CRISPR/Cas9-mediated gene silencing, we interrogated whether these low frequency mutations promote epithelial-to-mesenchymal transition, migration and tumor dissemination in human CCA cells.
Results: The in vivo screening showed that *K-Ras* alone was insufficient to initiate tumor formation. In combination with our gRNA library, however *K-Ras*-driven tumors developed within 8 weeks. Exome sequencing of these tumors identified CRISPR-induced mutations in 53 genes which facilitated mutant *K-Ras*-induced tumor growth. We found a range of chromatin modifiers, including Ncor1, that upon deletion, together with *Tp53* loss and *K-Ras*^{G12D} over-expression, resulted in metastatic CCA. Although animal survival and tumor burden were not significantly different compared to those harboring *K-Ras*^{G12D};*Tp53*$^{-/-}$ tumors, *K-Ras*^{G12D};*Tp53*$^{-/-}$;*Ncor1*$^{-/-}$ mice presented tumors in various sites other than the liver. Importantly, histological analysis of the primary tumors with metastatic potential revealed phenotypic changes in cancer cells as well as differences in the stroma. Furthermore, deletion of *NCOR1* in human CCA cell lines increased their migratory capacity.
Conclusion: Low-frequency mutations in chromatin modifying genes, such as Ncor1, cooperate with common driver mutations to promote tumor progression and dissemination by altering cancer cell properties and modifying the tumor microenvironment.

SAT-092
Brown adipose tissue activation: a novel strategy to prevent/treat the hepatocarcinogenesis promoted by metabolic lipotoxicity
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Background and aims: Metabolic dysfunction-associated steatotic liver diseases (MASLD) reached pandemic proportions, resulting in increased incidence of hepatocellular carcinoma (HCC). Brown adipose tissue (BAT) is composed of brown adipocytes consuming fatty acids and glucose to produce heat, thanks to uncoupled respiration in their mitochondria. In addition to its thermogenic function, evidence showed a secretory role for BAT which releases "batokines." Interestingly, among the batokines already described, some are known to be involved in hepatocarcinogenesis. We aim to show that active BAT protects against MASLD-promoted HCC by releasing protective factors targeting the liver.
Method: We displayed a set of animal and cell-based experimental strategies: HCC-induced mouse model was obtained with diethylnitrosamine injection followed by carbon tetrachloride treatment for 3.5 months. Mice were maintained at 21°C (active BAT) or at 30°C (inactive BAT) during all procedure. Parameters of carcinogenic development (number/size of tumors), potentially altered intracellular pathways (immunoblot) and gene expression were determined. To mimic hepatic steatosis and the first steps of MASLD *in vitro*, hepatocytes were treated with palmitate prior to brown adipocyte exposure. Trans-well co-culture technique was then employed to study hepatocyte/brown adipocyte direct interactions. Intracellular proliferative signaling and metabolism were analyzed by qPCR and immunoblots.
Results: The exposure of mice to 30°C produced a suppression of BAT activity (*Ucp1*, *Pgc1a* repression). An increase in the size of tumors was observed in this group, although the quantity of tumors remained unchanged compared to control animals. This was associated with increased activity of p44-MAPK in the liver. *In vitro*, the exposure of brown adipocytes with hepatocytes induced an increased expression of batokines (*Fgf21, Cxcl14, Gdf15, Metrnl, Kng*) in brown adipocytes, while palmitate-treated hepatocytes induced a reduction of *Ucp1* expression in brown adipocytes, indicating a possible inactivation of the cells. On the other side, the presence of brown adipocytes caused the hepatocytes to decrease their proliferation (decreased PCNA).
Conclusion: All together those results point out a crosstalk between BAT and liver encouraging the idea that active BAT could secrete molecules able to protect against hepatocarcinogenesis. Further research remains necessary to identify those factors, which may be valuable to treat/prevent HCC.

SAT-095
Selective targeting of integrin avβ8 effectively suppresses tumor growth in the new PSC-associated cholangiocarcinoma model (SB CCA.Mdr2-/- mouse)
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Background and aims: We have published a new model of cholangiocarcinoma (CCA) in Mdr2-/- with primary sclerosis cholangitis (PSC)-like disease (termed SB CCA.*Mdr2-/-*) which recapitulates predisposition to CCA in human PSC. Systemic TGF-β blockade

has been reported to enhance anti-tumor efficacy of immune checkpoint inhibitors, but its development has been hindered by systemic toxicity. Here we report therapeutic efficacy of selective antibody targeting of TGFb-activating integrins avβ6 and avβ8 in comparison to pan-TGFb inhibition in our SB CCA.*Mdr2*-/- model.
Method: Ten-week old Mdr2-/- mice with advanced congenital PSC-like progressive biliary disease were subjected to hydrodynamic tail vein injection of sleeping beauty transposon-transposase system with activated forms of AKT (myr-AKT) and Yap (YapS127A). Neutralizing antibodies for pan-TGF-β (1D11), integrin avβ8 (C6D4), or integrin avb6 (3G9) alone and with anti-PD-1 mAb were administered into tumor-bearing mice 1–4 weeks post transduction, in comparison to IgG control or anti-PD1 (n = 10–16/group). Expression of TGF-β1, integrin β6, PD-1, PD-L1, and CK7 were analyzed by immunohistochemistry (IHC), integrin β8 was determined by in situ hybridization. Tumor burden was analyzed by CK7+ tumor numbers and mRNA levels of AKT and YAP1. Desmoplastic stroma of the tumors was analyzed via Sirius Red morphometry.
Results: In our SB CCA.*Mdr2*-/- model, TGF-β1 expression was prevalent in all CCA tumors and 88.2% of CCA tumors expressed various levels of integrin b6 and were positive for integrin β8 mRNA. PD-L1+ tumor cells, PD-1+ and CD8+ infiltrating lymphocytes were enriched in desmoplastic CCA tumors. However, anti-PD-1 alone was not efficacious. Monotherapy with 1D11 or 3G9 led to a trend of decreased tumor burden, but only C6D4 significantly reduced tumor growth (CK7+ tumor numbers) compared to the IgG group (30.00 ± 4.68 vs. 59.87 ± 5.67, p = 0.0109). Combination of 1D11/anti-PD-1 showed only a trend to enhance the efficacy of pan-TGFβ mAb alone. Interestingly, C6D4/anti-PD-1and 3G9/anti-PD-1 combinations did not show synergistic anti-tumor activity. Tumor burden assessed by mRNA levels of transgene oncogenes YAP1/AKT or morphometric analysis of CK7+ tumors showed that monotherapy with the C6D4 alone was superior to combination therapy with anti-PD-1 as a CCA treatment. Collagen morphometric analysis showed that the 1D11 potently attenuated desmoplastic reaction in all CCA tumors. Integrin avβ8- or avβ6-targeting resulted in diminished desmoplastic reaction in only a subset (about 50%) of tumors, which suggested that anti-tumor efficacy was not primarily driven by suppression of desmoplastic tumor stroma.
Conclusion: We show that integrin avβ8 is required for desmoplastic CCA growth and represents a novel therapeutic target for CCA. These data support clinical development of avβ8 integrin-selective inhibitors for CCA.

SAT-096-YI

Reduction in lipid accumulation, inflammation and hepatocellular carcinoma development after protease-activated receptor 2 inhibition through 1-Piperidinepropionic acid

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Background and aims: the lack of specific treatments, combined with a rising incidence, has made Hepatocellular carcinoma (HCC), Metabolic-Associated Steatotic Liver Disease (MASLD) and Metabolic-Associated Steatohepatitis (MASH) major challenges in modern hepatology. Protease-Activated Receptor 2 (PAR2) is a membrane receptor involved in inflammation, lipid accumulation and tumour development. Recently 1-Piperidinepropionic acid has been discovered as an effective inhibitor of PAR2. This study aims to evaluate the effect of 1-PPA on liver steatosis, inflammation and HCC development.
Method: C57BL/6J mice transgenic overexpressing SerpinB3 (C57/TG), fed on a CDAA diet and injected with diethylnitrosamine (DEN) were divided into two groups (n = 8 each) and treated with 1-PPA or placebo. HCC development was confirmed by liver histology. Microsomal triglyceride transfer protein (MTP) activity was quantified in liver tissue using a specific assay. qPCR of macrophage M2-polarization markers was also carried out. Human liver organoids were cultured with different steatogenic conditions (Oleic Acid and SB3) and treated with 1-PPA and lomitapide, an inhibitor of VLDL export. Lipid and ROS accumulation was quantified using BodiPY and MitoSOX respectively.
Results: 1-PPA treatment led to a lower number of hepatic nodules development (n = 1.5 vs n = 5, p < 0.05), a reduced mean tumoral mass (0.04 vs 0.1 g, p < 0.01) and a blunted expression of different markers of macrophage M2-polarization (ARG2, YM1, MRC1, COX2, NOX2, TNF-alpha). An increased MTP activity in the liver resulted in a reduction in histological steatosis score and paralleled an elevation in serum triglycerides in 1-PPA-treated mice (0.23 vs 0.16 mg/dL, p < 0.05). Human liver organoids cultured with both Oleic Acid and SB3 showed a significant increase in lipid and ROS accumulation and treatment with 1-PPA reverted this effect which was erased by contemporary treatment with lomitapide, suggesting a role in VLDL export mediated by this molecule.
Conclusion: 1-PPA treatment reduced lipid accumulation and M2-macrophage polarization in a mouse model of MASH-induced liver carcinogenesis resulting in lower HCC development. 1-PPA treatment affects lipid accumulation stimulating VLDL secretion.

SAT-097

Protein kinase R-like endoplasmic reticulum kinase in hepatic stellate cells promotes hepatocellular carcinoma progression via the p38delta mitogen-activated protein kinase/interleukin-1beta axis

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Background and aims: Palmitic acid (PA), whose absorption from the intestines is increased in metabolic dysfunction-associated steatohepatitis (MASH), is involved in endoplasmic reticulum (ER) stress and interleukin (IL)-1beta production in hepatic stellate cells (HSCs). In this study, we focused on Protein kinase R-like endoplasmic reticulum kinase (PERK), an ER stress sensor protein, and aimed to clarify the process of IL-1beta production via PERK in HSCs and the mechanism of MASH-related hepatocellular carcinoma (HCC) progression.
Method: The human HSC cell line (LX-2) was treated with PA. Reverse transcriptase–polymerase chain reactions and western blotting were used to measure PERK and IL-1beta levels. LX-2 cells were transfected with PERK siRNA and PERK plasmids, and the IL-1beta levels were measured. In addition, the PERK knockdown cells were treated with PA, and the change in IL-1beta was examined. Enzyme-linked immunosorbent assays were used to measure the IL-1beta concentration in the conditioned medium (CM) from LX-2 cells treated with PA. The human HCC cell line (HepG2) was cultured with the CM from LX-2 cells under different conditions, and its proliferative, migratory,

and invasiveness abilities were assessed by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), scratch, and Transwell assays. RNA-seq was performed using RNA extracted from the control and the PERK knockdown cells treated with PA to identify intermediate molecules in the PERK-mediated IL-1beta production pathway. Changes in the identified molecule's levels due to PERK modulation were examined. We also investigated whether modulating the identified molecule's levels changes IL-1beta production.
Results: PA increased the PERK and IL-1beta levels in LX-2 cells. IL-1beta was increased by PERK plasmid transfection and decreased by PERK siRNA transfection. The increase in PERK and IL-1beta induced by PA treatment was suppressed in PERK knockdown cells. The IL-1beta concentration in the CM from LX-2 cells treated with PA was increased. The CM from LX-2 cells treated with PA enhanced the proliferation, migration, and invasion of HepG2 cells; however, these effects were suppressed by PERK knockdown. RNA-seq analysis identified p38delta mitogen-activated protein kinase (MAPK) as an intermediate molecule between PERK and IL-1beta. PERK modulation changed the p38delta MAPK expression. Furthermore, p38delta MAPK modulation changed the IL-1beta production.
Conclusion: In the MASH-related HCC tumor microenvironment, PA induces ER stress and activates PERK in HSCs. PERK promotes IL-1beta production via p38delta MAPK. The IL-1beta secreted by HSCs promotes HCC progression by enhancing the proliferation, migration, and invasiveness of HCC cells. Targeting the p38delta MAPK/IL-1beta axis via PERK in HSCs may be a novel therapy for MASH-related HCC.

SAT-098

Infiltration of CD69- T cells in tumor tissue reflects longer recurrence-free survival in surgically resected hepatocellular carcinoma

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Background and aims: Tumor-infiltrating T cells in hepatocellular carcinoma (HCC) are heterogeneous, which can be separated into the CD69+ tissue-resident T cell population and the CD69- circulating T cell population. However, the impact of these distinct T cell populations on patient prognosis remains controversial and further studies are needed.
Method: We collected HCC (tumor) and farthest liver tissues (non-tumor) obtained during hepatectomy in 57 HCC patients with various etiologies of chronic liver disease. The patient cohort included the following etiologies: hepatitis B virus (HBV, 49%), alcohol-related liver disease (16%), HBV combined with alcohol-related liver disease (HBV+Alc, 21%), and unknown etiology (14%). Single-cell dissociation and flow cytometry were performed to assess the expression of CD69+ and CD69- T cells, and the correlation between these populations and recurrence-free survival (RFS) was evaluated.
Results: The expression levels of CD69+/CD69- subpopulations within CD4+ and CD8+ T cells in both non-tumor and tumor tissues exhibited patient-specific variability. These populations exhibited different phenotypes depending on alcohol etiology. The frequency of the CD69- population was lower in both non-tumor and tumor tissues, while the CD69+CD103+ and CD69+CD103- subpopulations were significantly increased in patients with alcohol etiology compared to those with non-alcohol etiology ($p < 0.05$). In tumor tissues, the mean fluorescence intensity (MFI) of PD-1 was significantly lower in CD69- cells compared to CD69+ cells across both CD4 and CD8 T cell populations ($p < 0.05$), suggesting that CD69- cells may possess a less exhausted phenotype. Additionally, we observed in further analysis of tumor tissues that the MFI of PD-1 in the CD69- population of both CD4+ and CD8+ T cells was higher in patients with alcohol etiology compared to those with non-alcohol etiology. Importantly, higher frequencies of CD69- T cells in tumor tissues correlated with decreased recurrence risk, suggesting a potential protective role against HCC recurrence.
Conclusion: We have identified distinct roles for tumor-infiltrating T cells in HCC tissues. CD69+ population is associated with immune exhaustion, which might be related to tumor aggressiveness. In contrast, the CD69- population among tumor-infiltrating T cells appears to play a crucial role within the tumor microenvironment, potentially related to liver inflammation and alcohol intake. Further studies are needed to elucidate the functional differences between these populations.

SAT-099

The liver artificial intelligence (lai) consortium: a benchmark dataset and optimised machine learning methods for MRI-based diagnosis of solid-appearing liver lesions

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Background and aims: The diagnosis of solid-appearing liver lesions on MRI is critical for determining treatment and prognosis. The complexity and variety of phenotypes and imaging across patients often makes this challenging, subjective, and time-consuming. To fast-forward the use of AI for liver imaging, the Liver Artificial Intelligence (LAI) consortium is constructing a large-scale benchmark dataset, developing optimized machine learning models, and rigorously validating the models in realistic clinical settings. All consortium members are available at https://lai-consortium.org/.
Method: Twelve hospitals across three continents are retrospectively collecting routine MRI scans of pathologically confirmed solid-appearing liver lesions. The dataset will contain both common and rare types of malignant (primary/metastatic) and benign lesions, with multiple MRI sequences. The project has no restrictions on age, sex, or underlying liver disease and aims to collect data from more than 3,000 patients, making it the largest publicly available MRI dataset of solid-appearing liver lesions.
Results: To date, the LAI dataset includes 486 patients, exceeding 2,500 MRI scans. These include 156 patients with hepatocellular carcinoma, 65 with intrahepatic cholangiocarcinoma, 139 with hepatocellular adenoma, and 126 with focal nodular hyperplasia. Each patient has minimally one T2-weighted MRI scan, with many also having dynamic contrast-enhanced T1-weighted scans covering pre-contrast, arterial, portal venous, delayed, or hepatobiliary phases.
Conclusion: The LAI dataset will serve as a key resource for the development and evaluation of AI algorithms designed to automate

the diagnosis of solid-appearing liver lesions using MRI. This dataset and the resulting algorithms have the potential to aid radiologists in their decision-making and assist in patient referrals to specialized centres.

SAT-100-YI

Multiomic insights into bile acid dysregulation, microbiome dysbiosis, and epigenetic modifications in metabolically associated non-B, non-C hepatocellular carcinoma: findings from multi-cohort studies and implications for early detection and therapeutic targeting

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Background and aims: Hepatocellular carcinoma (HCC) is the sixth most diagnosed cancer globally and the third leading cause of cancer death. Metabolic-associated HCC is rising in prevalence. Early-stage HCC is often asymptomatic; a cure is possible only if detected early. With serum α-fetoprotein (AFP) and ultrasound, current surveillance has limited early detection sensitivity (63%). Previously, we identified significant plasma bile acid (BA) dysregulation among metabolic-associated HCC patients. These findings, consistent with research from the Singapore Chinese Health Study (SCHS) and HELIOS, prompted further investigation into the mechanisms of BA dysregulation and their utility as early detection biomarkers superior to today's guidelines.
Method: We applied a multi-omics approach encompassing metagenomic, metabolomic, transcriptomic, and epigenetic analyses. Metagenomic and targeted BA metabolomic analyses were performed on 50 stool samples from ELEGANCE, including 16 HCC controls and 9 high-risk patients who later developed HCC, using shotgun sequencing and LC-MS/MS. Validation involved 196 high-risk patients (27 progressed to HCC) and 64 HCC-positive controls. Bulk RNA sequencing was conducted on tumours and adjacent tissues from 115 PLANet patients. To assess epigenetic involvement, preliminary Nano-ChIP sequencing on three patients explored histone modifications, focusing on H3K27 acetylation (H3K27ac).
Results: Metagenomic profiling showed reduced protective gut bacteria (e.g., R. bromii) and increased pathogenic species (e.g., C. hylemonae) in HCC patients' stool. Similarly, functional profiling of stools highlighted elevated BA metabolism enzymes (log10 relative abundance $\sim$1.7, $p = 5.2 \times 10^{-4}$). Metabolomic analysis confirmed dysregulated BA homeostasis, with severe plasma BA derangements preceding the clinical diagnosis of HCC (FDR < 0.05). Transcriptomic analysis showed significant upregulation of CYP7A1 (log2FC = 1.68, $p = 1.41 \times 10^{-4}$) and Small Heterodimer Protein (SHP) downregulation (log2FC = −1.28, $p = 8.18 \times 10^{-6}$), indicating a critically disrupted Farsenoid X Receptor (FXR) – SHP axis. Nano-ChIP sequencing revealed increased H3k27ac at the CYP7A1 promoter, implicating histone acetylation in the upregulation of BA synthesis.
Conclusion: This study uncovers a novel mechanism linking sustained bile acid dysregulation with HCC development through metabolic and epigenetic pathways. Alterations in gut microbiota composition, toxic BA metabolites, and disrupted FXR/SHP feedback loops contribute to hepatotoxicity and inflammation. Plasma BA profiles emerge as promising early biomarkers, potentially surpassing current surveillance methods. These findings provide a foundation for microbiome-targeted interventions, epigenetic therapies, and enhanced early detection strategies, offering new opportunities to improve HCC outcomes.

SAT-101

Defective liver endothelial autophagy occurring in metabolic dysfunction-associated steatotic liver disease promotes hepatocellular carcinoma

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is becoming the main risk factor for hepatocellular carcinoma (HCC). Although the key role of liver endothelial cells (LEC) in the progression of chronic liver diseases towards cirrhosis is recognized, their role in HCC development is less described. Moreover, the role of LEC autophagy in HCC development

remains to be discovered. We aimed to evaluate the role of endothelial autophagy in HCC development.
Method: (1) LEC were isolated from fresh human liver. We compared the transcriptome (RNAseq) of non-tumoral (NT) LEC of patients without (n = 10) or with MASLD (n = 15). Within the MASLD-LEC, we compared patients who developed (n = 10) or not (n = 5) HCC, and the LEC from NT and tumoral MASLD patients. (2) Endothelial autophagy-deficient mice (*Atg5$^{lox/lox}$;VE-cadh-Cre+;* n = 18) and littermate controls (*Atg5$^{lox/lox}$*, n = 16) received diethylnitrosamine to induce HCC, and High-fat diet (HFD) to mime MASLD. We used MRI to assess the development of HCC and RNAseq and mass spectrometry analysis (LC-MS/MS) to compare the transcriptome and the proteome NTL in the different groups of mice.
Results: (1) We showed that autophagy genes of NT-LEC in MASLD patients were downregulated compared to NT-LEC from patients without MASLD (NES = –2.65; p = 1e-10). Additionally, autophagy was further reduced in NT-LEC of patients with HCC compared to NT-LEC of MASLD patients without HCC. Compared to NT-LEC, LEC from HCC of MASLD patients displayed increased autophagy (NES 2.35; p = 2e-09). (2) In vivo, tumors were detected earlier in *Atg5$^{lox/lox}$;VE-cadh-Cre+* mice than in *Atg5$^{lox/lox}$*. In addition, tumors in *Atg5$^{lox/lox}$;VE-cadh-Cre+* mice were larger than those observed in *Atg5$^{lox/lox}$* mice (23 mm^3 vs 2 mm^3, p = 0.03). Tumors appeared earlier (10 vs. 11 months old, respectively) and grew faster in *Atg5$^{lox/lox}$* on HFD than in *Atg5$^{lox/lox}$* on CD (58.8 mm^3 vs 18.8 mm^3, respectively). We found that (i) autophagy deficiency in LEC promotes liver carcinogenesis, acting as an initial trigger, and (ii) that HFD is an additional trigger promoting tumor growth. Comparative transcriptomic and proteomic analysis of the NTL showed *Atg5$^{lox/lox}$;VE-cadh-Cre+* CD mice have decreased autophagy genes (Atg5, Beclin-1), downregulated anti-oxidative genes stress response, increased expression of pro-apoptotic (Bax) and liver DNA damages (Xrcc1) markers compared to *Atg5$^{lox/lox}$* CD mice. Deficient mice revealed an important modulation of oxidative stress pathways.
Conclusion: Our results provide evidence of the oncogenic effect of endothelial autophagy deficiency in the development of MASLD-related HCC. This highlighting the contributive role of liver endothelial cells, could provide a therapeutic target.

SAT-102

The role of Activating Factor 4 (ATF4) in the immunosuppressive phenotype of beta-catenin mutant hepatocellular carcinoma

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Background and aims: Endoplasmic Reticulum Stress (ERS) and Unfolded Protein Response (UPR) are elevated in cancer, but their role in cancer immunogenicity remains unclear. This study aimed to: (1) identify ERS/UPR activation signatures in human Hepatocellular Carcinoma (HCC) and their relationship with the Tumor Immune Microenvironment (TIME); (2) develop a syngeneic immunocompetent model to study UPR under CTNNB1 mutation background; (3) explore synergies between UPR modulation and anti-PD1 therapy in HCC.
Method: HCC cohorts from TCGA and ICGC were analyzed using graph-based methods to define gene regulatory networks linked to ERS/UPR. Hydrodynamic tail vein injection of plasmids with the Sleepy Beauty transposon system was used to create Ctnnb1-mutated cell lines overexpressing Myc. In vivo subcutaneous tumor models were developed in immunocompetent mice. Cellular and molecular mechanisms were studied using primary macrophages, flow cytometry, western blot, RT-PCR, RNA sequencing, and metabolic assays.
Results: UPR activation is altered in HCC, as evidenced by increased HSPA5/BIP expression and hyperactivation of UPR transcription factors (TFs) across HCC datasets. UPR activation stratified patients into three clusters: protein synthesis and folding (PFS), protein turnover (PT), and DNA damage response (DDR). The PT cluster correlated with beta-catenin-mutated HCC and an immunosuppressive TIME. Knockout (KO) of UPR TFs in Ctnnb1-mutant cell lines led to reduced UPR gene expression. Viability assays revealed that these cells were highly dependent on UPR signaling and more sensitive to ER stress. Tumor growth studies showed variable results: ATF4 KO slowed tumor growth, ATF6 KO increased growth, and XBP1 KO had no effect. ATF4 KO tumors exhibited enhanced antitumor immune infiltration with elevated CD4+ T cells and reduced tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). Additionally, dendritic cells and CD4+ T cells expressed low levels of PD-L1 and PD-1, respectively.
Conclusion: Three distinct UPR activation states characterize HCC subsets, correlating with genetic drivers, metabolism, and immune infiltration. ATF4, but not XBP1 or ATF6, is essential for immune evasion in Ctnnb1-mutated HCC. Targeting ATF4 presents a promising therapeutic strategy in HCC.

SAT-103

HDAC7 drives malignancy by preventing FBXW7-mediated ubiquitination degradation of YAP1 in hepatocellular carcinoma

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Background and aims: Liver cancer is a malignancy with high morbidity and mortality rates. Histone deacetylase 7 (HDAC7), a member of the histone deacetylase family, participates in multiple cellular pathophysiological processes and activates relevant signaling pathways to facilitate the progression of different tumors. It is urgent to investigate the potential mechanism of HDAC7 in liver cancer.
Method: The Cancer Genome Atlas database (TCGA), including DNA methylation and transcriptome sequencing data, was utilized to identify the crucial oncogene associated with DNA methylation and cancer progression in liver cancer. Data from the TCGA and RNA sequencing for 94 pairs of liver cancer tissues was used to explore the correlation between HDAC7 expression and clinical parameters of patients. DNA methylation sequencing was used to detect the DNA methylation levels in liver cancer tissues and cells. RNA sequencing, cytokine assays, immunoprecipitation (IP) and mass spectrometry (MS) assays, protein stability assays, and ubiquitination assays were performed to explore the regulatory mechanism of HDAC7 in liver cancer progression. Patient-derived xenografts and tumor organoid models were established to determine the role of HDAC7 in the treatment of liver cancer using Lenvatinib.
Results: Based on the public database screening, HDAC7 was identified as a tumor promoter regulated by DNA methylation.

HDAC7 expression was significantly higher in liver cancer tissues and was associated with the dismal prognosis in patients with liver cancer. RNA sequencing showed that HDAC7 is associated with the Hippo signaling pathway, focal adhesion, wound healing, regulation of epithelial-mesenchymal transition (EMT), and ubiquitin-protein ligase binding. IP/MS assays confirmed that HDAC7 activated Yes-associated protein 1 (YAP1) and its downstream signaling pathways by interacting with YAP1. Mechanistically, HDAC7 inhibited YAP1 ubiquitination and maintained its protein stability by competing with the E3 ubiquitin ligase, FBXW7. Additionally, HDAC7 knockdown-induced YAP1 downregulation significantly enhanced the therapeutic efficacy of Lenvatinib against liver cancer.
Conclusion: HDAC7 promotes liver cancer progression by preventing FBXW7-mediated YAP1 ubiquitination and degradation, suggesting that inhibition of the HDAC7-YAP1 axis may be a potential target for liver cancer treatment.

SAT-104
Impact of environmental pollution and the aryl hydrocarbon receptor signaling pathway on hepatic carcinogenesis
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Background and aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related mortality worldwide. Although alcohol consumption, viral hepatitis and metabolic dysfunction-associated steatohepatitis (MASH) are established risk factors for HCC, exposure to persistent organic pollutants (POPs) also contributes to this global burden. Among POPs, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic dioxin. Its effects are largely mediated by activation of the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that regulates the expression of detoxification enzymes. Although exposure to TCDD has been associated with the development of liver cancer, the effects of TCDD on the liver at the cellular and molecular level remain poorly understood. This study aimed to characterize the mechanisms underlying the hepatotoxic effects of TCDD.
Method: C57BL/6 male mice were used in two experimental protocols: the first protocol involved chronic exposure to TCDD (4 μg/kg per week by gavage) for 12 months, the second protocol combined TCDD exposure with an HCC induction model, where mice received a single injection of N-nitrosodiethylamine (DEN, 25 mg/kg) at 14 days old and biweekly carbon tetrachloride (CCl_4, 0.2 ml/kg) starting at 8 weeks for 7 weeks, along with TCDD at the same dose. AhR pathway activation was assessed through immunofluorescence labeling of Cyp1A1, a target gene of the AhR pathway, and CD31, a marker of endothelial cells. The hepatotoxic effects were studied by analyzing inflammation, fibrosis, tumor development, and endothelial dysfunction using RT-qPCR and histological methods. These endpoints were further analyzed in genetically modified mice with endothelial-specific AhR signaling pathway loss (Cdh5CreErt2; AhRflox/flox) to assess the role of the endothelial AhR pathway on the hepatotoxic effects of TCDD.
Results: Chronic exposure to TCDD induces liver inflammation, fibrosis and tumor development. Furthermore, chronic administration of TCDD to mice subjected to a model of HCC exacerbates liver inflammation, fibrosis, and tumor development. In both models, TCDD strongly activates the AHR pathway, as expected in hepatocytes due to their role in xenobiotic metabolism, but also in liver sinusoidal endothelial cells (LSECs). In addition, TCDD increases the hepatic expression of markers of endothelial dysfunction. Importantly, liver inflammation, fibrosis and hepatic carcinogenesis are reduced in mice with conditional AhR deletion in endothelial cells and exposed to TCDD.
Conclusion: Our results demonstrate that TCDD promotes liver inflammation, fibrosis and HCC development, which are partly mediated through the endothelial AhR pathway. This study contributes to the understanding of how environmental pollutants impact liver carcinogenesis and points to potential therapeutic targets to mitigate these effects.

SAT-105
Spatiogenomic characterization of malignant transformation in dysplastic nodules
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Background and aims: Although hepatocellular carcinomas (HCC) frequently arise from dysplastic nodules (DN) in cirrhotic livers, the molecular mechanisms driving this progression remain unclear. We aimed to identify key components and mechanisms of liver cancer development from DN.
Method: We performed high-resolution spatial transcriptomics on nodule-in-nodule HCCs, analysing 56,528 tissue spots from 11 patients. Concurrently, we conducted deep whole-genome sequencing on matched nontumor, DN, and HCC tissues.
Results: Spatial transcriptome sequencing identified a total of 36 final ST clusters, comprising 17 HCCs, 11 DNs, 1 HCC/DN border, 2 cirrhotic tissues, and 5 stroma-related clusters. Based on differential gene expression analysis on the ST clusters, DN clusters exhibited significantly higher activity of the Insulin-like Growth Factor pathway and inflammation-related pathways than RN clusters. HCC clusters were characterized by high activities of cell cycle signaling and beta-catenin-related pathways. Notably, AFP expression was confined to advanced HCC clusters, limiting its utility as an early-stage HCC marker. Deep WGS results for the nodule-in-nodule samples was revealed that most prevalent mutation event was *CTNNB1* mutations (40.0%). Hepatitis B virus integration into *TERT* promoter was found in 71.4% of the HBV-related tumor cases.
Conclusion: Our ST data identified the distinct characteristics of DN and HCC clusters across tumours. Hepatitis B virus integration and CTNNBI1 may be the key events in the malignant transformation from the DN.

SAT-106
CD40–Integrin α5β1 and CD27-CD70 axes: novel mechanisms driving HCC progression in chronic hepatitis C
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Background and aims: Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality worldwide, often arises in the context of chronic hepatitis C (HCV). Even after achieving a sustained virological response (SVR) with antiviral therapy, HCV patients remain at risk for HCC. Immune checkpoint proteins (ICPs), such as soluble (s) and membrane-bound (m) forms of CD27, CD28, and CD40, play critical roles in immune regulation and tumor progression. This study investigates the prognostic and mechanistic roles of these ICPs in HCC development and progression.
Method: Using multiplexed immunoassays, the levels of 16 sICPs were profiled in serum samples from 168 HCV-SVR patients over 17 years. Additionally, mCD27, mCD40, and their ligands were examined

in HCC tissues and cell lines. The CD27-CD70 and CD40-integrin α5β1 pathways were explored through methylation analysis, co-culture experiments, RNA sequencing, and inhibitor studies.
Results: At baseline, elevated levels of AFP and nine sICPs, including sCD27, sCD28, and sCD40, were observed in patients who later developed HCC. These levels declined during antiviral therapy but rebounded at the time of HCC occurrence. Baseline levels of sCD27 ≥4104, sCD28 ≥1530, and sCD40 ≥688 pg/mL were significant predictors of HCC development. Mechanistically, sCD27 promoted HCC cell proliferation through the CD27-CD70 axis, with CD70 hypomethylation contributing to its robust expression in tumor areas. CD27-CD70 interaction activated ERK1/2 signaling, enhancing cell cycle progression. In poorly differentiated HCC, mCD40 was highly expressed, correlating with low promoter methylation. Co-culture of HCC cells with CD40L+ CD4+ T cells elevated CD40 expression and activated IFN-γ-mediated JAK1/STAT3 signaling, enhancing tumor survival. Blocking both CD40 and integrin α5β1 reduced apoptosis avoidance, highlighting their interplay in tumor progression.
Conclusion: Elevated baseline sCD27, sCD28, and sCD40 levels are potential biomarkers for HCC in HCV-SVR patients, reflecting immune dysregulation even before antiviral therapy. Mechanistically, the CD27-CD70 and CD40–CD40L-integrin α5β1 pathways promote HCC progression by supporting cell proliferation and survival. These findings provide insights into immune-tumor interactions and suggest targeting these pathways as therapeutic strategies in HCC.

SAT-111
Carbonic anhydrase 9 as a circulating biomarker and therapeutic target in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab
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Background and aims: Two combinational Immunotherapies, atezolizumab/bevacizumab (Atez/Bev) and durvalumab/tremelimumab (Dur/Tre) are currently recommended as a 1st line therapy for unresectable hepatocellular carcinoma (HCC). This study aimed to identify blood-based biomarkers for predicting the response and guiding treatment selection for combination immunotherapy in patients with advanced HCC.
Method: We profiled 92 pre-treatment plasma proteins using Proximity Extension Assay (PEA) technology in a discovery cohort of 78 unresectable HCC patients treated with Atez/Bev. Carbonic anhydrase 9 (CA9) levels were evaluated via Enzyme-Linked Immunosorbent Assay in a validation cohort of 89 Atez/Bev-treated HCC patients and 48 patients treated with Dur/Tre. The impact of CA9 modulation on the tumor immune microenvironment and combination treatment efficacy was tested in a syngeneic HCC model.
Results: PEA identified elevated circulating proteins, including CA9, IL-8, CSF-1, and IL-6, in patients with progressive disease under Atez/Bev. High plasma CA9 levels were linked to poor disease control and shorter survival under Atez/Bev in both discovery and validation cohorts. Circulating CA9 protein was the independent predictor of therapeutic resistance and poor survival upon Atez/Bev therapy. Circulating CA9 proteins were derived from HCC tumor cells and tumoral CA9 conferred resistance to the combinational immunotherapy of anti-PD-L1/VEGF antibodies via immunosuppressive phenotype and enhanced angiogenesis signaling. The inhibition of CA9 improved the efficacy of anti-PD-L1/VEGF therapy. Pre-treatment CA9 levels could stratify patients likely to benefit from Atez/Bev versus Dur/Tre therapy.
Conclusion: CA9 is a circulating biomarker predicting response to combination immunotherapy and a potential therapeutic target in advanced HCC.

SAT-112
Role of hypoxia on the progression and survival of hepatocellular carcinoma in hypoxia-inducible factor 1 alpha knockout bi- and tri-dimensional in vitro models
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Background and aims: Primary liver cancer, being hepatocellular carcinoma (HCC) the main type, remains on the most fatal neoplasm, with increasing incidence and mortality rates worldwide. Although hepatocarcinogenesis can be triggered by a variety of exogenous and endogenous factors, hypoxia -a reduction in the oxygen supply to cells- plays a crucial role in tumor progression and chemotherapy resistance through dysregulation of multiple cellular pathways. Hypoxia-inducible factor 1 alpha (HIF-1 alpha) is the primary regulator of the cell's adaptive response to hypoxia in HCC, driving alterations in several molecular pathways involved in tumorigenesis and poor patient prognosis. Therefore, our aim was to determine the impact of HIF-1 alpha on HCC in our bi- and tri- dimensional (2D and 3D) models.
Method: We analyzed HIF-1 alpha expression in Huh-7 and PLC/PRF/5 cell lines, using 100 µM $CoCl_2$ to simulate and activate the adaptive hypoxic response. Protein expression and localization were examined by Western blot and immunofluorescence with laser confocal imaging, respectively, while gene expression was evaluated using qRT-PCR. CRISPR/Cas9 technology was employed to create HIF1A knockout (KO) clones to assess the role of this factor, and KO efficiency was confirmed by DNA sequencing. Cell viability and proliferation were assessed using the MTT assay and nuclear Ki67 protein level determination, respectively. Wound healing capacity was analyzed through inverted optical microscopy. Additionally, 3D models derived from both wild-type (WT) and KO cell lines were generated. Tumor growth was monitored in all 3D models, with hypoxia and cell death evaluated using the Image-iT Red Hypoxia Reagent and Calcein-AM with propidium iodide staining, respectively. Statistical analyses were conducted with GraphPad Prism 8, considering differences significant at $p < 0.05$.
Results: Huh-7 and PLC/PRF/5 cell lines demonstrated elevated HIF-1 alpha expression under hypoxic conditions. Following gene modification with CRISPR/Cas9 technology, HIF1A KO clones exhibited a marked reduction in cell viability and a lower proliferation index. Wound healing capacity was also diminished in the absence of HIF-1 alpha. Furthermore, the HIF1A KO 3D models showed a slower growth rate compared to the WT model, with a physiological hypoxic state observed in the tumor core of both HCC spheroid types (WT and KO). However, the KO spheroids displayed significantly larger regions of cell death. These findings highlight a critical pro-survival role of HIF-1 alpha in HCC.
Conclusion: Altogether, these findings suggest that HIF-1 alpha expression and stabilization promotes tumor cell survival and progression under hypoxia in our HCC cell models, highlighting the inhibition of HIF-1 alpha activity as a potential therapeutic target to restrain tumor progression and increase patients' survival.

SAT-113

The intratumoral microbiome in HCC and its impact on treatment response

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Background and aims: Intratumoral bacteria are increasingly recognized as influential within the tumor microenvironment (TME), impacting cancer progression and response to therapy. However, their role remains poorly unexplored in hepatocellular carcinoma (HCC), the third most common cause of cancer-related mortality worldwide. We recently reported two distinct HCC TME subtypes in patients treated with atezolizumab+bevacizumab (atezo+bev): *ImmunePos*, characterized by CD8+ T effector cells and CXCL10+ macrophages and associated with atezo+bev responses, and *ImmuneNeg*, lacking immune cell infiltration. Here we aimed to investigate the clinical significance of tumor resident bacteria in response to atezo+bev in HCC.

Method: We characterized the intratumoral microbiome in 247 HCC samples from patients treated with atezo+bev from the IMbrave150 and GO30140 clinical trials. RNAseq was used to profile the HCC-resident microbiome at the genus level. Transcriptomic reads were screened for microbial content with the PathSeq pipeline in the Genome Analysis Toolkit. Reads aligning to the human GRCh38 genome were removed, and the remaining reads were mapped to microbial reference genomes. To filter out contaminants and adjust for batch effects, we retained only genera with a relative abundance of $\geq 10^{-3}$. The association between bacterial prevalence (relative abundance present in >10% of samples) and abundance with progression-free survival (PFS), overall survival (OS), and our TME classification was evaluated.

Results: Previous analysis revealed a unique microbiome signature for HCC. Here we show that the prevalence of *Bacillus* in HCCs of atezo+bev treated patients, was associated with a significantly longer PFS ($p = 0.006$) and a trend toward prolonged OS ($p = 0.075$) compared to those without *Bacillus*. In addition, *Bacillus* prevalence and abundance were significantly higher in atezo+bev responders (prevalence: $p = 0.0029$, abundance: $p = 0.0032$ vs non-responders), and especially increased in ImmunePos responder tumors (prevalence: $p = 0.0019$ vs non-responders; abundance: $p = 0.031$ vs ImmuneNeg responders; $p = 0.0005$ vs non-responders).

Conclusion: We identified *Bacillus* associated with a significantly longer PFS and with a trend towards longer OS in atezo+bev-treated patients. Moreover, responders, particularly those associated with ImmunoPos features, showed significantly higher abundance and prevalence of *Bacillus*.

SAT-114

Modulation of mitotic stress-induced activation of the cGAS/STING signaling pathway by DNA demethylation

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Background and aims: Hepatocellular carcinoma (HCC) is classified as a "genomically unstable" cancer due to the typical presentation of chromosome breakage and aneuploidy. Recent investigations demonstrate that micronuclei, which are formed as a consequence of such genotoxic stress, have the capacity to induce an innate immune response through the cytosolic DNA-sensing cGAS/STING pathway. Inhibition of the spindle assembly checkpoint kinase TTK/MPS1 by novel compounds such as CFI-402257 targets these effects through deteriorated aneuploidy, followed by increased activation of the cGAS/STING signaling axis and Type I interferon expression. However, cancer cells have evolved mechanisms that enable them to tolerate aneuploidy. These include epigenetic silencing of the key signaling proteins cGAS and STING by DNA methylation. The objective of this study was to examine the impact of the DNA methyltransferase inhibitor decitabine on these relationships.

Method: The effects of the DNA-demethylating agent decitabine on cGAS and STING expression was assessed in Hep3B hepatocellular carcinoma cells (cGAS- and STING-absent) and non-tumorigenic THLE5b cells (cGAS- and STING-low). Cells were pre-treated with decitabine prior to TTK/MPS1-inhibition by CFI-402257. We investigated the level of aneuploidy by FACS analysis, performed proliferation and cytotoxicity assays, investigated the activation of the cGAS/STING signaling axis using Western blotting, and quantified the expression of related cytokines by qPCR.

Results: Western blot analysis of THLE5b cells, pre-treated with decitabine revealed an increase in the expression of both cGAS and STING, as well as an enhanced activation of the cGAS/STING pathway following consecutive CFI-402257 treatment. Quantitative PCR demonstrated elevated expression of cGAS/STING-specific cytokines, including IFNβ and CXCL10. In Hep3B cells, decitabine was observed to restore STING expression; however, it failed to affect cGAS expression and did not influence the activation of the pathway or the cytokine response. Cytotoxicity induced by CFI-402257 was observed to be significant in both cell lines. Prior decitabine treatment did not augment this effect; rather, it led to a decrease in proliferation rate.

Conclusion: The present study demonstrates that decitabine is capable of reversing the epigenetic silencing of STING in Hep3B and THLE5B cells. However, this does not appear to be sufficient to restore the activation of the cGAS/STING signaling pathway and the associated innate immune response. Further investigation is required to evaluate the impact of decitabine on cGAS/STING activation, particularly with regard to its antiproliferative effect, which counteract mitotic stress-induced cytotoxicity.

SAT-115-YI

A novel panel of Methylated DNA markers for hepatocellular carcinoma

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Background and aims: There is increasing interest in the use of blood based Methylated DNA Markers (MDM) to detect Hepatocellular Carcinoma (HCC) recurrence after treatment.
This study aims to develop an MDM panel to supplement existing surveillance methods, to monitor and detect early HCC recurrence following therapy.
Method: A literature search was performed to identify MDM candidates, followed by bioinformatic analysis of publicly available Illumina 450 K and EPIC methylation array databases of tissue and cell free DNA (cfDNA). Assay candidates were designed, undergoing stepwise validation, first *in-silico*, then against bisulfite modified cell line DNA with quantitative PCR.
The 4 marker MDM panel (MDM4) was validated in 23 paired tissues samples of HCC and background non-HCC liver using digital PCR (dPCR). For proof-of-concept, the MDM4 was tested in plasma samples, which were collected prior to HCC therapy, then every 3–6 months until disease progression or study dropout.
Results: 26 MDM candidates were identified. Bioinformatic analysis was performed to demonstrate test performance of MDM candidates across 9 methylation array datasets of 720 HCC, 389 non-HCC liver tissue and cfDNA datasets. Logistic regression train-test sets in a 70:30 proportion demonstrated good theoretical performance of the MDM4 panel in tissue with a test set AUC 0.95, and AUC 0.90–0.95 in 4 validation sets. Wet lab validation was performed with cell line DNA, allowing selection of assay candidates and identification of positive and negative cell line controls. A control MDM assay (*COL2A1*) was validated. For tissue validation with dPCR, the MDM4 and control demonstrated sensitivity 0.96 (95% CI 0.79–1.00), specificity 1.0 (95% CI 0.83–1.00) using logistic regression.
For proof-of-concept, plasma sample results of 8 patients are presented. 3 patients who received surgical resection, SIRT or TACE had detectable MDM4 despite radiological complete response (CR). Of these, 2 patients had elevated AFP (37 and 430 IU/mL). All developed progressive disease within 3 months of detectable MDM4. Three patients who remained in CR during follow up (14–16 months) had undetectable MDM4 and AFP at each time point. Two patients with radiological detectable disease for 11 months while receiving systemic therapy (1 had a preceding TACE) had detectable MDM4 at each time point. Of these, 1 had persistently elevated AFP (2090–18000 IU/mL) and another with AFP in the normal range (2–7 IU/mL).
Conclusion: A dry and wet lab biomarker pipeline allowed the development and validation of an MDM4 and COL2A1 control, a novel assay panel to detect HCC recurrence following treatment. This panel performed well in tissue validation and shows early promise in proof-of-concept plasma sample analysis. A prospective observational study (ACTRN 12623000762651) has completed recruitment of 160 patients and continues to accrue plasma samples.

SAT-116

Singel-cell transcriptomics reveal DDX1 as a driver of cancer stemness and tumorigenesis in hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) comprise diverse cells with distinct biological characteristics. Within a tumor bulk, liver cancer stem cells or stem-cell like cells play a pivotal role in tumor initiation, progression, metastasis and chemoresistance of HCC. We aim to explore the intratumor heterogeneity through single-cell transcriptomic profiling and find out the key driver of cancer stemness in HCC.
Method: We integrated single-cell RNA sequencing (scRNA-seq) and bulk RNA sequencing of HCC to reveal key cell subpopulation and therapeutic target that determine the stemness and tumorigenesis of HCC. Furthermore, in vitro and in vivo study were performed to unveil the underlying mechanism.
Results: scRNA-seq was conducted on 19518 cells from twelve primary HCC samples. After cluster analysis, Cytotrace analysis and Scissor analysis of heterogeneous malignant cells revealed that cells with high stemness were enriched in Scissor+ cell subpopulation, which was associated with poor prognosis. Next, integrated analysis with bulk RNA-sequencing profiles indicated that dead box helicase 1 (DDX1) was a key driver of cancer stemness and tumorigenesis in HCC. Furthermore, DDX1 was found to be highly expressed in HCC tissues and liver cancer stem-cell like cells. In vitro and in vivo assays for the first time showed that the stem cell-like properties of HCC cells were inhibited by DDX1 depletion, as evidenced by the decreased size and number of formatted spheres, the downregulated expressions of C-MYC, OCT4, and NANOG proteins, as well as the reduced proportion of CD133+ cells. In addition, depletion of DDX1 expression also restrained proliferation, migration and invasion, yet facilitated apoptosis of HCC cells. Overexpression of DDX1 exhibited opposite effects on regulating stemness and tumorigenesis of HCC. Mechanically, high-throughput sequencing, IP-MS, and RIP analysis unveiled that DDX1, as an RNA binding protein, can bind to C-MYC mRNA to enhance its mRNA stability, leading to enhanced C-MYC target genes expression. In addition, DDX1 can bind to FSCN1 mRNA to improve its mRNA translation efficiency, resulted in increased cell motility and metastasis. Furthermore, depletion of DDX1 significantly enhanced the efficacy of sorafenib in HCC in vitro and in vivo.
Conclusion: We revealed intratumor heterogeneity of malignant cells of HCC through single-cell transcriptomic profiling and highlighted the crucial role of DDX1 in regulating stemness and tumorigenesis of HCC, and provided potential therapeutic strategy for HCC patient.

SAT-117

High-resolution quantitative reconstruction of microvascular architectures in mouse hepatocellular carcinoma models

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Background and aims: Alterations in liver vascularization play a remarkable role in liver disease development, including

hepatocellular carcinoma (HCC), but remain understudied. This study evaluated the hepatic microvascular imaging method and provided high-resolution quantitative anatomical data on the characteristics and architecture of liver vasculature in wild-type (WT) mice and HCC mouse models.

Method: C57BL/6 mice were injected with Akt/Ras or Sleeping Beauty transposon to induce HCC. Liver tissues from normal and Akt/Ras mice underwent hematoxylin and eosin, Masson's trichrome, Ki67, and lymphatic endothelial receptor-1 staining. Using cutting-edge high-definition fluorescence micro-optical sectioning tomography, high-precision microvascular visualization of the liver was performed in WT and Akt/Ras HCC mice. The distinctive feature of the fMOST technique lies in its continuous liver tissue slicing with an axial step size of 2 μm, capture images simultaneously, and real-time counterstaining using PI. As a result, our approach obviates the need for a decellularization process.

Results: The sectioned volumes of normal and HCC liver tissues were 204.8 mm^3 and 212.8 mm^3, respectively. The microvascular systems associated with the tissues of Akt/Ras HCC mice were twisted, disordered, and compressed by tumor nodules. In the four tumor nodules, the path of the hepatic artery was more around the tumor edge, whereas the portal vein occupied the central position and constituted the main blood vessel entering the tumors. The porosity of HCC and paracancerous cirrhotic tissues was significantly less than that of normal tissues. The radii of the central vessels in the hepatic sinusoid of paratumoral cirrhotic tissues were significantly higher than those of normal tissues; however, the hepatic sinusoid density of paratumoral cirrhotic tissues was lower.

Conclusion: This research provides a deeper understanding of the normal liver microvasculature and alterations in cases of cirrhosis and HCC, which complements scientific insights into liver morphology and physiology. This straightforward research approach involving the novel 3D liver microvasculature can be used in multiscale physiological and pathophysiological studies regarding liver diseases.

SAT-118

The liver microenvironment of MASH and MetALD HCCs: a spatial transcriptomics analysis

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Background and aims: MASH accounts for 20% of HCCs in the Western world and is the leading cause of HCC in patients without cirrhosis. The higher propensity for HCC development without cirrhosis in MASH compared with other etiologies underscores the unique metabolic and inflammatory micro-environment that cooperate with extrahepatic cancer drivers associated with metabolic syndrome and, when present, alcohol consumption. Here we investigate the metabolic and inflammatory microenvironment of MASH HCC using Digital Spatial Profiling (DSP) technology in multiple tumour (T) and non tumour (NT) regions of interest (ROIs) from surgical resection samples of cirrhotic and non cirrhotic patients with HCC related to MASH and MetALD.

Method: The study population comprised 5 cirrhotic (K) and 4 non cirrhotic (F1/F2/F2/F3) SLD HCC patients. Six had no alcohol consumption (F1/F2/K/K/K) and 3 were MASLD predominant MetALD (F2/F3/K). Spatial resolution of RNA expression from >1,800 genes was assessed using the GeoMx® Cancer Transcriptome Atlas in T and NT ROIs of FFPE (Formalin-Fixed Paraffin-Embedded) tissue samples. A masking approach was used to define homogeneous areas of interest (AOI) containing PanCK or CD45 labelled cells in each ROI. All cells present in each AOI in the tumor or in the non-tumoral liver were analyzed separately as a mini-bulk RNA-Seq.

Results: 95 ROIs (range 9–17 ROIs per sample) have been analyzed. After QC 82 ROIs were retained for a total number of 38938 PanCK positive cells (hepatocytes, cholangiocytes and tumor cells) and of 4239 CD45 positive cells. Principal Component Analysis of all ROIs showed a clear separation between PanCK AOIs and CD45 AOIs in T vs NT. Focusing on CD45 ROIs, we found that the inflammatory infiltrate, richer in NT liver, displays distinct transcriptional profiles in T vs NT; with 13 down-regulated and 26 up-regulated differentially expressed genes. CD45 AOIs enrich oxidative phosphorylation and integrins signaling pathways and downregulate lymphocyte effector pathways in T tissues. WGCNA (weighted gene co-expression network analysis) of all CD45 ROIs identified 5 modules of highly connected and co-expressed genes (hub genes) associated with the tumor status. Additional modules were specific for CD45 AOIs stratified according to the presence of cirrhosis, MASH or Met-ALD. Cell type deconvolution analysis of CD45 and PanCK AOIs stratified according to tumor status show an enrichment of Tregs, central venous LSECs and stellate cells in tumor vs non-tumor tissue.

Conclusion: Our DSP analysis allowed to obtain a highly granular spatial resolution of the transcriptome and the microenvironment in specific subgroups of MASH HCCs.

SAT-124-YI

Harnessing human immune system mouse models to validate NADPH oxidase 1 inhibition as a treatment for hepatocellular carcinoma

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Background and aims: NADPH oxidases (NOX) are reactive oxygen-producing enzymes of which the isoform NOX1 is present in the tumor microenvironment (TME) of hepatocellular carcinoma (HCC) and promotes HCC development and metastasis. NOX1 inhibition (NOX1i) has been shown to alter the TME in classical HCC models and might serve as a therapeutic target. However, implementation in the clinic is hampered by low translatability of these classical HCC models. Here, we employed next-generation human immune system (HIS)-HCC models that enable investigation of treatments in the context of human immune responses, and provide evidence for NOX1 inhibition as strategy to target the TME in HCC.

Method: Two HIS-HCC models were set up to investigate NOX1i in the context of human innate or adaptive immune responses, with a focus on the monocyte/macrophage or T-cell compartment respectively. For the myeloid model (My-HIS), irradiated NSG-QUAD mice were reconstituted with human cord blood-derived CD34+ cells, and human orthotopic HCC tumors were induced 4 weeks post engraftment. For the T cell-HIS model, orthotopic HCC tumors were induced in NSG mice, and mice were reconstituted with human T cells

using healthy peripheral blood mononuclear cells. Mice received NOX1i (ML171) or vehicle twice per week for 3 weeks.
Results: In the My-HIS-HCC model, humanization in livers and tumors reached 30–50% and consisted of monocytes, macrophages, dendritic cells, NK cells and B cells. Significantly lower human CD45+ cells were observed in tumor and surrounding tissue of NOX1i-treated My-HIS-HCC mice. NOX1i did not affect macroscopic tumor growth in My-HIS-HCC mice. However, the expression of HCC and proliferation markers was lower in tumors of NOX1i-treated My-HIS-HCC mice. This was accompanied with significantly lower expression of cytokines, chemokines, growth factors and markers involved in cancer progression upon NOX1i. Humanization in the T cell-HIS-HCC model reached up to 70% and primarily consisted of T cells, with significantly reduced percentages in livers of NOX1i-treated mice. Within the population of CD4+ T cells, mainly Th2 cells were encountered in liver and tumor tissue without differences between groups. NOX1i did not affect tumor size nor the expression of HCC and proliferation markers in the T cell-HIS-HCC model. However, as in the My-HIS-HCC model, the expression of cytokines and markers involved in cancer progression was significantly lower in tumor tissue of NOX1i-treated, compared to untreated, T cell-HIS-HCC mice.
Conclusion: Our data show that NOX1i effectively alters the TME in humanized HCC models, with the most pronounced effects observed in mice harboring human monocytes and macrophages, the My-HIS-HCC model. This aligns with previous reports on the therapeutic potential of NOX1i in classical HCC models by affecting monocyte/macrophage function and favors translation to the clinic.

SAT-125
Targeting Annexin A1 improves immunotherapy efficacy by remodeling the macrophage-related immunosuppression for hepatocellular carcinoma
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Background and aims: Anti-PD-L1-based immunotherapy combination strategy as first-line treatment for unresectable hepatocellular carcinoma (HCC). However, the objective response rates remain limited. It is an urgent need to find biomarker targets that can predict responses to anti-PD-L1 therapy and overcome resistance to immunotherapy. Annexin A1 (ANXA1) plays a critical role in inflammation, immunity and tumorigenesis. We previously demonstrated ANXA1 facilitates HCC progression by modulating macrophage-induced immunosuppressive microenvironment (Song ZH, et al. BIOCHEM PHARMACOL 2023). In this study, we sought to investigate the potential of ANXA1 as a target for immunotherapy in HCC.
Method: We employed bioinformatics to evaluate the relationship between ANXA1 expression and immune cell infiltration, as well as its correlation with immune checkpoints in HCC. Single-cell analysis elucidated the role of ANXA1 in shaping the heterogeneity of the HCC tumor microenvironment. We investigated its expression, prognostic significance, and clinical relevance in HCC tissue microarrays. We used a co-culture system to evaluate the immunomodulatory effects of ANXA1 in crosstalk between macrophages and lymphocytes. Flow cytometry was conducted to validate the effects of ANXA1 on promoting immune escape in various HCC animal models. Furthermore, we examined different levels of ANXA1 expression influenced the efficacy of anti-PD-L1 immunotherapy and synergistic therapy *in vivo*.
Results: We found that ANXA1 expression was associated with immunity, and positively correlated with PD-L1 expression. The single-cell analysis highlighted ANXA1's critical role in development and differentiation of immune cells. In HCC samples, ANXA1 was overexpressed in the macrophages and correlated with poor prognosis and advanced clinical stages. ANXA1 contributed to an immunosuppressive microenvironment and facilitated immune escape in HCC, mainly by promoting macrophages M2-like polarization, thus inhibiting CD8+ T cells infiltration and functional activation, enhancing regulatory T cells infiltration, and PD-L1 expression. Lower levels of ANXA1 were found to sensitize responses to anti-PD-L1 therapy.
Conclusion: Our results suggest that ANXA1 induces immune escape through remodeling macrophage phenotypes and may serve as a predictive biomarker of response to anti-PD-L1 therapy. Targeting ANXA1 could be considered an effective immunotherapeutic strategy for overcoming resistance to immunotherapy in HCC.

SAT-126
The genetic alterations in circulating tumor cells correlate with the clinical outcomes of hepatocellular carcinoma by large-scale whole-genome sequencing
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Background and aims: Hepatocellular carcinoma (HCC), typically occurring in the setting of chronic liver disease and cirrhosis is the third leading cause of cancer death globally. However, less than 20% of HCC patients are diagnosed at an early stage and may undergo curative therapies. On most occasions, liver biopsy is inaccessible in HCC patients due to the potential risk of hemorrhage and tumor dissemination. Moreover, a single biopsy specimen containing a small amount of tumor tissue may not represent the whole HCC tumor due to heterogeneity. In this context, individualized treatment for HCC patients remains to be defined, and predictive biomarkers are urgently needed to inform treatment selection, prognostication, and monitoring for treatment response. Circulating tumor cells (CTCs) are tumor cells that have been shed or migrated from the primary tumor into circulation. Although CTCs are usually very rare in blood and may be highly heterogeneous, they contain complete genomic and proteomic information that may reflect both the evolution of the tumor and the current status of the disease. Therefore, CTCs should be regarded as a less invasive alternative to tissue biopsy and a novel way to obtain a comprehensive understanding of the heterogeneous tumor and its progression. Microfluidic-based technology for enriching and isolating CTCs could increase the detection rate and meanwhile maintain CTC viability such that subsequent analysis can be done to reveal molecular features of CTCs.
Method: In the present study, we applied a microfluidic-based platform to obtain CTCs in 276 HCC patients, 60 cirrhosis patients and 20 healthy donors. The isolated CTCs were then subjected to whole genome sequencing.
Results: The number of CTCs was associated with advanced stage and unfavorable prognosis. Through analyzing the genetic spectrum of HCC CTCs, we found the combination of mutations in NAV2, SPTAN1, DOCK6, PI4KA was significantly associated with HCC patient overall survival. Specific gene panels can predict the prognosis of HCC patients in the BCLC-C stage, receiving targeted therapy, immunotherapy or intervention therapy. Two molecular subtypes could be identified according to CTC mutations. Cluster 1 and cluster 2 patients respectively response better to targeted therapy and immunotherapy. Finally, we found several CTC-specific mutated genes that might drive the formation of CTCs.
Conclusion: The present study revealed the genomic landscape of HCC CTCs in a large-scale cohort and the clinical significance of genetic alterations in CTCs. We also generated a novel sub-typing system according to CTC mutations, which are associated with clinical

outcomes. Finally, we identified the CTC-specific mutated genes. This study demonstrates the clinical utility of CTCs genome sequencing. It provides insights into the genomic features of HCC CTCs, which lay the foundation for further basic and clinical studies.

Liver tumours – Therapy

TOP-130-YI

Deep learning derived radiomics with advanced machine learning outperforms clinical biomarkers in predicting outcomes after atezolizumab plus bevacizumab for advanced hepatocellular carcinoma

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Background and aims: Atezolizumab plus bevacizumab is a first-line therapy for advanced hepatocellular carcinoma (HCC). However, only a small proportion of patients respond to therapy, and pretreatment precision biomarkers are lacking. This study integrated clinical data and radiomic data derived from pre-treatment imaging to predict post-treatment outcomes in patients receiving immunotherapy (ICI).
Method: 162 consecutive patients from two international centres (ICL and AP-HP) receiving atezolizumab plus bevacizumab for advanced HCC were retrospectively reviewed. Deep learning auto-segmentation models were used to generate whole liver and cancer masks from pre-treatment CT imaging. Radiomic features derived from segmented masks and baseline clinical variables were used to predict 12-month mortality, using seven supervised machine learning models in combination with thirteen feature selection techniques in the ICL cohort. Radiomic, clinical and integrated radiomic-clinical models were developed using ensemble learning. Unsupervised K-means clustering identified high- and low-risk patient groups. Model performance was evaluated on the AP-HP cohort.
Results: The radiomic and integrated radiomic-clinical models had AUCs of 0.91 (95% confidence interval (CI) 0.81–0.98) and 0.73 (95% CI 0.55–0.87) respectively, significantly outperforming ALBI grade (AUC 0.48, 95% CI 0.32–0.64, $p < 0.001$) and Barcelona Clinic Liver Cancer (BCLC) stage (AUC 0.61, 95% CI 0.44–0.71; $p < 0.001$) in the ICL cohort. The models maintained good performance in the AP-HP cohort (radiomic: AUC 0.69, 95% CI 0.57–0.80; integrated radiomic-clinical: 0.75, 95% CI 0.64–0.85), with the integrated model outperforming ALBI grade (AUC 0.59, 0.48–0.69, $p = 0.030$) and BCLC stage (AUC 0.59, 95% CI 0.50–0.69, $p < 0.001$). Integrated model-derived high-risk patients had significantly shorter median overall survival in both the ICL (5.9 months, 95% CI 2.6–9.7 vs. 28.2 months, 95% CI 18.1–38.6 months; $p < 0.001$) and AP-HP cohorts (6.6 months, 95% CI 3.2–10.3 vs. 16.0 months, 95% CI 11.3–27.2 months; $p < 0.001$). Similarly, the model stratified high- and low-risk patients based on progression-free survival (ICL: 2.7 months, 95% CI 1.8–6.7 vs. 15.4 months, 95% CI 8.8–20.8 months; $p < 0.001$; AP-HP: 2.9 months, 95% CI 2.0–7.4 vs. 6.4 months, 95%CI 5.1–10.7 months; $p = 0.016$).
Conclusion: Radiomic-based models can predict mortality after ICI therapy in patients with advanced HCC. Deep learning in combination with machine learning model can stratify patients into risk groups, allowing for precision treatment strategies.

TOP-147

Multi-omics analyses identify a novel HCC subtype with better response to immune checkpoint inhibitor therapies

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Background and aims: The overall efficacy of the comprehensive treatment for hepatocellular carcinoma (HCC) patients is unsatisfactory. It is imperative to discover distinct molecular subtypes to achieve accurate diagnosis and treatment.
Method: In this study, whole transcriptome sequencing was performed on tumor and adjacent non-tumor tissues across 242 patients with hepatocellular carcinoma (HCC) and 51 patients with intrahepatic cholangiocarcinoma (ICC). Whole exome sequencing was performed in selected samples of each cancer subtype. Single-cell RNA sequencing was performed on fresh primary tumor samples from 15 HCC patients and 8 ICC patients.
Results: The HCC tumors were clustered into four subtypes, and we identified a new subtype of HCC called immune checkpoint inhibitors (ICI) therapies response HCC (IR-HCC). This subtype exhibits transcriptional similarities to intrahepatic cholangiocarcinoma (ICC) rather than the other subtypes of HCC. Single-cell RNA sequencing and multiplex immunofluorescence analyses provided evidences of a pre-dysfunctional immune microenvironment in IR-HCC tumors, indicating they may have a better response to immunotherapy. Importantly, IR-HCC exhibited a notably unfavorable outcome in the absence of immunotherapy. However, it showed a more favorable response to ICI therapies in a prospective cohort of HCC patients. TP53, PIK3R1, OR6P1, and CHIT1 were identified as the driver genes of the IR-HCC subtype. A 29-gene expression signature was developed and externally validated to distinguish the IR-HCC subtype from the broad HCC patient.
Conclusion: Collectively, our comprehensive multi-omics analyses have identified a novel HCC subtype called IR-HCC, exhibiting significant similarities in metabolism, immune infiltration, gene mutations, and overall survival to ICC. IR-HCC showed superior responsiveness to ICI therapies, providing a promising option for precision medicine-based treatments of HCC.

TOP-148

Microwave ablation versus single-needle radiofrequency ablation for the treatment of HCC up to 4 cm: a randomized control trial

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Background & Aims: Radiofrequency ablation (RFA) is the standard treatment for small hepatocellular carcinoma (HCC), specifically for tumors less than 3 cm in size and numbering fewer than 3, excluding surgical candidates. Microwave ablation (MWA) is an innovative approach believed to have theoretical benefits over RFA; however, these advantages are yet to be empirically verified. Therefore, we aimed to evaluate and compare the effectiveness of MWA and RFA in managing HCC tumors up to 4 cm in size.
Methods: In this multicenter randomized controlled trial conducted across five centers in Japan, eligible participants had up to four tumors, each up to 4 cm in size, and were not considered for surgery. Patients were randomly assigned to undergo MWA or RFA. The primary outcome was the rate of local tumor progression (LTP), while secondary outcomes included overall survival (OS) and intra- and extrahepatic recurrence-free survival (RFS) at the end of the 2-year follow-up.
Results: A total of 240 participants were screened from July 12, 2018, to December 7, 2021. Four participants were excluded: three did not meet inclusion criteria, and one died of unknown cause during treatment. Consequently, 119 (130 lesions) and 117 (136 lesions) participants were treated with MWA and RFA, respectively. The proportion of lesions with LTP at the 2-year follow-up was significantly lower in the MWA group (20 [16.4%] lesions) than in the RFA group (38 [30.4%] lesions) (risk ratio, 0.54; p = 0.007). OS and both intra- and extrahepatic RFS did not significantly differ between groups.
Conclusion: MWA is more effective than RFA in reducing local tumor progression for HCC tumors up to 4 cm.However, no differences were observed in OS and RFS.

FRIDAY 09 MAY

FRI-079
Prognostic value of early change in neutrophil to lymphocyte ratio after atezolizumab plus bevacizumab treatment for hepatocellular carcinoma

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Background and aims: Atezolizumab puls bevacizumab has been used for advanced hepatocellular carcinoma (HCC). However, there is lack of predictive biomarkers for assessing response to atezolizumab plus bevacizumab. The aim of this study was to investigate the predictive value of early changes in neutrophil to lymphocyte ratio (NLR) in patients with advanced HCC treated with atezolizumab plus bevacizumab.
Method: This retrospective study enrolled 59 patients receiving atezolizumab plus bevacizumab for advanced HCC. NLR was calculated at the initiation of atezolizumab plus bevacizumab and repeated at 3 weeks.
Results: According to the Response Evaluation in Solid Tumors at an initial evaluation after 3 cycles of treatment, rates of partial response (PR), stable disease (SD), and progressive disease (PD) were 22.0%, 49.2%, and 28.8%, respectively. Median overall survival (OS) were significantly associated with initial tumor responses. Median OS of PR, SD, and PR were 20 months, 14 months, and 12 months, respectively (P = 0.041). NLR changes at 3 weeks was confirmed as predictor of initial tumor response. The mean NLR ratios in patients who achieved PR, SD, and PD were 1.81, 2.99, and 3.42, respectively (P = 0.043). Additionally, a mean NLR ratio of 1.95 or higher at 3 weeks had a specificity of 78.3% and a sensitivity of 69.2% for predicting non-objective responses.
Conclusion: A change in NLR at 3 weeks is associated with initial tumor responses, which in turn, are related to survival outcomes. This association suggests that monitoring NLR changes during treatment can provide valuable prognostic insights into tumor response and subsequent patient survival.

FRI-080
TACE combined with ICIs plus MTT after 125I irradiation stent placement in patients with hepatocellular carcinoma and main portal vein tumor thrombosis (PATENCY II)

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Background and aims: Patients with hepatocellular carcinoma (HCC) and main trunk (Vp4) portal vein tumor thrombosis (PVTT) have a poor prognosis, and current treatment options provide limited benefits. We aimed to assess the safety and efficacy of transcatheter arterial chemoembolization (TACE) combined with immune checkpoint inhibitors (ICIs) plus molecular targeted therapy (MTT) after irradiation stent placement (ISP) as first-line treatment for these patients.
Method: This multicenter retrospective cohort study enrolled 444 patients with HCC and Vp4 PVTT treated with either ISP, TACE, ICIs, and MTT (ISP-containing quadruple group, n = 131) or with ICIs and MTT (ICIs-MTT group, n = 313) between January 2020 and May 2023. Propensity score matching was used to balance the groups. The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival (PFS), objective response rate (ORR), PVTT response, patency of portal vein, and safety.
Results: After propensity score matching (1:2), 127 patients from the ISP-containing quadruple group were matched with 220 patients from the ICIs-MTT group. The median OS (10.3 months, interquartile range [IQR]: 9.1–11.5 vs 8.6 months, IQR: 7.6–9.6; *P* = 0.004), PFS (6.1 months, IQR: 4.9–7.3 vs 3.5 months, IQR: 2.9–4.1; *P* < 0.001), and ORR (52.8% vs 27.7% with RECIST version 1.1; 58.3% vs 29.1% with mRECIST) were higher in the ISP-containing quadruple group than in the ICIs-MTT group. The ISP-containing quadruple group also demonstrated a higher PVTT positive response rate (64.6%) than the ICIs-MTT group (20.5%). Median stent patency was 10.4 months (IQR: 8.2–12.7). Grade ≥3 adverse events were observed in 37 patients (29.1%) in the ISP-containing quadruple group and 56 patients (25.5%) in the ICIs-MTT group (*P* = 0.456).
Conclusion: Following ISP, treatment combining TACE with ICIs plus MTT can significantly prolong OS and PFS in patients with HCC and Vp4 PVTT and is generally well-tolerated.

FRI-081
Transcatheter arterial chemoembolization combined with immune checkpoint inhibitors plus molecular targeted therapy after 125I irradiation stent placement in patients with hepatocellular carcinoma and main portal vein tumor thrombosis (PATENCY II)

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Background and aims: Patients with hepatocellular carcinoma (HCC) and main trunk (Vp4) portal vein tumor thrombosis (PVTT) have a poor prognosis, and current treatment options provide limited benefits. We aimed to assess the safety and efficacy of transcatheter arterial chemoembolization (TACE) combined with immune checkpoint inhibitors (ICIs) plus molecular targeted therapy (MTT) after irradiation stent placement (ISP) as first-line treatment for these patients.
Method: This multicenter retrospective cohort study enrolled 444 patients with HCC and Vp4 PVTT treated with either ISP, TACE, ICIs, and MTT (ISP-containing quadruple group, n = 131) or with ICIs and MTT (ICIs-MTT group, n = 313) between January 2020 and May 2023. Propensity score matching was used to balance the groups. The

primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival (PFS), objective response rate (ORR), PVTT response, patency of portal vein, and safety.
Results: After propensity score matching (1:2), 127 patients from the ISP-containing quadruple group were matched with 220 patients from the ICIs-MTT group. The median OS (10.3 months, interquartile range [IQR]: 9.1–11.5 vs 8.6 months, IQR: 7.6–9.6; P = 0.004), PFS (6.1 months, IQR: 4.9–7.3 vs 3.5 months, IQR: 2.9–4.1; p < 0.001), and ORR (52.8% vs 27.7% with RECIST version 1.1; 58.3% vs 29.1% with mRECIST) were higher in the ISP-containing quadruple group than in the ICIs-MTT group. The ISP-containing quadruple group also demonstrated a higher PVTT positive response rate (64.6%) than the ICIs-MTT group (20.5%). Median stent patency was 10.4 months (IQR: 8.2–12.7). Grade ≥3 adverse events were observed in 37 patients (29.1%) in the ISP-containing quadruple group and 56 patients (25.5%) in the ICIs-MTT group (p = 0.456).
Conclusion: Following ISP, treatment combining TACE with ICIs plus MTT can significantly prolong OS and PFS in patients with HCC and Vp4 PVTT and is generally well-tolerated.

FRI-082
Conversion ability of systemic therapy in patients with hepatocellular carcinoma: a multicenter international study. On behalf of the converse survey collaborative study group
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Background and aims: Novel Systemic treatments have profoundly revolutionised the treatment of hepatocellular carcinoma (HCC), with relevant advantages in terms of objective response rate (ORR) and duration of response. This multicentre study aims to evaluate the "real-life" conversion ability of systemic therapies to curative options (liver transplant, hepatic resection, or ablation) in patients with HCC.
Method: This multicentre retrospective study used aggregate data from Italian and International centres, treating at least ten adult patients with Atezolizumab plus Bevacizumab (AB) or Lenvatinib (LE) as 1 line therapy from 2019 to 2023. Patient-level exclusion criteria were: suitability for curative or loco-regional therapies; Child C; BCLC stages 0, A; previous systemic treatment for HCC; previous liver transplantation. The primary end-point was the rate of "actual conversion" to curative treatment options (liver transplant, hepatic resection or ablation). Secondary end-points were the "potential conversion" rate and ORR. Potential conversion was defined as HCCs with a tumour burden score <8 (without extra-hepatic disease) and alpha-fetoprotein level <1000 ng/ml at the maximum objective response (partial or complete) to therapy. A meta-analytic approach was used to analyse centre-level aggregate data.
Results: We enrolled 32 Italian centres (Italian database) that treated 1,247 patients (597 with LE, 650 with AB) and 14 international centres (International database) that treated 1,044 patients (333 with LE, 711 with AB). Although the ORR rates were high in the Italian (29% with AB and 22% with LE) and International databases (29% with AB and 27% with LE), the actual conversion rates were meagre (3% with AB and 2% with LE in Italy; 5% with AB and 4% with LE in the International database). Conversely, the potential conversion rates were consistent: 17% with AB and 12% with LE in Italy, 19% with AB and 15% with LE in the International database.
Conclusion: The results of this multicentre study confirm LE and AB's worldwide effectiveness. However, they also highlight a significant discrepancy between actual and potential conversion rates in real life. These findings suggest that there is probably a clinical underestimation of the conversion potentialities of systemic therapy in HCC, with the majority of clinicians preferring to maintain patients in systemic treatment. Only well-designed prospective studies will prove whether this "under-conversion" has a negative prognostic impact on these patients.

FRI-083-YI
Histologic predictors of response to atezolizumab and bevacizumab in hepatocellular carcinoma biopsies
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Background and aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Atezolizumab and bevacizumab is the first line therapy in unresectable HCC, which has shown superiority over sorafenib. Only 33% of patients respond to treatment according to mRECIST in the original trial (IMbrave150). Whereas few molecular factors has been associated to response, no routinely histological factors has been described. Our objective was to identify histologic features associated with response to atezolizumab-bevacizumab.
Method: We conducted a monocentric retrospective study between 2019 and 2023 including 108 pre-treatment biopsies of patients with unresectable HCC treated by atezolizumab-bevacizumab. CT scans at 3 months were used to define responders as partial or complete response according to mRECIST (modified Response Criteria In Solid Tumors). Histologic criteria were reviewed by two liver pathologists, including subtype according to the World Health Organization (WHO) classification based on predominant pattern and VETC phenotype (>55% of Vessels Encapsulating Tumoral Clusters, based on HES stain and confirmed with CD34 immunohistochemistry).
Results: HCC was mainly observed in male patients (n = 96, 89%) and in cirrhotic liver (n = 67, 62%). HCCs were mainly classified as "not other specified" (NOS, 48%). The most frequent observed subtypes were macrotrabecular massive (MTM, 26%), squirrhous (SQ, 10%) and steatohepatitic (SH, 9%). Clear cell subtype (CC) was rarely observed (4%). VETC phenotype was present in 12 patients (11%). Response at 3 months was assessable in 93 patients (86%), the remaining 15 patients having been lost to follow-up or died before the 3-month CT scan. 40% of patients (n = 43) were classified as responders, distributed as follow: 70% in NOS group (n = 30), 16% in MTM group (n = 7), 5% in SQ group (n = 2) and 5% in SH group (n = 2) (p = 0.015). In univariate analyses, factors negatively impacting response were MTM subtype (Odds ratio (OR): 0.30 [0.10; 0.83], p = 0.025) and SH subtype (OR: 0.16 [0.02; 0.71], p = 0.029), whereas VETC phenotype positively impact response (OR: 5.49 [1.28; 37.9], p = 0.038). In multivariate analysis, adjusted for clinical variables that may influence outcome (AFP, Child-Pugh, macrovascular invasion, extra-hepatic disease and previous locoregional treatment), VETC phenotype, MTM and SH subtype were still impacting response.
Conclusion: VETC phenotype, MTM and SH subtypes impact the response to atezolizumab-bevacizumab in unresectable HCC. These criteria, easily assessable on biopsy, could be used to stratify patients on response to atezolizumab-bevacizumab. These results should be confirmed in a larger cohort.

FRI-084
Real world treatment patterns and outcomes for hepatocellular carcinoma (HCC) patients receiving transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) in the TARGET-HCC registry
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Background and aims: The goal of this study was to describe baseline characteristics, treatment patterns, and outcomes among patients with intermediate or advanced HCC who received TACE or TARE as their first treatment in a real-world setting.
Method: The TARGET-HCC registry includes patients with HCC receiving standard of care treatment. Medical records are collected retrospectively for up to 3 years before enrollment and prospectively for up to 5 years. Adults (≥18 years) diagnosed with HCC (Barcelona Clinic Liver Cancer (BCLC) stage B or C) within 3 years of enrollment between January 2017–July 2024 in the United States, who received TACE or TARE as first HCC treatment were eligible for this study. Evaluated outcomes included real world tumor response to TACE or TARE based on radiology reports or clinical notes, overall survival, and TACE or TARE unsuitability defined by tumor size, portal vein thrombosis, extrahepatic metastases, or liver dysfunction.
Results: Of 230 patients, most had stage (BCLC) B at diagnosis (71%), median age was 64 years, White (67%), and 15% were Hispanic or Latino. Among response-evaluable patients after the first round of TACE or TARE, the most common response was partial response (PR, 56%), followed by progressive disease (PD, 21%), complete response (CR, 13%) and stable disease (SD, 10%). Across two rounds, the most common response pattern was CR/PR – CR/PR (52%), CR/PR – SD/PD (22%), SD/PD – SD/PD (14%), and SD/PD – CR/PR (12%). After initial TACE or TARE treatments, 57% of patients in this cohort were subsequently treated with systemic therapy, 21% with ablation, and 12% underwent liver transplantation. Median overall survival from initial diagnosis among patients with at least one round was 42 months (95% CI: 36 – NE) for those with a CR or PR in the first round, and 25 months (95% CI: 19–44) for those with SD or PD. Median overall survival from initial diagnosis among patients with at least two rounds of therapy was 38 months (95% CI: 32 – NE) for those with a response pattern of CR/PR – CR/PR across the first two rounds and 24 months (95% CI: 18 – NE) for those with CR/PR – SD/PD. The rate of TACE or TARE unsuitability was 66% after the first round of TACE or TARE, and 69% after the second round. Only 20% of patients received systemic therapy after the first round of TACE or TARE, and only 24% of patients received systemic therapy after the second round.
Conclusion: Patterns of follow-up treatment and outcomes varied among patients with intermediate/advanced HCC receiving TACE or TARE as their first treatment in a real-world setting. Approximately two thirds of evaluated patients may be considered unsuitable for TACE or TARE after a first or second round of treatment, but less than a quarter of these patients received systemic therapy. Educational efforts and multidisciplinary care can help increase guideline-concordant care aiming to improve outcomes for patients with unresectable HCC.

FRI-085
Microwave ablation versus liver resection for patinets with hepatocellular carcinomas

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Background and aims: Microwave ablation (MWA) represents an emerging ablative therapy that surpasses previous methods by achieving higher temperatures and creating larger ablation zones within shorter time periods. This study aimed to compare therapeutic outcomes of MWA and liver resection in real-world clinical practice.
Method: This study enrolled 178 patients with 259 nodules who underwent either MWA or liver resection between January 2015 and July 2023. Local tumor progression (LTP)-free survival, overall progression (OP)-free survival, and overall survival (OS) were assessed based on treatment modality of the index nodule.
Results: Of a total of 178 patients, 134 patients with 214 nodules received MWA and 44 patients with 45 nodules underwent liver resection. The median follow-up period was 2.0 ± 1.5 years. Annual incidence of LTP was 3.7% for MWA and 1.4% for liver resection. Treatment modality showed no significant impact on LTP-free survival. For nodules larger than 3 cm, LTP-free survival was not affected by treatment modality. Similarly, OP-free survival and OS were not influenced by the choice of treatment modality.
Conclusion: In conclusion, MWA and liver resection demonstrated comparable treatment outcomes in terms of local tumor control, overall recurrence, and survival.

FRI-086-YI
Long-term survival outcomes in patients receiving atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma: an update of the AB-real study

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Background and aims: Atezolizumab plus bevacizumab (A+B) is an established first-line treatment option in patients with unresectable hepatocellular carcinoma (HCC). Long-term survival outcome data are sparse and identification of patients achieving durable benefit from A+B remains an unmet need.
Method: From the AB-real cohort, a prospectively maintained registry of 1426 patients treated with A+B across 23 centres in Europe, Asia and America, we accrued 1284 patients receiving A+B as frontline systemic treatment and included those within Child-Pugh Class A and Eastern Cooperative Oncology Group and (ECOG) performance status 0–2 (n = 989). We estimated median overall (OS) and progression-free survival (PFS) and performed landmark survival analyses at 24 and 36 months (m) from A+B initiation. We explored characteristics associated to long-term survival, including radiologic response by RECIST v1.1 criteria, using uni- and multivariate regression.
Results: We included 989 patients with unresectable HCC. Overall, 770 (77.9%) had Barcelona Clinic Liver Cancer stage C, due to the presence of either macrovascular invasion (n = 243, 24.6%) and/or extrahepatic spread (n = 504, 51.0%) and ECOG PS 0–1 (n = 971, 98.2%). Viral aetiology was the most common cause of liver disease (HCV n = 199, 20.1% and HBV n = 471, 47.6%). After a median follow-up of 22.8 months (95%CI 21.6–24.0), 407 patients progressed to A+B and 540 patients died. Median OS was 18.5 months (95%CI 14.9–18.8 months) and median PFS was 7.9 months (95%CI 6.9–8.9 months). Overall response rate (ORR) was 29.0%, including 5.6% complete responses, whereas disease control rate was 75.3%. In the whole study population, landmark 24 m OS rate was 26.1% and 36 m OS rate was 9.6%. Patients achieving a radiologic response had higher 24 m (53.6%) and 36 m (30,5%) OS rates compared to those achieving disease control, with 24 m OS rate of 34.2% and 36 m OS rate of 14.2%. In landmark analyses at 6 m, achievement of a radiologic response was significantly associated with long-term benefit when compared to achieving a stable disease (HR 0.40, 95%CI 0.23–0.68) or a PD (HR 0.22, 95%CI 0.19–0.42, p < 0.001).
Conclusion: More than a quarter of A+B recipients with unresectable HCC are alive 2 years from treatment initiation. Probability of long-term survivorship is predicated upon achievement of an objective response, highlighting the importance of radiologic reassessment as a method to individualise prognostication in A+B recipients.

FRI-087
Immune cell profiling predicts response to Atezolizumab-Bevacizumab in advanced hepatocellular carcinoma

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Background and aims: Atezolizumab combined with bevacizumab is the current frontline treatment for advanced hepatocellular carcinoma. Despite numerous studies, predicting patient response to this therapy remains challenging.
Method: Patients with advanced hepatocellular carcinoma receiving atezolizumab-bevacizumab therapy were enrolled. Blood samples were taken at baseline and two weeks after treatment initiation. Peripheral blood mononuclear cells (PBMCs) were isolated for analysis. Eight patients were selected based on initial response: four responders (complete or partial response) and four non-responders (progressive disease). Single-cell RNA sequencing (scRNA-seq) was performed on the PBMC samples.
Results: Patients with favorable prognoses exhibited higher frequencies of γδ T cells, CD4+ T cells, CD8+ T cells, and both classical and non-classical monocytes in their peripheral blood mononuclear cells (PBMCs) before treatment compared to those with poor prognoses. After treatment, patients with positive outcomes showed a notable increase in proliferating lymphocytes. Importantly, a specific subpopulation of CD8+ T cells, designated as cluster 4, emerged as a potential biomarker for treatment response. This cluster, characterized by high expression of the proliferation marker MKI67 and inhibitory checkpoint genes such as PDCD1, HAVCR2, and CTLA4, was more prevalent in the pre-treatment PBMCs of patients with favorable prognoses. Moreover, patients with better outcomes exhibited a significant increase in the frequency of this cluster after treatment, suggesting its potential role in predicting and mediating response to the combination therapy.
Conclusion: This study mapped the diverse circulating immune cell populations in advanced hepatocellular carcinoma patients before and after atezolizumab-bevacizumab treatment. A distinct subgroup of CD8+ T cells emerged as a promising biomarker for predicting

treatment response, potentially aiding in personalized therapy decisions for this aggressive cancer.

FRI-088

Exosomal miR-30a-5p: a promising biomarker for predicting response to Atezolizumab-Bevacizumab therapy in advanced hepatocellular carcinoma

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Background and aims: Atezolizumab and bevacizumab combination therapy is currently the first-line treatment for advanced hepatocellular carcinoma. However, iVdentifying a reliable biomarker to predict treatment response remains challenging. This study aimed to discover exosomal miRNA biomarkers that could forecast positive responses to this combination therapy.
Method: Blood samples were collected from patients with advanced hepatocellular carcinoma before they began treatment with atezolizumab and bevacizumab. Patients were categorized into two groups: responders, who exhibited stable disease or showed partial or complete response to the treatment, and non-responders, who demonstrated disease progression. To isolate the exosomes, the serum samples were concentrated using a qEV concentration and isolation kit. Following this, exosomal RNA were extracted from the concentrated samples. The extracted RNA was then subjected to small RNA sequencing using next-generation sequencing (NGS) technology to identify the miRNAs present in the samples. Decision tree analysis was employed to identify miRNAs from the top 100 most expressed that effectively differentiated between responders and non-responders.
Results: The research included a total of 16 patients, evenly divided between responders and non-responders, with a predominance of male subjects and a high prevalence of viral-induced hepatocellular carcinoma in both groups. Next-generation sequencing analysis identified a total of 1076 miRNAs, among which 12 exhibited significant differential expression between the responder and non-responder groups. Notably, three miRNAs - let7c-5p, miR-30a-5p, and miR192-5p - were found to be significantly elevated in the responder group. Further analysis using decision tree methodology identified 30 miRNAs from the top 100 most expressed, with miR-30a-5p emerging as a particularly promising candidate, showing significantly higher levels in responders ($p = 0.0047$). The increased expression of miR-30a-5p in responders was subsequently confirmed through quantitative reverse transcription PCR validation. Additionally, in vitro experiments demonstrated that transfection of miR-30a-5p into HepG2 cells resulted in decreased cell migration and proliferation, suggesting a potential mechanistic link between this miRNA and treatment response.
Conclusion: Exosomal miRNAs show promise as potential biomarkers for predicting response to atezolizumab-bevacizumab therapy in advanced hepatocellular carcinoma. This research provides a foundation for further investigation into using these biomarkers to optimize treatment strategies for patients with this aggressive form of liver cancer.

FRI-089-YI

Integrating quality of life and overall survival to quantify benefit from frontline systemic therapy options in unresectable/advanced hepatocellular carcinoma: a network meta-analysis

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Background and aims: While overall survival(OS) remains the primary endpoint in the treatment of unresectable/advanced hepatocellular carcinoma(HCC), health-related quality of life(HR-QoL) is a crucial complementary outcome in the face of widening treatment options. Whilst various immune checkpoint inhibitor(ICI) combinations have been proven superior to tyrosine kinase inhibitor (TKI), no comparative evidence exists for their impact on HR-QoL. This network meta-analysis(NMA) aims to compare the effect of different first-line treatments for advanced HCC on HR-QoL and integrate treatment-induced survival benefit with impact on HR-QoL.
Method: We performed a systematic literature search of databases to identify all randomized phase 3 clinical trials published through November 2024. Studies were included if they compared TKI monotherapy with ICI-based therapies in first-line for unresectable/advanced HCC and report time to deterioration of HR-QoL scores. Only HR-QoL items reported ≥5 studies were analysed. A frequentist NMA was performed using sorafenib as the comparator. The minimum distance criterion(MDC) approach was employed to combine HR-QoL and OS by minimizing the statistical distance between observed results and a theoretical optimal point where both outcomes are maximized. Lower MDC corresponds to improved net benefit across both HR-QoL and OS.
Results: Ten studies, enrolling 7,268 patients treated with Sorafenib, Lenvatinib, Nivolumab, Tislelizumab, Durvalumab, Atezolizumab+Bevacizumab, Sintilimab+IBI305, Durvalumab+Tremelimumab, Nivolumab+Ipilimumab, Atezolizumab+Cabozantinib, Lenvatinib+Pembrolizumab, Camrelizumab+Apatinib were included. Seven HR-QoL items were reported in ≥5 studies: global health status/

quality of life(GHS/QoL), physical functioning(PF) and fatigue, assessed by EORTC quality of life questionnaire(QLQ)-C30 and jaundice, pain, abdominal swelling, and fatigue, assessed by EORTC QLQ-HCC18. Atezolizumab +Bevacizumab showed the highest probability of reducing the risk of deterioration of GHS/QoL(85%), abdominal swelling(95%), jaundice(89%), and pain(86%). Tislelizumab showed the highest probability of reducing the risk of deterioration of PF(96%) and fatigue, assessed by both QLQ-C30(98%) and QLQ-HCC 18(86%). When GHS/QoL was combined with OS, Atezolizumab+Bevacizumab outperformed other treatments, with the best MDC(0.19), followed by Sintilimab+IBI305(0.37) and Lenvatinib+Pembrolizumab(0.56).
Conclusion: Atezolizumab plus Bevacizumab was associated with the highest magnitude in reducing the risk of deterioration of most HR-QoL domains compared to other systemic therapies. Integrated assessment of OS with HR-QoL assessed by MDC suggests atezolizumab plus bevacizumab to provide the best balance between QoL preservation and OS benefit compared to other systemic therapy options in unresectable/advanced HCC.

FRI-090
Incidence of radiation pneumonitis following resin-based yttrium-90 selective internal radiation therapy

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Background and aims: Selective Internal Radiation Therapy (SIRT) with Yttrum-90 (Y-90) microspheres is a widely used locoregional therapy for a broad spectrum of hepatocellular carcinoma (HCC). Radiation pneumonitis is a rare but potentially fatal complication that occurs due to tumour-induced arteriovenous shunting of radiation particles into the lung. The safety dose to the lung was not well established for resin-based Y-90 SIRT but up to 30Gy is accepted as the safety limit. This study aims to evaluate the incidence of radiation pneumonitis after resin-based Y-90 SIRT for unresectable HCC.
Method: Consecutive patients treated with SIRT Y-90 resin microspheres for unresectable HCC between January 2008 and May 2019 at the National Cancer Centre Singapore and Singapore General Hospital were reviewed. Patient demographics, liver function, HCC tumour burden, chest computer-tomography (CT) findings, dosimetry parameters were recorded. Radiation pneumonitis was diagnosed based on the presence of respiratory symptoms and/or pulmonary infiltrates on imaging for which radiation pneumonitis cannot be excluded radiologically. Pre-treatment angiography and technetium-99m-labelled macroaggregated album (Tc-99 m MAA) study were performed for all patients to calculate lung shunt fraction and to estimate the lung dose. Dosimetry analysis was performed using either the partition model or body surface area (BSA) model.
Results: Of the 472 patients reviewed, 8 patients (1.6%) were diagnosed with radiation pneumonitis. The median follow up is 9.9 months (range, 4.5–13.2 months). One patient had Child-Pugh B7 liver cirrhosis whereas the rest of the patients were Child-Pugh A5-6. All 8 patients had HCC beyond the up-to-seven criteria. Half of the patients had no reported respiratory symptoms despite pulmonary infiltrates reported on CT thorax. All except one patient had bilateral pulmonary infiltrates or ground glass changes on CT thorax for which radiation pneumonitis is a differential diagnosis. Lung-shunt fractions range from 10.3% to 25% (median 9.6%; range, 8.4%–14.1%) and the predicted lung dose ranges from 10.3–21.9 Gy (median 13.5 Gy; range, 12.7–19.9 Gy). Onset of symptoms or imaging diagnosis ranges from 2–7.1 months post Y-90 SIRT (median 3.0 months; range, 2.6–3.7 months). Two patients required a tapering course of prednisolone for persistent dyspnoea or dry cough, but none required supplementary oxygen or other respiratory support.
Conclusion: Radiation pneumonitis is a rare complication of resin Y-90 SIRT and patients may be completely asymptomatic despite routine imaging shows pulmonary infiltrates suspicious of radiation pneumonitis. It may occur despite limiting the predicted lung dose to 25Gy. Only a small proportion of the patients require a tapering course of prednisolone treatment for persistent symptoms.

FRI-091-YI
The "A-B-C" cluster-based classification reveals distinct outcome trajectories in patients with hepatocellular carcinoma under atezolizumab/bevacizumab

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Background and aims: Patients with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab and bevacizumab exhibit variable outcomes. We aimed to identify clinically meaningful subgroups using machine learning to assess their association with oncological outcomes.
Method: In this international multicenter study across 12 centers, we included patients with unresectable HCC receiving first-line atezolizumab and bevacizumab. Baseline clinical, biological, and tumor characteristics were collected. Hierarchical clustering analysis was performed on a derivation cohort and validated in a validation cohort. Clusters were correlated with overall survival (OS), progression-free survival (PFS) and radiological response per RECIST 1.1.
Results: Among 1,399 patients (85% male; 75% with cirrhosis; 39% with portal vein invasion; 35% with metastasis), divided into derivation (n = 958) and validation (n = 409) cohorts, we identified three distinct subgroups: Cluster A (47.5% of patients): older age, higher body mass index, preserved liver function, multiple small tumors; Cluster B (11%): presence of VP1/VP2 portal vein thrombosis, higher hepatitis B and lower metabolic syndrome prevalence; Cluster C (41.2%): moderate liver dysfunction, elevated alpha-fetoprotein levels, and either VP3/VP4 portal vein thrombosis or high tumor burden. Cluster A had longer OS (median not reached) compared to Clusters B (18.2 months) and C (14.1 months; $p < 0.0001$), lower rates of progressive disease (25.1% vs. 34.3% and 41.2%; $p < 0.0001$), and longer PFS (median 10.93 vs. 7.73 and 6.10 months; $p < 0.0001$). Clusters correlated with prognosis across BCLC stages and specific patterns of disease progression ($p < 0.001$).
Conclusion: The Atezolizumab-Bevacizumab-Cluster (A-B-C) classification identified subgroups of patients with different prognostic trajectories. These clusters were associated with survival outcomes and patterns of disease progression, potentially informing personalized therapeutic strategies and clinical trial design in patients with unresectable HCC.

FRI-092-YI
Patterns and outcomes of recurrence after thermal ablation for hepatocellular carcinoma
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Background and aims: Recurrence rates after thermal ablation for hepatocellular carcinoma (HCC) remain high, but the patterns of recurrence and post-recurrence outcomes are not well characterized. This study aimed to investigate the recurrence patterns and long-term post-recurrence survival (PRS) in patients with HCC after thermal ablation.
Method: A retrospective analysis was conducted on 824 patients who underwent thermal ablation for HCC between 2007 and 2023. Recurrence patterns, post-recurrence treatments, and factors influencing PRS in patients with recurrence within and beyond Milan criteria were evaluated.
Results: During the median follow up of 54.5 month, 536 patients developed HCC recurrence. Among them, 67.4% and 32.6% patients experienced early and late recurrence, respectively, while 83.8% and 16.2% had recurrence within and beyond Milan criteria, respectively. Among patients with recurrence within Milan criteria, early recurrence (hazard ratio (HR) = 1.412, $p = 0.015$), recurrence tumor size >2 cm (HR = 1.510, $p = 0.002$), AFP >20 ng/mL (HR = 1.391, $p = 0.009$), ALBI grade 2–3 (HR = 1.675, $p < 0.001$), and FIB-4 score >3.25 (HR = 1.761, $p < 0.001$) were independent predictors of PRS. Among patients with recurrence beyond Milan criteria, diabetes mellitus (HR = 4.011, $p < 0.001$), macrovascular invasion (HR = 2.542, $p = 0.001$), AFP >400 ng/mL (HR = 1.867, $p = 0.039$), ALBI grade 2–3 (HR = 2.722, $p = 0.002$), and FIB-4 score >3.25 (HR = 2.421, $p = 0.018$) were independent predictors of PRS. Based on the predictors of RFS, a risk model for recurrence within Milan criteria stratified patients into 4 risk groups, with median PRS of 103.7, 65, 48.7 and 28.6 months, respectively ($p < 0.001$). A risk model for recurrence beyond Milan criteria stratified patients into 3 risk groups, with median PRS of 70.1, 24.7 and 8.1 months, and probability of downstaging to Milan criteria of 70.4%, 39.3% and 3.4%, respectively ($p < 0.001$).
Conclusion: Post-recurrence survival in patients with recurrent HCC after thermal ablation is significantly influenced by the pattern of recurrence, tumor burden, and host-related factors. These findings may guide post-recurrence treatment strategies, informing the timing of referral for salvage liver transplantation, and designing future clinical trials.

FRI-095
Hepatic artery infusion chemotherapy(HAIC) combined with Lenvatinib and Camrelizumab for hepatocellular carcinoma(HCC) with portal vein tumor thrombus(PVTT): a prospective longitudinal real-world study
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Background and aims: Hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) predicts a poor prognosis. The aim of this study was to evaluate the efficacy and safety of hepatic artery infusion chemotherapy(HAIC) combined with lenvatinib and camrelizumab in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT).
Method: This study was a single-arm, open-label prospective trial (ChiCTR2200063129). Eligible patients with advanced HCC accompanied by PVTT were enrolled to receive HAIC combined with lenvatinib and camrelizumab. The primary endpoint was progression-free survival (PFS), while the secondary endpoints included objective response rate (ORR), overall survival (OS), and safety.
Results: Between September 2022 and October 2023, 70 patients were successfully enrolled. The objective response rate (ORR) was 88.6% (62 out of 70 patients) based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST), which included 14 cases (20%) of complete response (CR) and 48 cases (68.6%) of partial response (PR). Additionally, 14.3% (10 out of 70 patients) underwent surgery, achieving a complete resection (R0) in all cases. The median PFS (mPFS) and median OS (mOS) were 11.3 and 23.6 months, respectively. The most common treatment-related adverse events were hypertension, proteinuria, rash, hand-foot syndrome, and

hematologic abnormalities. The incidence rates of grade 1, 2, 3, and 4 adverse events were 32.9%, 48.6%, 18.6%, and 11.4%.
Conclusion: For patients with HCC complicated by PVTT, the combination of HAIC with camrelizumab and lenvatinib shows promising clinical efficacy, and the toxicity is acceptable.

FRI-096
Effects of pre-transplant locoregional therapies on dropout rates and survival outcomes in patients with hepatocellular carcinoma: a propensity-matched analysis of the United Network for Organ Sharing (UNOS) database

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Background and aims: Locoregional therapies (LRTs) ranging from thermal ablation to intraarterial therapies are the cornerstone of treatment for hepatocellular carcinoma (HCC), however the long-term outcome of these therapies in patients undergoing liver transplantation is not well understood. This study aims to determine the effect of undergoing locoregional therapy prior to orthotropic liver transplantation on rates of dropout from transplant lists, and survival rates.
Method: This study analyzed data from the UNOS registry spanning January 2002 to January 2024, focusing on patients with HCC who were on the liver transplantation waiting list. Patients were divided according to the type of LRTs they received. A propensity score matched analysis was performed, incorporating covariates such as exemption score, alpha-fetoprotein (AFP) levels, MELD score, Child-Pugh, AlBI score, age, and gender to evaluate the effect of LRT on dropout. Furthermore, an inverse probability of treatment weighting (IPTW) Cox regression was utilized to assess the impact of LRTs on survival outcomes.
Results: The UNOS database had 150,274 patients with HCC listed for liver transplantation. Out of these patients, 117,271 patients were maintained on the list and were granted an exception point for receiving a new liver, while 48,836 have had different types of LRTs. Of the 33,003 patients who did not receive an exception point, 8,411 had received LRTs. Patients who underwent any form of LRTs exhibited a significantly lower risk of dropout from the transplant list (hazard ratio [HR]: 0.783, $P < 0.01$). Among the different types of LRTs, arterial therapies had the most pronounced effect on reducing the likelihood of dropout (HR: 0.756), followed by percutaneous ablative therapies (HR: 0.781) and external beam radiation therapy (HR: 0.84). Survival data post-liver transplantation was available for 24,963 patients who had received LRTs. The findings indicated that LRTs were significantly linked to a lower overall risk of mortality, showing an HR of 0.6 ($P < 0.01$). More specifically, the HRs for survival were 0.38 at 1 year ($P < 0.01$), 0.19 at 5 years ($P < 0.01$), and 0.18 at 10 years ($P < 0.01$). All LRT groups exhibited significant improvements in survival rates, with intra-arterial therapies leading to the most significant decrease in 5-year mortality, followed by percutaneous ablation and external beam radiation therapy (HR: 0.21, HR: 0.22, and HR: 0.24, respectively; all $P < 0.01$).
Conclusion: LRTs result in a significant reduction in dropout rates and improvement in post-transplant survival in patients with HCC. Patients who underwent arterial therapies had the most substantial benefit and lowest dropout rate. Additionally, LRTs were linked to better long-term survival outcomes, especially for intra-arterial therapies, which showed a significant decrease in mortality rates at 1-, 5-, and 10-years following transplantation.

FRI-097
Bridging and long-term impact of pre-orthotopic liver transplant transjugular intrahepatic portosystemic shunt (TIPS) creation: a propensity-matched analysis using the united network for organ sharing (UNOS) database

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Background and aims: Transjugular Intrahepatic Portosystemic Shunt (TIPS) plays a crucial role in bridging patients with portal hypertension and its complications while they await a transplant. However, there is a paucity of evidence regarding the pretransplant bridging and long-term survival effects of TIPS. This study aims to determine the pretransplant bridging and long-term overall survival (OS) effects of TIPS creation in patients undergoing orthotropic liver transplantation (OLT) by performing a propensity-matched analysis.
Method: The UNOS database was retrieved on Jan 2024, containing data from 1992 to 2023. Patients who underwent TIPS prior to liver transplantation were matched to non-TIPS patients using propensity score matching based on key demographic and clinical variables, including age, gender, BMI, hepatocellular carcinoma (HCC) status, and pre-transplant MELD/PELD scores. A Cox proportional hazards regression model was used to assess associations between TIPS placement and survival.
Results: The matched analysis revealed no significant differences between the TIPS and non-TIPS groups in terms of age (mean age: 56.3 years in TIPS vs. 56.2 years in non-TIPS), gender distribution (69% male in both TIPS and non-TIPS), BMI (mean: 28.00 in both TIPS and non-TIPS), or pre-transplant MELD/PELD scores (mean: 23.3 in TIPS vs. 23.2 in non-TIPS). The propensity score distance measure equaled 0.098 in both groups. Among TIPS patients, 11,178 (52.9%) underwent OLT, compared to 153,884 non-TIPS patients, of whom 58.8% underwent OLT. The TIPS patients were significantly more likely to be delisted from OLT waitlist in subsequent follow-ups ($P = 0.01$). A log-rank test performed on delisting data also showed a significant difference between the TIPS and non-TIPS groups ($p = 0.0001$). When focusing only on patients with HCC, 918 (64.8%) of TIPS patients underwent OLT, compared to 14,710 (62.4%) of non-TIPS patients, without statistically significant difference ($P = 0.072$). Sub-analysis of patients with HCC showed no significant difference in OS between TIPS and non-TIPS patients ($p = 0.8$).
Conclusion: Our findings show that while TIPS is essential for managing acute or chronic complications of portal hypertension in cirrhotic patients, liver transplant candidates who undergo TIPS creation are at a higher risk of drop out. TIPS creation in liver transplant candidates may be associated with lower survival rates during long term post-OLT, with the difference being most apparent in 5 year follow up. In patients with HCC, TIPS was not associated with significant differences in overall survival post-OLT. These findings highlight the nuanced impact of TIPS on post-transplant outcomes, emphasizing the need for individualized risk assessment and further

research to refine patient selection criteria for TIPS in the context of liver transplantation.

FRI-098

Nodule US-elastography: enhancing diagnostic and monitoring toolkits for predicting treatment response and prognosis in hepatocellular carcinoma post-TACE

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Background and aims: Transarterial chemoembolization (TACE) is a minimally invasive procedure primarily used for treating hepatocellular carcinoma (HCC), especially in patients with BCLC stage B. Post-TACE evaluations typically use enhanced CT or MRI after 4–6 weeks to minimize inflammation and artifact interference. However, this delay may hinder early identification of residual tumors in patients with incomplete ablation. This study aims to investigate the potential of US-Elastography (US-E) to predict therapeutic response and recurrence of HCC after TACE by measuring tumor stiffness (TS) before and after treatment.
Method: This prospective cohort study included 108 patients undergoing TACE for solitary HCC. Tumor evaluation included Contrast-Enhanced Ultrasound (CEUS) imaging before TACE, at 3 days post-therapy, and at 1, 3, and 6-month intervals during follow-up. Tumors were classified based on the CEUS LI-RADS TRA 2024 algorithm. US-E was used to assess TS pre-TACE and at 1, 3, and 6 months post-TACE. Nodule size and location, as well as biological markers were also collected. Follow-up lasted for a median of 12 months, with tumor recurrence and survival as primary outcomes. Statistical analyses, including Log-Rank tests and Cox regression, were performed to identify predictors of recurrence and survival.
Results: The average recurrence time after TACE was 7.2 months, and the 1-year overall survival rate was 88.7%. 51.3% of patients had progression-free survival over the 1-year follow-up period. Tumor size and prothrombin time were significant predictors of survival, while AST levels predicted recurrence. US-E measurements indicated an average TS of 41.3 ± 10.8 kPa pre-TACE, reducing to 22.7 ± 8.8 kPa 1 month after TACE. Higher TS levels before and after TACE were associated with lower overall survival rates and shorter progression-free periods. Kaplan-Meier analysis demonstrated marked differences in survival and progression-free survival between high and low TS groups.
Conclusion: US-Elastography provides valuable prognostic information by measuring tumor stiffness in HCC patients treated with TACE. High TS levels correlate with greater recurrence risk and poorer survival outcomes. Additionally, TS measured 1 month post-TACE significantly predicts treatment response and recurrence, suggesting that US-E could serve as a useful tool for early post-treatment evaluation.

FRI-099

Systematic review of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma with tumor thrombus extension to the inferior vena cava or right atrium

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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths and represents a significant global health challenge. In advanced stages, a subset of patients may develop tumor thrombosis in the inferior vena cava (IVC) with extension into the right atrium (RA), potentially leading to complications such as pulmonary embolism and cardiac tamponade, which can significantly reduce survival. This systematic review aims to assess the efficacy of stereotactic body radiation therapy (SBRT) in managing HCC patients presenting with tumor thrombus involvement of IVC or RA.
Method: As per the SWIM (Synthesis Without Meta-analysis) guidelines, systematic search of PubMed, EMBASE and Cochrane library was performed from inception until Nov 15th, 2024 with manual searches of reference lists to identify articles published in English language using the MeSH terms like 'HCC', 'SBRT', 'tumor thrombus', 'inferior vena cava extension', and 'right atrium' combined with different Boolean operators (and/or). Statistical analysis was done using SPSS version 23. Primary endpoint of survival analysis was done using Kaplan–Meier method. Secondary end point was overall response rates and toxicities. *p*-value <0.05 was considered significant.
Results: Our search yielded a total of 3 case reports and 5 case series with a total of 67 patients. The median age was 68.8 years (range 49–81), predominantly male (83.5%), AFP >400 was noted in 38 patients (56.8%). Due to macrovascular invasion, all patients were BCLC stage C and included patients with Child Pugh A5-B7 (CP-A 77.7%). Median gross tumor volume was 29.8 (24.04–41.19) cc. All patients were treated synchronously for the intrahepatic tumor and right atrial tumor thrombus. All patients received prior therapies (TACE, surgery, TKI etc). The median disease-free survival and overall survival (OS) for all reviewed patients were 9.7 months and 12.2 months, respectively. The OS at 1 year, 2 year, and 3 year was 52.8%, 20.4% and 12.9%, respectively. Complete response was noted in 14 (21%), partial response in 37 (55.1%) and stable disease in 10 (15%) patients. Grade 1 toxicities were noted in almost all patients and grade 2 in 13 (19.5%) patients. No patients experienced grade 3 or higher toxicities or any elevation of myocardial enzymes. Worsening of CP scores by ≥2 points was noted in 3 (2.9%) patients.
Conclusion: This systematic review highlights the potential of SBRT as a feasible and effective treatment option for HCC with tumor thrombus extension to the inferior vena cava or right atrium. The therapy demonstrated encouraging outcomes, with median overall survival reaching 12.2 months and manageable toxicity profiles. Most patients experienced either a partial or complete tumor response, with minimal severe adverse effects or significant hepatic function deterioration. These findings support SBRT as a safe and viable therapeutic approach in this challenging clinical scenario.

FRI-100

Laparoscopic liver resection as a treatment for early-stage hepatocellular carcinoma in patients with and without portal hypertension: a case-control study

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Background and aims: Early-stage Hepatocellular Carcinoma (HCC) involves patients with single tumors or up to three nodules, each no larger than 3 cm, preserved liver function, and good performance status. Liver transplantation is the ideal treatment, but it is not universally available. In this context, Laparoscopic Liver Resection (LLR) offers comparable outcomes and is recommended for patients with a Hepatic Venous Pressure Gradient (HVPG) <10 mmHg, i.e., without clinically significant portal hypertension (CSPH). However, no definitive HVPG cutoff contraindicating LLR exists. This study aimed to compare perioperative and short-term outcomes of LLR in cirrhotic patients with early-stage HCC, with and without CSPH.
Method: This retrospective case-control study included 40 cirrhotic patients with early-stage HCC who underwent LLR between 2016 and

2023 at a university hospital. Clinical and demographic variables, indirect signs of portal hypertension, and HVPG were recorded. Patients were divided into two groups based on the presence or absence of CSPH (HVPG > 10 mmHg or clinical signs of portal hypertension). The non-CSPH group included 15 patients (37.5%), and the CSPH group included 25 patients (62.5%), with a median HVPG of 16 mmHg (range: 11–26). The median follow-up was 25 months (range: 2–89 months). Perioperative variables and outcomes up to 90 days post-surgery, as well as clinical follow-up data, were compared. Fisher's exact test and Kaplan-Meier survival analysis with the log-rank test were used for statistical analysis. A p-value <0.05 was considered statistically significant.

Results: There were no differences in baseline characteristics or preoperative tumor size between the groups. A total of 78% of LLRs were anatomical segmentectomies. Four hemi-hepatectomies were performed in the non-CSPH group, while only segmentectomies were performed in the CSPH group. Intraoperative variables, including blood loss, transfusion requirements, operative time, use of the Pringle maneuver, and conversion to laparotomy rates, showed no significant differences. No 90-day mortality was observed, and severe morbidity rates were comparable between groups (Clavien-Dindo ≥III: 7% in non-CSPH vs. 8% in CSPH). Similarly, no significant differences were found in postoperative rates of ascites (13.3% vs. 24%), post-hepatectomy liver failure (13.3% vs. 0%), encephalopathy (0 vs. 4%), postoperative hepatic decompensation (20% in both groups), or pulmonary or abdominal infections. The median ICU stay was 4 days for both groups. Positive surgical margins (R1) were also similar (7% in non-CSPH vs. 12.5%). Overall survival rates at 1 and 3 years were 100% and 78%, respectively, with no significant differences between groups (p = 0.1448).

Conclusion: In cirrhotic patients with CSPH, early postoperative outcomes and short-term overall survival were comparable to those in cirrhotic patients without CSPH at our center.

FRI-101

Viral etiology of hepatocellular carcinoma as an independent determinant of survival for patients receiving tyrosine kinase inhibitor treatment

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Background and aims: Increasing evidence indicate the etiology of hepatocellular carcinoma (HCC) influencing response to systemic therapy. Tyrosine kinase inhibiors (TKIs) play a key role in systemic therapy of HCC; however, studies exploring the effect of HCC etiology on TKI treatment outcomes are limited. We aim to investigate whether viral etiology impacts the therapeutic response to TKIs.

Method: We identified HCC patients treated with TKIs (sorafenib, lenvatinib, cabozantinib, regorafenib) from January 2008 to June 2024 from a population-wide registry in Hong Kong. Virus-related HCC was defined as patients with any virological or serological evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, including a positive hepatitis B surface antigen, detectable HBV DNA or positive antibody to HCV (anti-HCV). Propensity score matching (PSM) in a 2:1 ratio for viral vs non-viral HCC was applied to match for age, gender, presence of type 2 diabetes (T2D), prior oncological therapies & metastatic status. The primary outcome was overall survival (OS) stratified by etiology of HCC (viral vs non-viral) in the propensity score matched population; secondary outcomes included subgroup analysis of OS stratified by viral types (HBV & HCV), TKI types, prior oncological therapies (curative & non-curative), age groups (≥65 & <65 years), and the presence or absence of T2D. The OS outcomes were evaluated using the Kaplan–Meier method and adjusted hazard ratios (HRs) were calculated using the Cox proportional hazards model.

Results: Among 2,995 HCC patients receiving TKI treatment, 2,434 (81.3%) patients were identified as virus-related HCC (90.4% HBV, 9.1% HCV, 0.5% co-infection); 561 patients (18.7%) were non-viral HCC. After 2:1 PSM, 1,074 viral HCC & 537 non-viral HCC were included. Kaplan-Meier analysis showed virus-related HCC, when compared to non-viral HCC, had worse OS (median 6.6 vs 7.0 months, p < 0.001) & higher risk of all-cause death (HR 1.23; 95% CI 1.10–1.38; p < 0.001). Subgroup analysis of HBV-related HCC showed similar findings, with a worse OS (median 6.6 vs 6.9 months, p < 0.001) & a 26% increased risk of all-cause death (HR 1.26; 95% CI 1.13–1.41; p < 0.001), as compared to non-viral HCC. Among patients receiving lenvatinib, a significantly better OS was observed in non-viral HCC versus viral HCC (median 10.0 vs 8.2 months, p = 0.02). Similar results were observed in patients receiving prior non-curative therapy (median 10.0 vs. 8.1 months, p = 0.014), patients <65 years (median 5.7 vs. 5.1 months, p < 0.001), patients with T2D (median 7.3 vs 7.2 months, p = 0.038) & patients without T2D (median 6.1 vs. 5.8 months, p = 0.0047).

Conclusion: Non-viral HCC patients receiving TKI treatment had significantly better OS when compared to viral HCC. The presence of a viral etiology may impact management decisions on the choice of first-line systemic therapy for advanced HCC.

FRI-102

Selective internal radiation therapy (SIRT) for HCC: real-world experience from a tertiary care center

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Background and aims: Selective internal radiation therapy (SIRT) with yttrium-90 is an endovascular treatment modality for patients with HCC across various clinical stages. The aims of study were to evaluate safety, tumour response and overall survival (OS) of SIRT in patients with HCC across the spectrum of the cancer stage.

Method: Patients treated with SIRT between February 2019 and September 2023 at King's College Hospital were retrospectively included from a prospective database. Demographic data and clinical details, prior and subsequent therapies, and adverse events, were collected. Tumour response was assessed by two experienced HPB radiologists independently using mRECIST criteria at 6 and 9 months post-procedure. OS was calculated from treatment to death or last visit.

Results: Fifty-six patients were identified, 87.5% male, with a median age of 68 years (IQR 61–75). The majority had cirrhosis (64%) with the most frequent underlying aetiologies of viral hepatitis (33.9%). For those who progressed to delivery of SIRT (n = 49) the median follow-up time was 24.5 (SD ± 14.4) months. Most patients were BCLC stage A (27, 54%), followed by stage B (32%) and stage C (14%), with 57% of the stage C patients having Vp3-4 involvement. The median number of tumours was 1 (IQR 1–2), with a median size of 7 cm (IQR 4.8–10.3). SIRT was the initial treatment in 68% of patients. By mRECIST criteria at 6 months, 18% achieved complete response (CR), 46% partial response (PR), 16% stable disease (SD), and 16% progressive disease (PD). At 9 months, 12% maintained CR, 32% PR, 6% SD, and 6% progressed further. Among patients with cancer progression, the

median time to progression was 9 months (IQR 3–14). Mean OS was 44.3 months (95% CI 34–53) for BCLC A, 32.5 months (95% CI 25–40) for BCLC B, and 32 months (95% CI 17–47) for BCLC C (log-rank p = 0.733). In patients who did not receive radical treatments post-SIRT, OS was 32 months (95% CI 20–44), 30.2 months (95% CI 22–39), and 32 months (95% CI 17–47) for BCLC A, B, and C, respectively (log-rank p = 0.822). Following SIRT, radical treatments were provided to 28% of patients, including 4 liver transplants and 10 resections, with 11 patients at BCLC stage A and 3 at BCLC stage B. Histological regression rates were as follows: 100% in two patients, > 90% in two, 50–90% in four, and 30–50% in five patients. Adverse events occurred in 19.6% (n = 11) of patients, including two arterial dissections, one pulmonary embolism, one right-sided portal vein thrombosis, three cases of decompensation with ascites, one case of radiation-induced liver injury, as well as a hypertensive crisis and atrial flutter with chest pain.

Conclusion: SIRT is a safe and effective treatment modality for HCC across various stages. We observed promising radiological response rates at 6–9 months, particularly for large lesions, whether used as a primary treatment or as part of a down staging strategy for curative interventions.

FRI-103

Prognosis of patients undergoing curative surgery for combined hepatocellular-choloangiocarcinoma

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Background and aims: Combined hepatocellular and cholangiocarcinoma(cHCC-CC) is one of the primary cancers that occur in the liver. Its prognosis has been compared to hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma(ICC), but the results are yet controversial. We analyzed the prognosis of cHCC-CC and compared to HCC and ICC at single center.

Method: The numbers of patients who underwent curative liver resections from April 1992 to January 2022 were 844 for HCC, 78 for ICC, and 26 for cHCC-CC in KCCH Seoul, South Korea. We retrospectively analyzed these three groups of patients. We used inverted probability treatment of weighting analysis (IPTW) to compare the prognoses of three groups of patients.

Results: After IPTW analysis, five-year overall survival of the HCC group, the ICC group, and the cHCC-CC group as 72% vs 85% vs 50% respectively (p = 0.025). Five-year recurrence free survival of the HCC group, the ICC group, and the cHCC-CC group as 46% vs 74% vs 42% respectively (p = 0.151).

Conclusion: cHCC-CC shows worst prognosis and survival among three groups. However, because of small sample size and limitations of retrospective study, additional large scale prospective studies are necessary.

FRI-104

Sorafenib plus transarterial chemoembolization versus sorafenib alone in advanced hepatocellular carcinoma (SELECT): a multicenter, phase 3, randomized, controlled trial

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Background and aims: Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related mortality, with a particularly poor prognosis for advanced-stage disease (Barcelona Clinic Liver Cancer stage C). This study aimed to assess the efficacy of sorafenib combined with transarterial chemoembolization (TACE) in patients with advanced HCC.

Method: SELECT was a randomized, multi-centre, controlled, phase 3 trial done at twelve centres in China. Eligible patients were aged 18 years or older and had advanced-stage HCC, Barcelona Clinic Liver Cancer stage C diseases, Child-Pugh class A liver disease. Participants were randomly assigned (1:1) with a computer-generated random sequence to sorafenib combined with transarterial chemoembolization or sorafenib alone. The primary endpoint was overall survival. Secondary endpoints were time to progression, tumor response rate, disease control rate and safety. Efficacy was analyzed in the intention-to-treat, per-protocol and as-treated populations. Safety outcomes were analyzed in the safety population. This trial is registered with ClinicalTrials.gov, number NCT01906216.

Results: Between September 7, 2013 and Dec 4, 2019, 199 patients were randomly assigned, 99 to the combination group and 100 to the sorafenib alone group. Hepatic virus infection was the predominant cause of HCC. At a median follow-up of 13.6 months (IQR 6.8–28.2), in the intention-to-treat population, median overall survival was 14.9 months (95%CI 10.5–19.3 months) in the combination group versus 11.9 months (95%CI 9.0–14.8 months) in the sorafenib alone group (HR 0.862 [95%CI 0.645–1.150]; P = 0.312). Median time to progression survival was significantly longer in the combination group than the sorafenib alone group (10.0 months [95%CI 6.4–13.6 months] vs 5.9 months [95%CI 3.1–8.7 months]; HR 0.686 [95%CI 0.515–0.954]; P = 0.016). In the per-protocol population, the median overall survival in the combination group was significantly longer than that in the sorafenib monotherapy group (HR 0.539 [95%CI 0.378–0.769]; P = 0.001). In the as-treated population, the median overall survival was also significantly longer in the combination group than in the sorafenib monotherapy group (16.9 months [95%CI 13.4–20.4] versus 9.5 months [95%CI 6.5–12.5]; HR 0.576 [95%CI 0.420–0.789]; P = 0.001). The time to progression was significantly improved in the combination group compared with sorafenib alone group in both the per-protocol and as-treated analyses. The overall incidence of adverse events was similar between the two groups.

Conclusion: Sorafenib combined with TACE improved survival in the per-protocol population but not in the intention-to-treat population. The significance of overall survival when combing systemic therapy with locoregional treatment for managing of advanced-stage HCC warrants further investigation.

FRI-105

Evolutionary learning-derived multimodal models integrating comprehensive imaging features to predict early recurrence of hepatocellular carcinoma after curative resection

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Background and aims: The accuracy of existing models for predicting early recurrence of hepatocellular carcinoma (HCC) after curative resection remains suboptimal. This study aimed to develop artificial intelligence-based multimodal models to enhance predictive accuracy by incorporating a larger dataset and integrating comprehensive imaging features.
Method: This study enrolled patients with HCC who underwent curative resection with complete clinical data (clinical cohort, n = 1477), complete dynamic CT images (clinical-image cohort, n = 588), and an external validation cohort from Hong Kong (n = 122). Patients were randomly assigned to training and test sets in a 7:3 ratio. Multimodal imaging features, including radiomics, 3D geometric properties, tumor morphology, and deep learning-derived latent features, were analyzed. Two evolutionary learning-based models, EL-CERSL (clinical features only) and EL-MERSL (clinical and imaging features), were developed to predict early recurrence of HCC within 2 years post-resection.
Results: The EL-CERSL and EL-MERSL models provided personalized predictions of 2-year recurrence-free survival (RFS). In the test set, the area under the receiver operating characteristic curves (AUCs) for EL-CERSL-preoperative, EL-CERSL-postoperative, EL-MERSL-preoperative, and EL-MERSL-postoperative models were 0.791, 0.774, 0.857, and 0.861, respectively, significantly outperforming the ERASL-pre and ERASL-post models (AUCs 0.733 and 0.747) and high-risk criteria from IMBrave050, KEYNOTE-937, EMERALD-2, and CheckMate-9DX trials (AUCs 0.607, 0.622, 0.643, and 0.543, respectively). In the external validation cohort, the AUCs of the EL-MERSL-preoperative and EL-MERSL-postoperative models were 0.801 and 0.808, respectively. Among IMBrave050-defined high-risk patients, the EL-MERSL-postoperative model classified 72.4% as low-risk and 27.6% as high-risk, with corresponding 2-year RFS rates of 70.2% and 20.6%, respectively.
Conclusion: The EL-CERSL and EL-MERSL models demonstrated significantly improved accuracy in predicting early HCC recurrence after resection. These models hold potential for guiding post-resection surveillance strategies and optimizing clinical trial designs by identifying high-risk candidates for adjuvant therapies.

FRI-106
Real-world treatment patterns and survival outcomes in patients with unresectable hepatocellular carcinoma (uHCC): the OREIOS - Middle East and North Africa (MENA) cohort

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Background and aims: With evolving systemic treatment (Tx) options for uHCC, OREIOS (NCT05239507) study was conducted to determine the Tx patterns and survival outcomes in patients (pts) with uHCC across Asia, Latin America and MENA.
Method: The MENA cohort of this non-interventional, retrospective study enrolled pts with unresectable Barcelona Clinic Liver Cancer (BCLC) (stage B or C advanced/metastatic HCC from Egypt, Kuwait, Oman, Saudi Arabia, and United Arab Emirates) during Jan 2017–Dec 2019. The primary endpoints were median overall survival (mOS) and survival rates at 12 and 24 months (m).
Results: Of 216 pts enrolled (median [range] age: 64.0 [35.0–97.0] yrs), 78.2% (169/216) were males, and 33.1% (52/157) were current/ex-smokers. The most common etiology was hepatitis C (54.5%, 114/209). At the index date (date of diagnosis of unresectable or advanced/metastatic HCC), most (70.8%, 153/216) pts had BCLC stage C with main portal vein invasion in 26.4% (57/216), > 50% liver involvement in 47.7% (103/216) and extrahepatic metastases in 40.7% (88/216). After index date, 8.4% (18/215) received loco-regional Tx and 13.4% (29/216) received transarterial chemoembolization (TACE). Majority (85.1% 126/148) received sorafenib in 1st line (1L) Tx; 15.3% (33/216) pts received 2nd line (2L) Tx, mainly nivolumab (57.6%, 19/33). The mOS (95% CI) of overall cohort was 14.2 (11.5–18.6) m, with OS rate of 55.4% at 12 m and 35.2% at 24 m. The mOS for BCLC B (N = 63) and BCLC C (N = 153) were 23.5 (18.6–27.9) m and 9.9 (8.0–14.1) m with 12 m OS rate of 74.6% and 47.4% and 24 m OS rate of 48.1% and 29.9%, respectively. The mOS (95% CI) for pts receiving tyrosine kinase inhibitors (TKIs; N = 135), immune checkpoint inhibitors (ICIs; N = 30), vascular endothelial growth factor (VEGF/VEGFR2) inhibitors (N = 4), and TACE (post index date) (N = 29) were 13.2 (8.7–18.3) m, 18.8 (10.7–27.9) m, 31.0 (25.2 – NA) m and 18.5 (13.2 – NA) m, with 12 m OS rate of 50.1%, 66.7%, 71.4%, 100% and 24 m OS rate of 33.5%, 40.0%, 100% and 48.6%, respectively. The median progression-free survival (mPFS) (95% CI) for overall was 9.1 (7.2–13.3) m, for pts with BCLC B was 9.0 (6.9–13.7) m and for BCLC C 9.7 (6.7–14.4) m and for pts receiving TKIs, ICIs, and VEGF/VEGFR2 inhibitors were 6.7 (4.8–8.9) m, 4.8 (3.2–8.1) m, and 3.6 (0.5–NA) m, respectively. BCLC stage B, alpha-fetoprotein level <400 ng/mL, Tx line, TKIs and ICIs were significantly ($p < 0.01$) associated with reduced risk of death whereas albumin level ≤4 g/dL, performance status >1 and portal vein invasion were significantly ($p < 0.05$) associated with increased risk of death.
Conclusion: In the OREIOS-MENA cohort, sorafenib was the most common Tx in 1L; however, only 15.3% received 2LTx. A mOS of about 14 m indicates the need for integration of optimum Tx strategies with novel agents and combination therapies in routine care to improve prognosis.

FRI-111
The role of immune cell composition potentially predicts response to atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma

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Background and aims: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide with limited therapeutic options especially at advanced stages. Recently, immune checkpoint inhibitors have shown remarkable efficacy in various kinds of solid cancers. The combination of atezolizumab plus bevacizumab is a first-line treatment in patients with advanced HCC, but is only effective in 30% of patients. Therefore, we elucidate the heterogeneity and plasticity of the various immune cell subsets in the course of checkpoint inhibitor-based treatment regimens in order to predict treatment responses and potentially identify optimal therapy candidates.
Method: We evaluated 98 patients with unresectable HCC, who received atezolizumab plus bevacizumab at our center (outpatient clinic of Charité - Universitätsmedizin Berlin) between April 2021 and March 2023 as first line therapy. We established a 27-color full spectrum flow cytometry panel in order to analyze blood-circulating, peripheral immune cell populations including checkpoint expression patterns and activation markers. Flow cytometry was performed

consecutively upon treatment application within the first three months and later on every three months at the timepoint of tumor staging. The correlation between the various immune cell populations and overall survival (OS) as well as progression-free survival (PFS) was statistically determined. Multiplex immunostainings on corresponding liver biopsies taken before therapy will additionally provide spatial and functional information.

Results: Immune-associated biomarkers like the expression of programmed cell death-ligand 1 (PD-L1) that correlate with therapeutic response in other solid tumors are not suitable for HCC. Interestingly, patients with a low number of neutrophils and low inflammatory marker show a better response and OS. In addition, the number of lymphocytes, especially of activated (CD25+ and HLA-DR+) T cells and their changes during therapy affected treatment responses. Differences between etiologies and therapeutic response or OS were not observed.

Conclusion: The peripheral immune cell composition and their changes during therapy with atezolizumab plus bevacizumab may serve as predictor checkpoint inhibitor-based treatment responses in patients with unresectable HCC.

FRI-112

Local control and survival after stereotactic body radiotherapy for hepatocellular carcinoma without macrovascular invasion

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Background and aims: Emerging evidence supports the use of stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC). Existing literature is mainly from North America/East Asia where the etiology is predominantly viral. The study analyses the outcomes of SBRT in our HCC patients without macrovascular invasion (MVI).

Method: Patients diagnosed to have HCC without MVI who underwent SBRT at our institution between 1st December 2019 and 30th June 2024 were evaluated. Patients with extrahepatic disease, prior rupture and more than 6 parenchymal lesions were excluded. Primary outcome of interest was local control. Overall survival (OS), Progression free survival (PFS) and adverse events (AE) were secondary end points.

Results: This retrospective study included 188 patients of whom 175 were eligible for analysis. Total number of lesions was 358. The Cohort was predominantly male (90%), non-viral (96.5%) with a median age of 68 years (44–87). Forty one (23.4%) patients received prior liver directed local treatment. Baseline Child Pugh Score (CPS) was A5/A6 in 58.8%, B7/B8/B9 in 36% and C10/C11 in 5.1%. Baseline albumin-bilirubin (ALBI) grade was 1 in 25.7%, 2 in 59.4% and 3 in 14.8% patients. Multiple HCCs were present in 44.5% patients. Median serum alpha fetoprotein (AFP) was 15 ng/ml (1–6389). Median size of largest lesion on a per patient basis was 4.2 cm (1.5–14). Median tumor size as a sum of all lesions per patient was 5.9 cm. Median gross tumor volume (GTV) was 42cc (1–900) while median total liver volume was 1208 cc. Median prescription dose was 35 Gray (Gy) in 5 fractions (27.5–50 Gy). Median value of mean uninvolved liver (liver-GTV) dose was 9.67 Gy. At the last follow-up (FU), 93 patients were alive. At a median FU of 16 months, the median OS was 24 months for the entire cohort. Median PFS was 17.6 months. Median OS for CPS A5/A6 patients was not yet reached. Median OS was 13.8 months for CPS B7/B8/B9 patients. Median OS for BCLC 0/A patients was not yet reached. Median OS for BCLC B patients was 24 months while median OS for BCLC C/D patients was 11.7 months. Local progression occurred in 18(10.2%) patients amounting to 28(7.8%) lesions. CPS decline >2 points in the absence of intrahepatic tumor progression occurred in 8.5% patients while ALBI grade declined in 19% patients. SBRT related gastrointestinal bleed occurred in 5 patients while one patient had a biliary stricture.

Conclusion: SBRT gives high rates of local control and comparable survival with acceptable AE profile despite significant number of patients with multiple lesions and relatively worse CPS in comparison to existing literature. Results from our large, mainly non-viral cohort, support the use of SBRT as an alternative to other local treatments in HCC patients without MVI.

FRI-113

Clinical outcomes of stereotactic body radiotherapy for hepatocellular carcinoma with macrovascular invasion in a predominantly non-viral cohort

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Background and aims: Non-viral etiology predominates Hepatocellular carcinoma(HCC) patients in our region distinct from North American/East Asian cohorts and is a minority in existing literature on Stereotactic Body Radiotherapy (SBRT) for HCC with macrovascular invasion (MVI). Aim of the study is to report clinical outcomes of SBRT in a large cohort of patients with HCC and MVI treated at our institution.

Method: Patients diagnosed to have HCC with MVI who underwent SBRT at our institution between 1st December 2019 and 30th June 2024 were evaluated. Patients with extrahepatic disease, retroviral infection, prior rupture and active second malignancy were excluded.

Primary outcome of interest was overall survival (OS). Progression free survival(PFS) and adverse events were secondary outcomes.
Results: The retrospective study included 112 patients of which 103 were eligible for analysis. Cohort was predominantly male (92%), non-viral (96.2%) with median age of 66 yrs. Baseline Child Pugh Score (CPS) was A5/A6 in 65%, B7 in 14.5% and B8 or higher in 20.5%. Baseline albumin-bilirubin(ALBI) grade was 1 in 21.3%, 2 in 63.1% and 3 in 15.5% patients. Degree of MVI was vp1/2 in 17.4%, vp3 in 29.1%, vp4 in 44.6% and hepatic vein or vena cava in 8.7%. Multiple HCCs were present in 47% patients. Median alpha fetoprotein (AFP) was 444 ng/ml. Median tumor size was 9 cm. Median gross tumor volume (GTV) was 348cc. Median total liver volume was 1407cc. Median prescription dose was 33 Gray(Gy) in 5 fractions. Median value of mean uninvolved liver dose was 14.18 Gy. At last follow-up (FU) 20 patients were alive. At a median FU of 12 months, median OS was 13.5 months for entire cohort, 14.8 months for CPS A5/A6 patients and 13.8 months for CPS A5/A6 patients with vp4 MVI. Median PFS was 6.6 months. Local progression occurred in 20 patients. CPS decline >2 points in absence of intrahepatic tumor progression occurred in 16.5% patients while ALBI grade declined in 31.5% patients. SBRT related gastrointestinal bleed occurred in 4 patients. On univariate analysis better CPS, ALBI Grade, lower mean dose to uninvolved liver, higher dose to GTV was significantly associated with better OS. On multivariate analysis only lower mean dose to uninvolved liver retained significance.
Conclusion: In our predominantly non-viral patient cohort, good clinical outcomes were obtained despite limited access to immunotherapy (IO), larger tumors, high median AFP and worse CPS. Median OS of 13.8 months in patients with CPS A and vp4 MVI far exceeds the reported survival for same subset in existing literature. Results from our large cohort adds to evidence for SBRT in HCC with MVI patients more so in non-viral etiology where inferior outcomes with IO have been reported. Patients with larger tumors in terms of size and tumor volume relative to liver volume than mostly reported can be treated with comparable degree of safety using appropriately tailored dose.

FRI-114

Liver resection versus trans-arterial chemoembolization for huge hepatocellular carcinoma (>10 cm): a nationwide propensity score adjusted analysis

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Background and aims: The treatment of hepatocellular carcinoma (HCC) >10 cm remains controversial. The ongoing debate regarding the treatment of patients with HCC > 10 cm is partly due to the necessity of tailoring treatment to individual patient conditions. This study aims to address the important controversy regarding the management of large HCC, focusing on providing insights into the comparative effectiveness of liver resection (LR) and Transarterial Chemoembolization (TACE).
Method: Patients registered in the Korean Primary Liver Cancer Registry (KPLCR) were selected. The KPLCR is a random sample consisting of approximately 15% of patients newly diagnosed with primary liver cancer registered in the Korean Central Cancer Registry (KCCR), which is a nationwide cancer registry and includes more than 95% of all cancer cases in Korea. The study design utilizes data from the KPLCR covering the years 2008 to 2017 to investigate the treatment outcomes for HCC larger than 10 cm. Starting with 15,307 cases, the study identified 9,310 HCC patients with follow-up data, excluding those with missing initial treatment data (n = 5,863) and follow-up loss (n = 132). From these, 7,662 patients with single HCC were selected, further excluding cases with multiple HCC (n = 1,394) and distant metastasis (n = 254). This refined the cohort to 504 patients with HCC tumors larger than 10 cm, who were then divided into two treatment groups: 122 patients underwent liver resection (LR), and 382 patients received TACE.
Results: After PSM, the baseline characteristics showed no significant differences between the LR group (n = 99) and the TACE group (n = 99). Before propensity score matching (PSM), the hazard ratio (HR) for LR was 3.41 (95% CI: 2.62–4.43, $p < 0.001$), indicating a significantly better survival probability for the LR group compared to the TACE group. After PSM, the HR for LR was slightly reduced to 3.06 (95% CI: 2.18–4.29, $p < 0.001$), but the survival advantage of LR over TACE remained highly significant. Before PSM, the HR for LR was 3.29 (95% CI: 2.59–4.17, $p < 0.001$), indicating a markedly better recurrence-free survival (RFS) for the LR group compared to the TACE group. After PSM, the HR for LR increased slightly to 3.37 (95% CI: 2.43–4.68, $p < 0.001$), maintaining the significant survival advantage of LR over TACE.
Conclusion: This study provides a comprehensive analysis of treatment outcomes for HCC > 10 cm, comparing LR and TACE using data from the KPLCR. The results indicate that LR is associated with significantly better OS and RFS compared to TACE, both before and after PSM.

FRI-115

Improving outcomes in unresectable hepatocellular carcinoma through proactive adverse event management with Atezolizumab-Bevacizumab therapy

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Background and aims: Since the success of IMbrave 150 and HIMALAYA trial, immune checkpoint inhibitors (ICIs) have become the first line systemic treatment for unresectable hepatocellular carcinoma (HCC). Recent studies also suggest that immune-related adverse events (irAEs) may enhance ICI efficacy and improve clinical outcomes. However, comprehensive evaluation of relationship between adverse event during the treatment and clinical outcome is still under investigation. Therefore, this study aims to comprehensively evaluate the clinical impact of adverse events during the atezolizumab plus bevacizumab for unresectable HCC patients on the clinical outcome.
Method: Consecutive patients treated with atezolizumab plus bevacizumab as first-line therapy for unresectable HCC were retrospectively reviewed. IrAEs and bevacizumab-related adverse events were evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0. In addition, all imaging studies obtained during the treatment course were reviewed to detect any imaging findings related to immune adverse reaction. The primary endpoint was the overall survival (OS), and the secondary endpoints was disease control rate (DCR).
Results: Among 198 enrolled patients, 12 had irAEs identified solely through computed tomography (asymptomatic imaging-detected adverse events group), while 56 experienced clinical symptoms of either irAEs (n = 28), bevacizumab-related adverse events (n = 19) or both (n = 9) (symptomatic adverse events group). The overall survival rate at 6, 12, 18, and 24 months were 100.0%, 82.5%, 82.5%, and 82.5% for asymptomatic AE group, 89.1%, 64.1%, 41.7%, and 40.5% for symptomatic AE group, and 72.3%, 48.3%, 31.3%, and 19.4% for no AE group, respectively. OS was significantly improved in both the asymptomatic and symptomatic AE groups compared to the no AE group (hazard ratio [HR]: 0.15, 95% confidence interval [CI]: 0.03–0.65, P = 0.01 for the asymptomatic AE group; and HR: 0.60, 95% CI: 0.40–0.89, P = 0.01 for the symptomatic AE group, both adjusted by inverse probability of treatment weighting). The DCR was significantly higher in the asymptomatic AE group (100.0%) and the symptomatic AE group (91.8%) compared to the no AE group (60.0%) (P < 0.001).

Conclusion: The occurrence of adverse events related to atezolizumab and bevacizumab in patients with advanced HCC, when appropriately managed, significantly improves OS and treatment response. Furthermore, as asymptomatic imaging-detected irAEs may serve as favorable prognostic factors, proactive detection through imaging studies could be beneficial.

FRI-116

The changing epidemiology of patients with HCC receiving a first-line systemic therapy: insights from ARPES and ARTE databases (2008–2024)

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Background and aims: The epidemiological characteristics of patients starting first-line systemic therapy for hepatocellular carcinoma (HCC) have changed over time. This study examines shifts in demographics and disease profiles since the first systemic therapy was introduced.

Method: We compared baseline characteristics of patients receiving frontline systemic treatments from two Italian multicenter nationwide datasets of systemic treatments: ARPES (sorafenib, 656 patients, 2008–2019) and ARTE (atezolizumab and bevacizumab [atezo/bev], 393 patients, 2022–2024). ARPES included cardiometabolic risk factors, allowing reclassification from NAFLD to MASLD.

Results: Compared to ARPES, patients in ARTE showed a higher prevalence of females (19.9% vs. 15.1%; $p = 0.047$), a trend toward older age, and an increase in single-etiology MASLD (17.6% vs. 8.8%, $p < 0.001$), with fewer viral cases. More patients with HCV were in sustained virologic response at treatment start (72.8 vs 9.1%, $p < 0.001$). Additionally, patients included in ARTE had better liver function (ALBI grade-1: 52.6 vs 18.7%, $p < 0.001$), highest rate of no prior surgical/locoregional HCC treatments (38.5% vs. 28.1%, $p < 0.001$), less prevalent BCLC-C stage due to fewer cases with macrovascular invasion (31.0% vs. 43.1%, $p < 0.001$) and similar rate of metastatic disease. Lower likelihood of previous surgical/locoregional treatments was confirmed in the intermediate-stage subgroup (19.9 vs 35.2%, $p < 0.001$). Tumors larger > 6 cm (14.9% vs. 10.0%, $p < 0.001$) and ECOG-PS > 0, (32.0% vs. 23.3%, $p < 0.001$) were also more common in the ARTE database.

Conclusion: The increased prevalence of MASLD, a decline in viral cases, high SVR rates in HCV, and less previous locoregional treatments are likely to contribute to better liver function and more patients with intermediate stage. The challenges of surveillance in patients with MASLD may explain the increase in cases with no prior treatment, larger tumors, and higher ECOG-PS scores.

FRI-117

Impact of sarcopenia on medium-long-term survival of patients with hepatocellular carcinoma treated with lenvatinib

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Background and aims: Sarcopenia, defined as the loss of skeletal muscle mass and function, represents a prognostic factor in patients with hepatocellular carcinoma (HCC). Lenvatinib, a tyrosine kinase inhibitor, has shown comparable efficacy to sorafenib but lacks data on the prognostic role of sarcopenia in Caucasian patients. Therefore, this study aims to evaluate the predictive value of sarcopenia and other clinical factors on survival in Italian HCC patients treated with lenvatinib.

Method: A retrospective analysis was conducted on 41 patients receiving lenvatinib. Sarcopenia was defined on skeletal muscle index (SMI) measurements from pre-treatment abdominal CT scans on transverse images crossing the 3rd lumbar vertebra. Data collected included patient demographics and laboratory data, liver function (MELD and Child-Pugh score), tumor characteristics, performance status, and survival outcomes. Male patients with SMI <53 cm^2/m^2 with a body mass index (BMI) ≥25 or with SMI <43 cm^2/m^2 with a BMI <25, and female patients with SMI <41 cm^2/m^2 regardless of BMI were identified as having sarcopenia. The primary outcome was overall survival (OS). The Kaplan-Meier method was used to estimate survival curves, and they were compared using the log-rank test. Univariate and multivariate analyses for OS were made using the Cox proportional hazards model and hazard ratio (HR) and corresponding 95% confidence interval (95%CI). The area under the receiver operating characteristic curve (AUROC) was used to evaluate the cut-off values ensuring the lowest false negative and false positive results (best cut-off) to dichotomize continuous variables.

Results: Sarcopenia was identified in 20 (48.8%) patients. The Cox analysis selected as independent prognostic factors significantly associated with low OS alpha1-fetoprotein (AFP) >150 ng/mL (HR 2.22; 95%CI 1.042–4.73; $p = 0.039$) and serum albumin <3.5 gr/dL (HR 3.33; 95%CI 1.42–7.83; $p = 0.006$) but not sarcopenia. However,

evaluating prognostic factors influencing medium-long-term survival [>12 months after lenvatinib start: 21 patients, with 12 (57.1%) sarcopenics], only the presence of sarcopenia (HR 3.66; 95%CI 1.07–12.5; p = 0.039) and serum albumin <3.5 gr/dL (HR 5.94; 95%CI 1.07–32.94; p = 0.042) emerged as independent prognostic factors associated with reduced medium-long term survival. Cumulative survival rates of patients with sarcopenia and/or serum albumin <3.5 gr/dL at 15, 18, 21 and 24 months were lower than those with normal albumin and no sarcopenia (46.2%, 36.9%, 9.2% and 0% vs 100%, 87.5%, 62.5% and 62.5%, respectively; p = 0.002).
Conclusion: Sarcopenia associated with low albumin levels significantly influences medium-long term survival of HCC patients treated with lenvatinib. Studies with larger cohorts of enrolled patients are warranted to validate these findings.

FRI-118

Statins in patients with advanced hepatocellular carcinoma (HCC) treated with atezolizumab/bevacizumab: a propensity score-matched cohort analysis from ARTE an italian prospective multicentric dataset

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Background and aims: Statins have been suggested to exert anticancer properties by modulating angiogenesis, fibrosis, inflammation, and the tumor microenvironment, generating interest in their clinical use for chronic liver diseases (CLD) and hepatocellular carcinoma (HCC) chemoprevention. However, the effects of statin therapy in patients treated with immune checkpoint inhibitors for CLD-associated HCC remain unknown. This study primarily aimed to assess the potential effects of statins on overall survival (OS) and progression-free survival (PFS) in patients with advanced HCC treated with atezolizumab and bevacizumab (A+B).
Method: The ARTE dataset, a retro-prospectively maintained database, includes 305 consecutive patients with unresectable HCC treated with A+B, enrolled from 12 tertiary care centers in Italy. From the original cohort, a 1:1 propensity score matching was performed to balance potential confounding factors between 63 patients on statin therapy and those not on statins. The primary outcomes were OS and PFS, while secondary outcomes included all-cause mortality, liver-related death, treatment interruption, and the incidence of liver decompensation events.
Results: Among the matched population of 126 patients, 75% had liver cirrhosis, with metabolic disfunction-associated steatotic liver disease (MASLD) being the most common etiology. Ninety-seven patients (32%) had diabetes. No significant differences were found between statin users and non-usersin terms of OS, PFS, or liver-related death. Additionally, the log-rank test revealed no significant difference between the groups in terms of treatment interruption due to liver decompensation events (p = 0.28).
Conclusion: Statin use did not have any impact on OS, PFS, or on reducing mortality or treatment interruption due to liver-related decompensation events in patients with advanced HCC treated with A+B.

FRI-119-YI

Evaluation of the intratumoral immune microenvironment in hepatocellular carcinoma treated with liver surgery after selective internal radiation therapy

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Background and aims: Selective internal radiation therapy (SIRT) is a promising treatment for locally advanced HCC, particularly as a bridge to liver resection (LR) or transplantation (LT), but its effect on tumor microenvironment/immune activation must be understood. The study aimed to evaluate the intra-tumoral immune microenvironment and gene expression profiles in HCC patients who underwent LR/LT post-SIRT and its impact on outcomes.

Method: Thirty-six HCC patients down-staged with SIRT before LR or LT at two French University Hospitals (Henri Mondor, Beaujon) between December 2014 and October 2023 were included. RNA was extracted from tumoral tissue of formalin-fixed paraffin-embedded surgical liver samples. RNA sequencing was performed to identify differentially expressed genes (DEGs). Immune infiltrates were estimated using the MCP-counter method. All statistical analyses were performed with R 4.2.0.
Results: Twenty-five HCC patients (84% male, median age 67 years, 80% with cirrhosis) treated with LR/LT post-SIRT were included in the final analysis. Thirteen patients (52%) were BCLC-C, 10 BCLC-B (40%), 2 BCLC-A (8%). According to RECIST1.1, ten patients (40%) achieved a complete response (CR) 6 months post-SIRT, 12 (48%) partial response (PR), and 3 (12%) stable disease (SD). Fourteen patients (56%) experienced tumor recurrence post-surgery, 11 (44%) died. Sixty-five DEGs were found in patients with CR *vs*. others. Enrichment analysis revealed that the *under*-expression of gene set pathways is related to the regulation of immune response, proliferation/carcinogenesis of an aggressive subtype of HCC, and prediction of early recurrence in CR cases compared to others. SD milieu showed significantly lower neutrophils (p = 0.027) than CR and myeloid dendritic cells (p = 0.049) than PR. No significant differences in immune infiltrates were observed between patients with and without HCC recurrence. Forty-nine DEGs were found in patients who developed recurrence compared to others: *up*-regulated genes were involved in the inflammatory response, HCC progression, and cell differentiation/growth. Gene enrichment analysis showed that *over*-expression of gene set pathways was related to immune response. The six genes more expressed in the top 10 enriched pathways were CXCL5, CXCL8, CLN8, EREG, TRIM29, and MT1G. Patients with MT1G and CLN8 > mean values had lower recurrence-free survival than those without (p = 0.044, p = 0.0022, respectively). Cox univariate analysis showed the mean of the six most *over*-expressed genes as independent predictors of recurrence (p = 0.002), also confirmed in the multivariate model (p = 0.010).
Conclusion: SIRT modulates the HCC immune microenvironment. CR showed a downregulated immune response, and patients with recurrence had an inflammatory profile in the tumor tissue. Thus, this may provide a rationale for testing neoadjuvant and adjuvant immunotherapy in this setting of patients.

FRI-120

Recompensation before first-line systemic therapy for hepatocellular carcinoma yields comparable survival to compensated cirrhosis

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Background and aims: The concept of "recompensation" in cirrhosis underscores the dynamic nature of the disease and its impact on prognosis. However, the effect of recompensation in patients with hepatocellular carcinoma (HCC) undergoing first-line systemic therapy remains unclear. We compared survival outcomes following first-line systemic treatments for advanced HCC among patients with compensated, decompensated, and recompensated cirrhosis.
Method: A Latin American multicenter, prospective cohort study was conducted from 2018 to 2024, involving patients with HCC and Child-Pugh class A or B7 who received systemic therapy. Patients with moderate to severe ascites, clinical jaundice, hepatic encephalopathy grades III-IV, or ECOG >2 were excluded. At the initiation of first-line therapy, patients with cirrhosis were categorized as compensated (never decompensated), decompensated, or recompensated. Kaplan-Meier survival analysis and Cox proportional hazard models were estimated.
Results: Among 306 patients receiving first-line systemic therapy (sorafenib 60.5%, atezolizumab + bevacizumab 29.7%, lenvatinib 9.1%). The median follow-up since first line systemic therapy was 9.2 months, with a median survival of 16.0 months (95% CI 12.9–18.3 months). Significantly lower survival was observed in patients with cirrhosis (n = 240) compared to non-cirrhotic patients HR 1.75 (P = 0.015), and in those with baseline Child Pugh score B (vs A) [adjusted HR 1.87; P = 0.005]. Among patients with cirrhosis, 30.4% had a history of hepatic decompensation. Of these, 57.5% (95% CI 45.4–69.0%) achieved recompensation over a median period of 12 months. At the time of first-line therapy initiation, 69.6% were compensated, 17.5% recompensated, and 12.9% decompensated. Median survival was significantly shorter in decompensated patients (8.6 months) compared to compensated patients (17.2 months) [aHR 1.91 (95% CI 1.04–3.5); P = 0.03]. No significant difference in survival was observed between recompensated and compensated groups [aHR 1.28 (95% CI 0.79–2.1); P = 0.31]. The primary reason for treatment discontinuation in both compensated and recompensated groups was tumor progression, and similar access to second-line therapies was observed.
Conclusion: Patients with advanced HCC and recompensated cirrhosis may benefit from systemic therapies. Therefore, a follow-up observation period is recommended before ruling out systemic treatment in decompensated cirrhosis.

FRI-121

Radiofrequency ablation is safe in patients with hepatocellular carcinoma and thrombocytopenia

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Background and aims: Radiofrequency ablation (RFA) is widely used in clinical practice because it is the curative and safe interventional procedure for very early and early-stage hepatocellular carcinoma (HCC). Thrombocytopenia is often considered a relative contraindication to RFA owing to a concern about an increased bleeding risk. Current clinical guidelines recommend a platelet count of 50×10^9/L as a safe threshold for patients undergoing RFA. This study aims to evaluate the efficacy and safety of RFA in cirrhotic patients with HCC and severe thrombocytopenia.
Method: A retrospective analysis was conducted on 166 cirrhotic HCC patients who underwent RFA at West China Hospital from January 2017 to January 2024. Patients were categorized into two groups based on preoperative platelet counts: Group A ($<50 \times 10^9$/L) and Group B ($\geq 50 \times 10^9$/L). The primary outcome was perioperative major hemorrhage, while secondary outcomes included overall survival (OS), tumor response, and postoperative complications.
Results: Perioperative major hemorrhage occurred in 2.4% of the patients, all of whom were in Group B. Postoperative complications were observed at similar rates in both groups, with no significant differences noted. There were also no statistically significant

differences between the two groups in overall survival (OS), with 1-year OS rates of 97.6% in Group A and 96.6% in Group B, and 3-year OS rates of 86.3% in Group A and 94.6% in Group B. Tumor responses were comparable between the groups as well.
Conclusion: RFA is a effective and safe treatment for cirrhotic patients with HCC, even with severe thrombocytopenia. A platelet count below 50×10^9/L should not contraindicate RFA.

FRI-122
Impact of hepatocellular carcinoma multidisciplinary team on treatment outcomes: an analysis from the Middle East and North Africa region

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Background and aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality worldwide. Its management is complex, requiring a multidisciplinary team (MDT) approach to optimize outcomes. This study aimed to evaluate the impact of MDT involvement on survival outcomes in HCC patients across the Middle East and North Africa (MENA) region.
Method: This retrospective cohort study included 1,250 HCC patients from Egypt, Oman, Saudi Arabia, and Türkiye (2016–2023). Diagnoses were based on the Liver Imaging Reporting and Data System (LI-RADS). Patients were grouped by MDT involvement: Group 1 (808 patients) and Group 2 (442 patients). Kaplan-Meier survival analysis assessed survival outcomes, with survival defined as the time from diagnosis to death or last follow-up. Statistical significance was evaluated using the log-rank test.
Results: The mean age was 66 ± 12 years, with 74.7% male and 99% having cirrhosis. One-third (32.8%) had advanced disease, and 34.7% had end-stage disease. Half (50.5%) had Child-Pugh class B/C liver function. Group 1 had significantly longer mean survival (25.18 months, 95% CI: 23.27–27.10) compared to Group 2 (14.81 months, 95% CI: 12.88–16.75). Median survival was 14.0 months for Group 1 and 7.0 months for Group 2. Survival at 12 months was 55.4% for Group 1 versus 34.2% for Group 2 ($P < 0.0001$). Group 2 had a 67.7% higher mortality risk (HR = 1.6771, 95% CI: 1.4712–1.9118).
Conclusion: MDT involvement significantly improves survival outcomes in HCC patients. This emphasizes the need for coordinated, specialized care to improve prognosis in diverse healthcare settings.

FRI-123
The dose of radiation absorbed by the tumor and the non-tumoral compartments does not impact peripheral immune markers after SIRT

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Background and aims: Selective Internal Radiation Therapy (SIRT) with Y90 microspheres is used to treat hepatocellular carcinoma (HCC) across tumor stages. Besides modulating the tumor micro-environment, SIRT may influence the immune response via a by-stander effect on immune cells that circulate through the tumor and non-tumor volume that absorbed radioactive beads. The NASIR trial has investigated the safety and efficacy of SIRT followed by nivolumab. This study investigates the peripheral immunological changes triggered by SIRT and their correlation with dosimetry parameters.
Method: Blood samples were collected from 39 patients enrolled in the NASIR trial before SIRT (t1) and three weeks after the procedure (t2). Immunological profiling was conducted using multiparametric flow cytometry. Voxel-based dosimetry analysis in post-SIRT PET imaging included a) the highest mean absorbed dose (Dmean) among the treated nodules for each patient, and the total tumor volume exposed to at least 120 Gy (V120), and b) the Dmean, maximum absorbed dose, and non-tumor liver volume receiving at least 30 Gy (V30).
Results: A significant reduction in total lymphocyte count was observed at t2 (−66.93%, CI 95% −68.71; −52.72; $p < 0.0001$), while other leukocyte populations remained unchanged. When subset populations were studied, a decline was observed in CD4, CD8, B, NK and NKT cells together with a marked increase in activated cells expressing programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG3), and T cell immunoglobulin and mucin-domain containing-3 (TIM3), as well as functional markers like CD39 and PD-1 ligand (PDL1). These changes were noted across CD4 and CD8 T cells, regulatory T cells, myeloid-derived suppressor cells (MDSCs), monocytes, and dendritic cells. However, these alterations were in most cases not linked to the dose of radiation absorbed by the tumor or non-tumor liver volumes. Exceptions included significant correlations between the highest Dmean or V120 with CD4 T cells expressing CTLA-4 or LAG3. Additionally, increases in NK cells and

dendritic cells were correlated with radiation exposure to the non-tumor liver, as measured by Dmean and V30.
Conclusion: SIRT-induced lymphopenia suggests immune modulation. However, the increase in immune checkpoints and functional markers across various immune subsets indicates a potential antigen recognition response, associated to activation or exhaustion, and provides a rationale for combining Y90 with immune check-point inhibition beyond anti-PD1 antibodies. These findings highlight the complex relationship between radiation and immune modulation, suggesting that radiation dose may influence immune pathways.

FRI-124

Sub-symptomatic Child-Pugh score 7 shows comparable survival outcomes to Child-Pugh score 6 in hepatocellular carcinoma patients treated with Atezolizumab and Bevacizumab

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Background and aims: Atezolizumab plus bevacizumab (Ate/Bev) has demonstrated remarkable outcomes and is now established as a first-line treatment for patients with advanced hepatocellular carcinoma (HCC), particularly those with a Child-Pugh score (CPS) of 5 or 6. However, given the limited data regarding its efficacy in patients with CPS 7, this study aims to evaluate the effectiveness of Ate/Bev in CPS 7 patients and to identify specific subgroups within CPS 7 that may benefit from this treatment.
Method: This study included patients with advanced HCC who received Ate/Bev as first-line therapy between September 2020 and December 2023 at six university hospitals. The primary outcome was overall survival (OS), while secondary outcomes included progression-free survival (PFS) at six months and treatment response. Within the CPS 7 group, patients were further subdivided into two groups based on combinations of CPS variables and their associated survival risks.
Results: Among the 340 included patients, those with CPS 5 (n = 169) demonstrated the highest overall survival (OS) and progression-free survival (PFS), followed by patients with CPS 6 (n = 87) and CPS 7 (n = 84) ($P < 0.05$). For the variables comprising CPS, the hazard ratio (HR) for OS increased with elevated total bilirubin (TB) levels and was lower in patients with mild ascites ($P < 0.05$). Regarding albumin levels, the HR for OS tended to decrease as albumin levels dropped to 2.8 g/dL. Based on these findings, CPS 7 patients were further classified into two subgroups: sub-symptomatic (TB <2 mg/dL, 3.5 > Alb ≥2.8 g/dL, and mild ascites) and symptomatic (other CPS 7). Compared to patients with CPS 6, those in the sub-symptomatic CPS 7 group exhibited comparable OS and PFS at six months, while symptomatic CPS 7 patients had significantly lower OS and PFS at six months ($P < 0.05$). Multivariate analysis identified symptomatic CPS 7 as a significant risk factor for both OS and PFS ($P < 0.01$).
Conclusion: This study suggests that Ate/Bev treatment can be effective in sub-symptomatic CPS 7 patients, highlighting the potential to broaden treatment eligibility for this population.

FRI-125

Real-world treatment patterns and outcomes among patients with hepatocellular carcinoma managed at a single centre in Switzerland

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Background and aims: Data on hepatocellular carcinoma (HCC) treatment patterns in Europe are limited, with no existing studies specifically focusing on Switzerland. This retrospective, observational study aimed to present real-world data on the characteristics, treatment patterns, and outcomes among patients with HCC in Switzerland.
Method: We performed a retrospective study between 1 January 2010 and 30 June 2022 on patients with HCC included in a prospective cohort at Inselspital in Switzerland. The index date was HCC diagnosis date. The analysis included patients with newly diagnosed HCC of Barcelona Clinic Liver Cancer (BCLC) stage 0 (very early), A (early), B (intermediate), or C (advanced) who were assigned to therapy. Patients were excluded if they had undergone liver transplantation, had fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma/HCC subtypes, or had less than 6 months of follow-up. Treatment patterns were assessed using descriptive statistics and time-to-event outcomes using the Kaplan–Meier method.
Results: Overall, 362 patients were included. Mean age was 67.1 years (standard deviation [SD] 9.9), 82% were male, and 75% had cirrhosis (of which 61% had Child-Pugh score A). The most common aetiology was alcohol-related liver disease (44%), and the most common comorbidities were diabetes (32%) and chronic hepatitis C virus (31%). Baseline disease stages were BCLC 0 (10%), BCLC A (44%), BCLC B (28%), and BCLC C (16%). The most common first treatment was ablation (41%) for BCLC A, embolisation (26%) for BCLC B, and first line (1L) systemic tyrosine kinase inhibitor therapy (54%) for BCLC C. Of BCLC C patients, 3.4% received 1L immunotherapy (atezolizumab/bevacizumab). In BCLC stage C patients, the median duration of 1L systemic therapy was 5.1 months (95% confidence interval [CI], 3.1–7.2). Sankey plots showed heterogeneous treatment patterns from baseline to end of follow-up for BCLC stages A–C, with some patients receiving up to 7 treatments. In BCLC stage A patients, the median time to recurrence following resection was 56.1 months (95% CI, 21.1-not available) and median time to relapse following ablation was 16.6 months (95% CI, 12.4–48.8), with 75% of patients who experienced recurrence having an early recurrence (within ≤2 years). In BCLC stage B patients, the median time to progression (TTP) following embolisation was 16.3 months (95% CI, 9.0–21.3). In BCLC stage C patients, from the start of 1L systemic therapy, the median TTP was 6.3 months (95% CI, 4.7–9.9), and median overall survival was 11.3 months (95% CI, 9.1–19.6).
Conclusion: These findings underscore the need for tailored treatments, enhanced surveillance, and novel therapies to improve patient outcomes. Further research should focus on optimizing treatment sequences and integrating emerging therapies to improve HCC management.

FRI-126

Predictors for postembolization syndrome in a cohort of patients with hepatocellular carcinoma

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Background and aims: Postembolization syndrome (PES) is a frequent complication of transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). Evolution of PES varies from complete remission under symptomatic therapy to decompensation of liver disease and increased mortality. The aim of this study is to determine predictive factors for the development of PES, thus

establishing a pre-interventional risk and possibly change the therapeutic strategy in these patients.
Method: We performed a retrospective observational study in 539 patients who underwent a first TACE procedure in our center between June 2017 and June 2024. We recorded demographic data, etiology and staging of liver disease, presence of comorbidities, liver function tests, inflammatory markers, location and size of HCC treated nodule. PES was defined as fever and upper right quadrant pain appearing 24–48 hours after the procedure. All procedures were performed using highly selective catheters, via the femoral artery.
Results: The mean age in the study lot was 63.25 ± 25.13 years, with a predominance of male gender (71.8%). Etiology of liver disease was as follows: 33.9% HCV, 19.4% HBV, 10.3% HBV + HDV, 15.7% MASLD, 17.4% alcohol-related and 2.9% idiopathic. The most frequent comorbidities in the group were: diabetes (24.4%), arterial hypertension (33.0%) and chronic kidney disease (14.2%). PES appeared in 48 patients (8.9%) and was managed medically; 3 patients presented acute decompensation of cirrhosis. The following risk factors for PES were demonstrated: viral etiology (OR = 1.45 95% CI [1.21–1.76] p = 0.03), age over 60 (OR 2.21 95% CI [1.98–2.52] p = 0.01), diabetes (OR 1.98, 95% CI [1.56–2.05] p = 0.03), nodule larger than 5 cm (OR 3.13, 95% CI [2.78–3.42] p < 0.01). Biochemical markers associated with PES were: C reactive protein >10 mg/dL (OR 1.87, 95% CI [1.51–2.07] p = 0.03) fibrinogen over 400 mg/dL (OR 2.13, 95% CI [1.95–2.43] p = 0.02) and ALT over 100 U/L (OR = 2.52 95% CI [2.31–2.83] p < 0.01).
Conclusion: In patients with risk factors for PES, close monitoring as well as preventive anti-inflammatory therapies may be indicated. Further analysis is required to make recommendations regarding treatment option changes to avoid PES occurrence if technically possible.

FRI-131
Updated network meta-analysis of first-line systemic therapies for advanced hepatocellular carcinoma: consistent role of TACE
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Background and aims: We conducted an updated network meta-analysis to evaluate and identify the optimal first-line treatment for advanced hepatocellular carcinoma (HCC) among all relevant transarterial and targeted therapies.
Method: We analyzed 25 phase 2 or 3 randomized controlled trials involving 14,148 patients with metastatic or unresectable HCC between 2008 and 2024, which evaluated 20 systemic agents and 4 transarterial interventions combined with systemic therapy, using sorafenib or lenvatinib as standard controls. Primary outcome was overall survival (OS), and secondary outcomes included progression-free survival (PFS) and grade 3–4 adverse events. Subgroup analyses were conducted to assess individual treatment efficacies in specific clinical settings.
Results: Transarterial chemoembolization (TACE) combined with lenvatinib provided the greatest improvement in OS compared to sorafenib, with a hazard ratio of 0.41 (95% confidence interval, 0.30–0.58), followed by sintilimab+IBI305 (0.57; 0.43–0.75), camrelizumab+rivoceranib (0.62; 0.48–0.80), atezolizumab+bevacizumab (0.66; 0.51–0.85), lenvatinib+pembrolizumab (0.77; 0.62–0.97), and tremelimumab+durvalumab (0.78; 0.64–0.95). These combinations, except tremelimumab+durvalumab, were also regimens significantly superior to sorafenib regarding PFS. TACE+lenvatinib was ranked first in OS analyses with the other current standard-of-cares (lenvatinib, atezolizumab+bevacizumab, and tremelimumab +durvalumab) as a control. TACE+lenvatinib, sintilimab+IBI305, and atezolizumab+bevacizumab demonstrated consistent significance in extending OS over sorafenib in subsets with portal invasion, extrahepatic metastasis, and hepatitis B. All immunotherapy-based combinations were significantly associated with a higher risk of adverse events than sorafenib.
Conclusion: Our first-line analysis consistently scored TACE+lenvatinib best for survival outcomes, followed by various immunotherapy-based combinations in advanced HCC. This hierarchy was sustained in aggressive tumors or hepatitis B carriers.

FRI-132
Non-selective beta blockers: mitigating hepatocellular carcinoma progression and enhancing sorafenib efficacy through Wnt/beta-catenin pathway modulation
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Background and aims: One of the main causes of cancer-related death globally is hepatocellular carcinoma (HCC). HCC is characterized by aggressive tumour growth and resistance to standard treatments like sorafenib (SOR). Growing evidence suggests that carvedilol (CAR) and other non-selective beta-blockers (NSBBs) may enhance therapeutic outcomes by modulating apoptotic pathways thereby slowing down tumour growth. Therefore, this study evaluates the effect of combined therapy of CAR and SOR on HCC growth, inflammatory cytokines, apoptosis induction, epithelial-to-mesenchymal transition (EMT) markers, and the Wnt/beta-catenin signalling pathway.
Method: A diethylnitrosamine (DEN)-induced HCC model was established in male Sprague Dawley rats, followed by treatment with SOR, CAR, or their combination. Tumour progression was assessed through macroscopic and histological analysis. Relative gene expression of EMT markers (Twist-1, Snail-1, Axin-1) and apoptotic markers (BAX, Bcl-2) was quantified using qRT-PCR across normal, positive control, and treated groups. Caspase-3 levels were measured by immunohistochemistry, whereas the levels of inflammatory markers (tumour necrosis factor alpha; TNF- α and IL-6), EMT markers (Twist-1 and Snail-1), and the apoptotic marker GSK-3beta were assessed using ELISA.
Results: Combination therapy reduced malignant nodules and preserved liver architecture compared to DEN-treated group. CAR treatment increased caspase-3 immunoreactivity and BAX expression as well as decreased Bcl2 levels, suggesting enhanced anti-proliferative potential. Notably, the combination therapy depicted anti-inflammatory potential by reducing IL-6 and TNF-α levels by 51% and 59%, respectively, in comparison to the DEN-treated group. Significant modulation was seen in EMT markers, with Snail-1 and Twist-1 downregulated in the combination group. Furthermore, an increase in both Axin-1 gene expression and GSK-3beta levels was observed, suggesting an interference with the Wnt/beta-catenin pathway.
Conclusion: These results might imply that CAR improves SOR's efficacy in HCC by suppressing tumour growth, promoting apoptosis, regulating inflammatory cytokines, and blocking EMT via Wnt/beta-catenin signalling pathway inhibition.

FRI-133
Immunoprofiling-based machine learning model predicts outcomes to pembrolizumab plus lenvatinib in patients with unresectable hepatocellular carcinoma
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Background and aims: Immunotherapy combinations are front-line treatment for unresectable hepatocellular carcinoma (uHCC), but outcome predictors remain challenging. Despite LEAP-002 trial failed to meet its primary endpoint, the combination of pembrolizumab and lenvatinib (PL) provide longer-term efficacy in responders. We aimed to investigate how immune profiling of uHCC correlates with responses to PL therapy.
Method: From July 2019 to July 2023, 51 patients undergoing front-line PL therapy for uHCC were prospectively enrolled. Pre-treatment peripheral blood mononuclear cells (PBMCs) were collected and analyzed for immunophenotyping and its association with tumor response. Twelve responders and eight non-responders were randomly assigned to develop a PBMC-based machine learning (ML) model for predicting tumor response. Remaining cases were allocated for model testing.
Results: During a median follow-up of 10.8 months (interquartile 5.3–19.1 months), 16 patients experienced objective tumor response, 22 had stable disease and 11 developed primary progression. Responders has higher percentages of total T cells, CD8+, PD1+CD4+, PDL1+CD8+ T cells and PD1+CD8+ NK cells, while PDL1+ monocytes were more prominent in non-responders. Through recursive feature elimination, six key immunotypic cells were identified, and a PBMC-based ML model was developed to predict tumor response using random forest technique (AUROC: 0.8084). In the validation group, the model effectively predicted tumor response with 85.7% accuracy (100% sensitivity, 66.7% specificity, AUROC: 0.9167).
Conclusion: Peripheral immune signatures are associated with the efficacy of PL combination immunotherapy in uHCC. A PBMC-based ML predictive model offers a non-invasive approach to identify patients likely to benefit from this treatment.

FRI-134

Impact of radiation dose on treatment response and survival outcomes in solitary hepatocellular carcinoma treated withY90 selective internal radiation therapy: a retrospective single-center study

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Background and aims: Selective internal radiation therapy using Yttrium-90 (Y90) microspheres has emerged as a promising locoregional treatment for unresectable HCC. Radiation dose delivered to the tumor is critical in treatment outcomes in Y90. While higher radiation doses have been associated with better tumor response and prolonged survival, the optimal dosing strategy remains a subject of research. We aim to evaluate the impact of the delivered radiation dose on treatment response and overall survival in patients with solitary HCC undergoing Y90 with resin microsphere.
Method: This is a retrospective study of consecutive patients treated with Y90 resin microspheres (SIR-Spheres, Sirtex Medical, USA) for solitary HCC between 2020 and 2023 at Singapore General Hospital. Excluded were patients lost to follow-up and those with other concomitant cancer. Patient demographics, clinical history, pertinent laboratory values and radiological findings were collected. Treatment response was determined using CT and/or MRI based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Ethical approval was granted by the Institutional Review Board (2023/2062).
Results: 269 patients received Y90 during the study period, of which 96 met the inclusion criteria. Of these patients, 43 were BCLC A and 53 were BCLC C stage at the time of diagnosis. The median follow-up duration was 19.5 months, calculated from the time of diagnosis to the most recent follow-up or date of death, whichever occurred first. The median overall survival (OS) for the whole cohort was not evaluable at time of analysis. 27 patients received high dose (>250 Gy) treatment (median = 350.29 Gy, IQR = 159.2 Gy). The median survival for BCLC C patients (n = 14/27) was 30.3 months (95% CI: 17.1 – NE). Among patients that received high dose treatment, three (11.1%) achieved complete response (CR), while majority had partial response (PR) 21/27 (78%), and 2/27 had stables disease (SD). Two patients were downstaged to resection and radiofrequency ablation respectively. The mean percentage response in tumor size shows a reduction of 22.5% (SD = 21.59%) from baseline.
Conclusion: A higher Y90 dose delivered to unresectable solitary HCC showed higher tumour responses but the optimal dosing strategy for maximizing treatment efficacy without increasing toxicity remains unverified. We planned future studies to explore the underlying mechanisms driving the variability in response to higher radiation doses.

FRI-135

Pre-treatment serum IgG levels predict immune-related adverse events in HCC patients treated with atezolizumab plus bevacizumab

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Background and aims: The advent of immune checkpoint inhibitors (ICI) has dramatically extended the prognosis for patients with hepatocellular carcinoma (HCC). However, the diagnosis and management of immune-related adverse events (irAEs) induced by ICIs have become critical challenges. This study aimed to identify predictive factors for irAEs in HCC patients treated with ICIs.
Method: We retrospectively analyzed 169 patients with unresectable HCC treated with atezolizumab plus bevacizumab. Risk factors for irAEs were identified in a training cohort of 112 patients and validated in a separate cohort of 57 patients. Adverse events were graded according to CTCAE version 5.0.
Results: Among all patients, 45 (27%) developed irAEs, including 27 in the training cohort and 18 in the validation cohort. The most common irAEs were endocrine disorders (17 cases), followed by skin disorders (10 cases). In the training cohort, patients who developed irAEs had significantly higher pre-treatment serum IgG levels compared to those who did not (median: 1592 vs. 1363 mg/dL, p = 0.03). No significant differences were observed in background liver disease, renal function, or hepatic reserve. Receiver operating characteristic (ROC) analysis showed that pre-treatment IgG was predictive for irAE occurrence (AUROC: 0.64), with an optimal cut-off value of 1375 mg/dL. Logistic regression analysis identified IgG > 1375 mg/dL as a significant predictor of irAEs (Odds Ratio [OR] 3.1, 95% Confidence Interval [CI] 1.1–8.5, p = 0.03). In the validation cohort, patients with IgG >1375 mg/dL had a significantly higher incidence of irAEs (44% vs. 16%, p = 0.04). Logistic regression analysis confirmed IgG >1375 mg/dL as a significant predictive factor (OR 4.1, 95%CI 1.1–14.6, p = 0.03).
Conclusion: Pre-treatment serum IgG levels may serve as a predictive biomarker for irAEs in HCC patients undergoing atezolizumab plus

bevacizumab therapy. These findings could guide patient management by identifying those at higher risk of irAEs.

MASLD – Clinical aspects except therapy

TOP-396-YI

Multimorbidity, disease clusters and all-cause mortality in people with metabolic dysfunction association steatotic liver disease in UK Biobank

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD), a hepatic manifestation of metabolic syndrome, is associated with various extrahepatic diseases. Multimorbidity is associated with adverse health outcomes. This study investigated the prevalence of extrahepatic multimorbidity, disease clusters, and their associations with all-cause mortality in people with MASLD.
Method: Using UK Biobank data, we identified MASLD cases based on liver steatosis and cardiometabolic risk factors. Multimorbidity was defined as the presence of ≥2 conditions from a predefined list of 46 diseases. Latent class analysis was used to derive disease clusters separately for males and females. Risk factors for cluster membership were identified using multinomial logistic regression, and associations with all-cause mortality were assessed using multivariable Cox regression.
Results: Among 118,751 participants with MASLD (mean age 57.5 years; 44% females), 25,842 (22%) had multimorbidity (25% of females, 27% of males). In females, five disease clusters were identified: respiratory (prevalence 30%), mental health (20%), cancer (13%), cardio/cerebrovascular (11%), and thyroid/respiratory/osteoarthritis (27%). In males, the clusters were respiratory (27%), cardiovascular (22%), mental health (13%), cerebrovascular (8%) and respiratory/cancer/osteoarthritis (29%). Asians were less likely to belong to the mental health cluster, while the cardio/cerebrovascular clusters were more common in smokers, but less common in females with high physical activity.
Over a median of 13-year follow-up, 13,609 deaths occurred (5,034 females). Multimorbidity was associated with significantly higher mortality, with hazard ratios (HRs) of 2.00 (95% CI: 1.91–2.09) in males and 1.76 (1.67–1.87) in females. Mortality risk varied by cluster. In males, the cardiovascular cluster had the highest hazard ratio (HR, 2.65 [2.48–2.84]), followed by cerebrovascular (2.42 [2.16–2.70]), with lower HR in mental health (1.57 [1.40–1.77]) and respiratory (1.58 [1.45–1.72]) clusters. In females, the cardiovascular cluster had the highest HR (2.97 [2.68–3.30]), followed by cancer (2.48 [2.23–2.77]), mental health (1.50 [1.33–1.70]) and respiratory (1.54 [1.40–1.69]) clusters.
Conclusion: Multimorbidity significantly increases mortality in MASLD population, with cardio/cerebrovascular and cancer clusters posing the highest risks. These findings highlight the need for integrated care models and targeted interventions that prioritize prevention of these diseases in MASLD populations.

TOP-409

Carriage of rare pathogenic APOB variants predispose to severe metabolic-associated steatotic liver disease and hepatocellular carcinoma

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has a strong inherited component, which is not fully accounted for by common genetic variation. Carriage of rare loss-of-function (LoF) variants in Apolipoprotein B (*APOB*) has been linked to increased susceptibility to steatosis, but the contribution to cirrhosis and hepatocellular carcinoma (HCC) is still disputed. This study aimed to determine the clinical impact of APOB gene variants in a cohort of patients with MASLD and advanced cirrhosis or HCC.
Method: We investigated the impact of LoF *APOB* variants in a clinical cohort of people with MASLD and advanced fibrosis or HCC (advanced MASLD; n = 510) vs. healthy controls, a family study (n = 43 and a meta-analysis of literature), and the population-based UK Biobank (UKBB) cohort (n = 416,331) on clinical outcomes and lipidomics/metabolomics/proteomics.
Results: LoF *APOB* variants were strongly enriched in patients with advanced MASLD vs. healthy controls (aOR 13.8, 95% c.i. 2.7–70.7, p = 0.002), being observed in 1 in 22 cases and associated with lower circulating lipids, but higher disease activity and fibrosis scores ($p < 0.05$). Through familial studies of probands with advanced MASLD, *APOB* variants segregated with inheritance of liver steatosis and fibrosis ($p < 0.05$). In UKBB cohort, we observed increased risk of cirrhosis and HCC in patients with MASLD (aOR 2.01, 1.51–2.53 and 4.01, 3.09–5.15, respectively), with the effect being larger for rarer variants (aOR 9.88, 8.8–10.96 and aOR 27.2, 25.26–29.08, respectively). Remarkably, we observed a dissociation between the impact of variants specifically affecting ApoB100 and very low-density lipoprotein (VLDL) secretion—showing a larger impact on circulating lipoprotein levels and the risk of cirrhosis—and those impairing ApoB48 and chylomicron secretion, which were associated with immunological biomarkers and a selective increase in the risk of HCC (aOR 5.9, 4.8–6.9).

Conclusion: Carriage of rare LoF *APOB* variants is associated with advanced MASLD, with distinct contributions from impaired secretion of VLDL and chylomicrons. Genotyping in patients with MASLD may improve risk stratification and case finding and enhance patient management.

TOP-410

When is a liver biopsy necessary? Predictive factors of autoimmune hepatitis in patients with metabolic dysfunction-associated steatotic liver disease and positive autoantibodies

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Background and aims: One in four people with metabolic dysfunction-associated steatotic liver disease (MASLD) presents positive autoantibodies, for which it is recommended to rule out the coexistence of autoimmune hepatitis (AIH). This entails performing liver biopsies (LB), many of which ultimately prove to be unnecessary. Despite the frequency of this situation, there are no established criteria to recommend or discourage performing LB.
Method: Prospective study. Patients with MASLD and antinuclear (ANA), anti-smooth muscle (ASMA), or anti-liver-kidney microsomal (anti-LKM) antibodies ≥1: 40 (+ve). Patients with positive anti-mitochondrial antibodies, absence of histological steatosis, another liver disease, contraindication for LB, or refusal were excluded. AIH was diagnosed according to the International AIH Pathology Group. Logistic regression analysis of significantly associated variables was performed.
Results: Between January 2022 and August 2024, 142 patients were included: 56 years old, 57% women, 37% with another immune disease, body mass index 30.3 kg/m², pre or type 2 diabetes 45%, alanine aminotransferase (ALT) 57 U/L, immunoglobulin G (IgG) 1247 mg/dL, ANA +ve 98.5%, ASMA +ve 9%, anti-LKM +ve 0.7%. Twenty-eight patients (19.7%; 95% confidence interval [CI 95%]: 14–27) had immune liver disease: 19 AIH, 3 primary biliary cholangitis (PBC), 4 AIH/PBC, 2 granulomatous hepatitis. Multivariate analysis identified the following variables as independently associated (odds ratio OR [CI 95%]): age 1.057 (1.009–1.108; p = 0.02), ASMA or anti-LKM +ve 6.569 (2.011–21.462; p = 0.002), ANA >1:640 5.293 (1.036–27.048; p = 0.045), IgG >1800 mg/dL 6.468 (1.147–36.482; p = 0.034), and elevated AST or ALT 6.576 (0.743–58.195; p = 0.045). Using logistic regression, the following model was obtained to suspect immune liver disease and recommend or rule out LB in patients with MASLD and positive autoantibodies: (0.056×age) + (1.883×elevated AST or ALT) + (1.867×IgG >1800 mg/dL) + (1.882×ASMA or anti-LKM ≥1: 40) + (1.666×ANA > 640). For a cutoff point of 5, the diagnostic performance was: sensitivity 88.9%, specificity 53.1%, positive predictive value 34.3%, negative predictive value 94.5%, area under the receiver operating characteristic curve 0.83 (95% CI 0.73–0.93, p < 0.001). Applying the model, 55/142 liver biopsies (39%) would have been avoided, and 25/28 (90%) patients with immune liver disease would have been identified.
Conclusion: One in five patients with MASLD and positive autoantibodies presents immune liver disease. Applying a simple model based on age, antibodies, IgG, and transaminases allows its identification, reducing the number of unnecessary liver biopsies.

TOP-411-YI

Disease state transitions across the spectrum of steatotic liver disease significantly affect long-term incidence of cirrhosis among a national cohort of veterans in the United States

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Background and aims: Steatotic liver disease (SLD) encompasses a spectrum of disease states with etiologies influenced by whether precipitating causes are mainly metabolic vs. alcohol related. In real-world settings, patients may transition from one SLD disease state to another due to changes in alcohol use. Data are lacking in understanding how disease state transitions (DST) among patients with SLD affect long-term outcomes. We aim to evaluate DST patterns and its impact on long-term risk of cirrhosis among a national cohort of U. S. Veterans with SLD.
Method: Using national Veterans Affairs data, U.S. Veterans with metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD, or alcohol-related liver disease (ALD) were identified from 1/1/2010 to 12/31/2019 (with follow-up through 9/30/2024) (MASLD = hepatic steatosis (HS) + ≥1 cardiometabolic risk [CMR] and no alcohol use [AUDIT-C = 0]; MetALD = HS + ≥1 CMR and low-level alcohol use [AUDIT-C 1–2 for women, 1–3 for men]; ALD = HS + high-level alcohol use [AUDIT-C >2 for women and > 3 for men]). Long-term follow up with repeated measures of AUDIT-C were evaluated to assess for DST between aforementioned categories. Competing-risks analyses (censored for death) evaluated the incidence of cirrhosis (per 100 person-years [p.y.]) stratified by DST and performed separately by index diagnosis of MASLD, MetALD, or ALD. Comparisons of cirrhosis incidence between groups utilized the z-statistic.
Results: We identified 726,276 Veterans with MASLD (93.0% men, 67.2% age ≥60 y), 512,061 with MetALD (93.4% men, 57.4% age ≥60 y), and 212,540 with ALD (94.6% men, 52.6% age ≥60 y). Over a median follow-up of 8.5 years (IQR 5.3–12.6), 24.2% of MASLD patients had DST to MetALD, 2.6% to ALD, and 73.2% did not have DST. Compared to MASLD patients without DST, cirrhosis incidence was similar in those with DST to MetALD (0.40 vs. 0.43 per 100-p.y), but significantly higher with DST to ALD (0.74 vs. 0.40 per 100-p.y., p < 0.01). Among patients with baseline MetALD, 14.4% had DST to ALD, 40.3% to MASLD, and 45.3% remained as MetALD. Compared to MetALD patients without DST, cirrhosis incidence was higher with DST to ALD (0.49 vs. 0.24 per 100-p.y., p < 0.01) or to MASLD (0.44 vs. 0.24 per 100-p.y., p < 0.01). Among patients with baseline ALD, 43.3% had DST to MetALD, 15.9% to MASLD, and 40.8% remained as ALD. Compared to patients who remained as ALD, cirrhosis incidence was significantly lower with DST to MetALD (0.54 vs. 0.80 per 100-p.y., p < 0.01), but increased with DST to MASLD (1.00 vs. 0.80 per 100-p.y., p < 0.01).
Conclusion: Among a national cohort of U.S. Veterans with SLD, a large proportion experience DST due to changes in alcohol use patterns, which led to changes in long-term incidence of cirrhosis. These data underscore the critical need for timely assessment and

interventions to address high-risk alcohol use as well as optimizing CMR in patients with SLD.

TOP-412

Long-term mortality in steatotic liver disease is greatest in those with a combination of metabolic dysfunction and excessive alcohol consumption

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Background and aims: Steatotic Liver Disease (SLD) encompasses a spectrum of liver diseases characterized by hepatic steatosis resulting from metabolic dysfunction (MetD), excessive alcohol consumption (EAC), or other causes. Although the new nomenclature for SLD subtypes separates distinct categories, there may be some overlap between metabolic dysfunction associated steatotic liver disease (MASLD), Met-ALD, Alcohol Associated Liver Disease (ALD) which can be further subclassified into and ALD with MetD and ALD without MetD. We aimed to assess the prevalence and all-cause mortality of SLD subtypes using datasets from two periods from the United States' National Health and Nutrition Saverys (NHANES).

Method: Data were analyzed from NHANES III (1988–1994) and NHANES (1999–2016) with linked mortality records through 2019. SLD was defined as the presence of hepatic steatosis by ultrasound (NHANES III and U.S. Fatty Liver Index (US FLI) (NHANES 1999–2016). SLD subtypes were defined according to the consensus nomenclature and ALD was subcategorized based on MetD as the presence or absence of any cardiometabolic risks.

Results: A total of 33,373 participants were included: NHANES III (N = 13,852, mean age: 42.6 years; 48.4% male; 80.7% with MetD) and NHANES 1999–2016 (N = 19,521, mean age: 46.6 years; 48.9% male; 89.4% with MetD). Among NHANES III participants, 25.95% had MASLD, 0.56% had Met-ALD, 1.47% had ALD with MetD and 0.27% had ALD without MetD. Similar data from NHANES 1999–2016 showed increasing prevalence rates for MASLD (33.73%) and MetALD (1.35%) but stable for ALD with MetD (0.30%), and ALD without MetD (0.08%). After a median follow-up of 22.8 years for NHANES III participants (272,124 person-years), 4,092 deaths occurred. Mortality rates (per 1,000 person-years) were highest in ALD with MetD (23.76), followed by MetALD (23.10), ALD without MetD (20.95), MASLD (19.69), and controls without SLD (12.75). In Cox proportional hazards models adjusted for age, sex, race, income, marital status, education, and smoking, all-cause mortality was significantly higher for MetALD (HR: 2.82; 95% CI: 1.44–5.51), ALD with MetD (HR: 2.37; 95% CI: 1.51–3.73), and MASLD (HR: 1.20; 95% CI: 1.06–1.35) as compared to controls ($p < 0.05$). Similarly, after a median follow-up of 10.3 years for participants in NHANES 1999–2016 (196,283 person-years), 1,485 deaths occurred with mortality rates being highest in ALD with MetD (19.39), followed by MetALD (17.58), MASLD (10.68), as compared to controls without SLD (5.63).

Conclusion: Among SLD, MASLD, Met-ALD and ALD with MetD are associated with higher mortality than non-SLD controls. Furthermore, mortality rates are greatest in those with a combination of EAC and MetD (ALD with MetD and Met-ALD). This data underscores the importance of accurate assessment of alcohol consumption and MetD in clinical practice.

THURSDAY 08 MAY

THU-372

Hypertension combined with hyperlipidemia increased the risk of extrahepatic malignancy in the MASLD population

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) has been rebranded as metabolic dysfunction-associated steatosis liver disease (MASLD), incorporating additional metabolic factors. A strong link between NAFLD or MASLD and an elevated risk of carcinomas has been established. However, the specific role of cardiometabolic factors in the MASLD population related to carcinomas has rarely been addressed. The objective of our research was to identify metabolic factors, their combinations, and comorbidities associated with cancer in the MASLD population.

Method: The MASLD population was extracted from a hospital-based database across 11 canters in China. This population was established based on diagnostic criteria that accounted for 105,058 cases, including those with extrahepatic cancer. SAS was employed for statistical analysis, including logistic regression, with a significance level set at $P < 0.05$.

Results: A total of 6707 (6.38%) individuals with extrahepatic carcinoma were identified within the MASLD population, comprising 3436 males (51.23%) and 2188 individuals aged 50 to 59 years (32.62%). Lung cancer, thyroid cancer, and breast cancer were the three most common extrahepatic carcinomas. All cancers were more prevalent in males, except for thyroid cancer, which was evenly distributed between genders. Factors such as aging, male gender, pre-diabetes (HbA1c 5.7–6.4% and 2-hour post-meal blood glucose 7.8–11.0 mmol/L), type 2 diabetes mellitus, hyperlipidemia, triglycerides exceeding 1.7 mmol/L (OR 1.20, 95% CI: 1.13, 1.27), lower HDL-C (OR 1.11, 95% CI: 1.05, 1.18), and LDL-C over 3.4 mmol/L (OR 1.18, 95% CI: 1.08, 1.30) were associated with an increased risk of extrahepatic malignancy. Notably, the combination of hypertension and hyperlipidemia raised the risk of extrahepatic cancer by 2.17-fold (OR 2.17, 95% CI: 1.94, 2.43), followed by T2DM, hypertension, and hyperlipidemia at 2.15-fold (OR 2.15, 95% CI: 1.94, 2.39), and T2DM with hyperlipidemia at 1.73-fold (OR: 1.73, 95% CI: 1.54, 1.95). The use of anti-metabolic agents also increased the risk of extrahepatic cancer in the MASLD population [hypoglycemic agent (OR 1.51, 95% CI: 1.40, 1.63); antihypertensive drug (OR 1.31, 95% CI: 1.22, 1.41); lipid-lowering agent (OR 2.75, 95% CI: 2.53, 2.99)]. FIB-4 less than 1.3 significantly reduced the risk of extrahepatic cancer. Additionally, abnormal liver function, viral hepatitis, chronic kidney disease, cirrhosis, obstructive sleep apnea syndrome, and polycystic ovarian syndrome also elevated the risk of extrahepatic carcinomas.

Conclusion: Hypertension combined with hyperlipidemia significantly increases the risk of extrahepatic malignancies. FIB-4 less than 1.3 notably reduces the risk of extrahepatic cancer. Obstructive sleep apnea syndrome and polycystic ovarian syndrome are independent risk factors for extrahepatic carcinoma.

THU-373

Metabolic dysfunction-associated steatotic liver disease (MASLD) in italian women: is liver fibrosis independent from menopause?

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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is an emerging health concern among women, with menopause influencing its onset and progression. This study aimed to explore the connection between menopause and liver fibrosis in MASLD.
Method: Between October 2014 and September 2024, 149 non-cirrhotic women were enrolled in our MASLD outpatient clinic. Patients underwent a thorough evaluation, including physical activity and diet quality assessments, using validated questionnaires (IPAQ and REAP-S scores). Significant liver fibrosis was defined as liver stiffness ≥ 7 kPa on 2D-elastography. 10-year cardiovascular (CV) risk was assessed with ESC scores, and insulin resistance with TyG index.
Results: Of 149 women, 41 were pre-menopausal (median age 46 years, 17.1% fibrotic) and 108 post-menopausal (median age 61 years, 27.8% fibrotic). Women with fibrosis were older (median age 64 vs. 56 years, $p < 0.001$) and had higher rates of arterial hypertension (AH 64.9% vs. 43.8%, $p = 0.026$), type 2 diabetes (T2DM 40.5% vs. 16.1%, $p = 0.002$), and insulin resistance (TyG index: 4.9 vs. 4.7, $p = 0.024$). BMI, frequency of menopause status, age at menopause were similar between fibrotic and non-fibrotic women. Multivariate logistic regression analysis revealed that age (OR 1.068, $p = 0.002$) and T2DM (OR 3.633, $p = 0.004$) were independently associated with fibrosis. Compared to non-fibrotic, fibrotic post-menopausal women had poorer diet quality (REAPS score: 26 vs. 31, $p = 0.018$), higher rates of AH (73.3% vs. 46.2%, $p = 0.011$) and T2DM (40% vs. 17.9%, $p = 0.016$), accounting for a higher risk for major CV events (11.1% vs. 6.1%, $p < 0.001$). Multivariate logistic regression analysis confirmed that AH (OR 2.959, $p = 0.024$) and T2DM (OR 2.752, $p = 0.039$) were independently associated with fibrosis in post-menopausal women.
Conclusion: Among the metabolic features of MASLD, T2DM appears to be the primary driver of liver fibrosis in both pre- and post-menopausal women, while AH is associated with significant fibrosis only in the latter group. The study also underscores the impact of diet quality, which can be particularly challenging for menopausal women, possibly due to socioeconomic factors.

THU-374

Longitudinal dynamics and predictors of hepatic fibrosis and steatosis in people living with HIV: an egyptian cohort study

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Background and aims: In the era of antiretroviral therapy, liver disease continues to be a major source of morbidity and mortality among people living with HIV (PWH). This study evaluated the longitudinal changes of liver fibrosis and steatosis, identifying predictors of progression and regression in Egyptian PWH.
Method: A retrospective analysis included PWH with or without hepatitis coinfection who consecutively underwent screening for liver fibrosis and steatosis by transient elastography and associated controlled attenuation parameter (CAP) at Cairo University Hospitals HIV clinic, Egypt from September 2022 to November 2024. Fibrosis progression was defined as development of significant fibrosis [liver stiffness measurement (LSM) ≥8 kPa], and fibrosis regression, defined as transitioning to LSM <8 kPa in patients with baseline significant fibrosis. Hepatic steatosis progression was defined as development of any grade hepatic steatosis (CAP ≥248 dB/m). Longitudinal changes in LSM and CAP were evaluated using linear mixed-effects models. Cox regression analysis was used to assess predictors of hepatic steatosis and fibrosis progression.
Results: Of 428 participants, 78.7% were male, median age was 35 years, 13% reported occasional alcohol intake and 13.3% had been cured of hepatitis C (HCV). Over a median follow-up of 11 months (IQR: 7–16), 8.24% (n = 36) had significant fibrosis at baseline. Fibrosis progression occurred in 3.66 cases per 100 person-years, while regression occurred in 42.6 cases per 100 person-years. Hepatic steatosis was present in 27.8% of participants at baseline, with progression observed in 28.98 cases per 100 person-years and regression in 60.12 cases per 100 person-years. Age, BMI, and detectable HIV viral load were significant predictors of fibrosis progression (hazard ratio [HR]: 1.04 /year, 95% CI: 1.02–1.06, $p < 0.001$; HR: 1.04/unit increase, 95% CI: 1.01–1.07, $p = 0.003$; and HR: 2.20, 95% CI: 1.30–3.75, $p = 0.004$, respectively). HCV positivity doubled the risk of fibrosis progression (HR: 2.08, 95% CI: 1.22–3.55, $p = 0.007$). BMI was the strongest predictor of steatosis severity, with CAP increasing by 1.95 units/BMI unit (95% CI: 1.35–2.55, $p < 0.001$). CAP also increased by 0.77 units/year of age (95% CI: 0.29–1.26, $p = 0.002$) and by 8.53 units/HbA1c category increment (95% CI: 0.32–16.73, $p = 0.042$). Longitudinal trends revealed significant increases in BMI ($\beta = 0.11$ units/month, 95% CI: 0.06–0.16, $p < 0.001$), HbA1c ($\beta = 0.07$ units/month, 95% CI: 0.02–0.11, $p = 0.006$), and LDL ($\beta = 0.48$ units/month, 95% CI: 0.17–0.78, $p = 0.002$).
Conclusion: A multidisciplinary approach is essential for managing liver health in PWH, addressing metabolic and HIV-specific factors to mitigate fibrosis and steatosis risks. Integrated care should prioritize routine liver monitoring, effective viral suppression, and targeted management of obesity and related comorbidities.

THU-375

Prevalence, clinical features and determinants of MASLD in Klinefelter syndrome: a cross-sectional study

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Background and aims: Klinefelter syndrome (KS) is associated with an elevated risk of metabolic disorders, yet the prevalence and characteristics of metabolic dysfunction-associated steatotic liver disease (MASLD) in this population remain unknown. This study aims to investigate the prevalence, clinical features and key determinants of MASLD in individuals with KS.
Method: This cross-sectional study included 65 patients with KS, who had normal testosterone levels with or without replacement therapy. MASLD was diagnosed based on evidence of liver steatosis identified through abdominal ultrasound and/or controlled attenuation parameter (CAP) measurement, combined with the presence of at least one cardiometabolic risk factor. Comprehensive anamnestic, clinical, imaging, and biochemical data were collected for analysis.

Results: The prevalence of MASLD in the study population was 47.7% (31/65). Patients with MASLD were significantly older (40.5 ± 10.6 years vs. 31.5 ± 13.1 years, $p = 0.001$) and had higher BMI (29.5 ± 3.3 vs. 24.8 ± 4.4, $p < 0.001$) and waist circumference (105.5 cm [100.0–115.0] vs. 90.0 cm [87.1–99.0], $p < 0.001$). Liver steatosis was present in all patients with MASLD (100%) compared to 5.9% of patients without MASLD ($p < 0.001$). The prevalence of diabetes was significantly higher in the MASLD group (29.0% vs. 5.9%, $p = 0.010$). At multivariable logistic regression analysis, BMI (OR: 1.34, 95% CI: 1.10–1.65, $p = 0.004$) emerged as the sole independent predictor of MASLD. Among the study population, 30 patients underwent FibroScan®/CAP evaluation. The median liver stiffness (KPa) value was 4.65 [4.1–5.4], with one patient presenting with advanced fibrosis (12.5 KPa). The median CAP value was 237.0 [201.0–261.5] dB/m. Correlation analysis revealed a significant negative relationship between CAP and IGF-1 levels (r = –0.60, 95% CI: –0.85 to –0.12, $p = 0.012$). In contrast, CAP was positively correlated with triglyceride levels (r = 0.37, 95% CI: 0.02 to 0.65, $p = 0.042$) and HOMA-IR (r = 0.44, 95% CI: 0.10 to 0.69, $p = 0.015$). Additionally, HOMA-IR showed a positive correlation with KPa values (r = 0.45, 95% CI: 0.10 to 0.69, $p = 0.014$).
Conclusion: MASLD is highly prevalent in patients with KS with a prevalence of 47.7%. BMI emerged as an independent predictor of MASLD. CAP values demonstrated a negative association with IGF-1 and positive associations with triglycerides and HOMA-IR. Moreover, HOMA-IR was positively correlated with liver stiffness. These findings highlight the importance of early detection and targeted interventions to mitigate MASLD and associated metabolic risks in this high-risk group.

THU-376-YI

A systematic review and meta-analysis - does metabolic dysfunction-associated steatotic liver disease increase the risk of cardiovascular disease above and beyond shared risk factors?

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with an increased risk of incident cardiovascular disease (CVD). However, despite CVD representing the leading cause of mortality in people with MASLD, it is unclear whether liver disease is an independent risk factor (RF) for CVD, or whether cardiometabolic RFs common to MASLD and CVD account for this risk. Equipoise exists in the literature, with studies conducted in liver centres suggesting that MASLD confers higher CVD risk regardless of metabolic RFs, and large epidemiological studies suggesting this is not the case. A systematic literature review and meta-analysis of observational studies was conducted to further delineate this relationship.
Method: Medline, Embase, and Cochrane databases were interrogated from database inception to November 2024 to identify eligible studies. Exclusion criteria incorporated: method of MASLD diagnosis (which required imaging, elastography or biopsy), alcohol consumption thresholds (<30 g/20 g daily equivalent for males/females respectively), presence of baseline CVD, and follow-up period. Cross-sectional studies were excluded. The primary outcome was overall incident CVD. Secondary endpoints were composite fatal/non-fatal CVD events (CVEs), atrial fibrillation (AF), acute coronary syndrome (ACS), CVD mortality, and stroke. Raw outcome data were extracted from selected studies and meta-regression analyses performed using random-effects models to synthesise pooled odds ratios (ORs) with 95% confidence intervals (CIs).
Results: Nineteen longitudinal prospective and retrospective cohort studies, reporting various cardiovascular endpoints, were identified for inclusion with aggregate data on 1,250,664 individuals. Median follow-up period was 8.4 years (IQR 5.7–10.0). MASLD was associated with an increased risk of any incident CVD (pooled OR 1.86 [1.24–2.78]; p = 0.005). This association remained significant following adjustment for sex and cardiometabolic RFs (OR 1.89 [0.31–3.47; p = 0.02; I2 = 94.3%]). MASLD was also associated with increased risk of combined fatal/non-fatal events in an adjusted model (OR 2.85 [-0.17–5.86]; p = 0.057). As expected, MASLD was associated with increased risk of incident ACS, AF, CVD mortality, and stroke; eligible study numbers did not permit full adjustment for all cardiometabolic covariates.
Conclusion: After adjusting for common cardiometabolic RFs, MASLD is associated with a modest but statistically significant increase in the risk of incident CVD. Our findings suggest increased vigilance for incident CVD may be warranted in MASLD patients, even after optimisation of cardiometabolic parameters. The relatively wide CIs for the ORs calculated in the fully adjusted models indicate a need for caution when interpreting these data. Further high-quality studies are needed to determine the impact of MASLD as an independent RF for both overall CVD and specific cardiovascular outcomes.

THU-381

Food insecurity is associated with poorer metabolic health in adults with MASLD but is not mediated by overall diet quality or total energy intake

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Background and aims: Food insecurity (FI) is a risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD), but its association with metabolic comorbidities in MASLD, and the role of overall diet quality and total energy intake in mediating these relationships, is unknown.
Method: We performed a cross-sectional analysis of adult participants (age ≥20 years) with MASLD from the National Health and Nutrition Examination Survey between 2005–2020. MASLD was defined by a US Fatty Liver Index of ≥30 in the absence of viral hepatitis or significant alcohol use (drinks/day: >4 in men, >3 in women). Participants were categorized as food insecure vs secure using the USDA Food Security Survey Module. Metabolic health outcomes were measured continuously (BMI, waist circumference, hemoglobin A1c, triglycerides, high-density lipoprotein (HDL), systolic [SBP] and diastolic blood pressure [DBP]). The Food Frequency Questionnaire measured total energy intake and diet quality, assessed by the Healthy Eating Index (HEI-2015; score range 0–100). We performed multivariable linear regressions to examine the association of (1) FI with metabolic outcomes, (2) FI with potential mediators (HEI-2015, total energy intake), and (3) mediators with metabolic outcomes controlling for age, sex, race-ethnicity, education, smoking, and alcohol use. If the associations were significant, we then evaluated if diet quality and energy intake mediated the effect of FI on metabolic outcomes (p < 0.05 and >10% mediating effect was considered significant).
Results: Of 4706 adults with MASLD, 1033 (22%) were food insecure. Adults who were food insecure, compared to food secure, were more likely to be Hispanic (33% vs 15%), foreign born (25% vs 12%), or uninsured (34% vs 12%) and less likely to be employed (51% vs 58%). Food insecure adults with MASLD also had higher mean BMI (36 vs 34 kg/m^2) and hemoglobin A1c (6.3% vs 6%), poorer diet quality (mean HEI-2015: 47 vs 50), but lower daily total energy intake (2030 vs 2140 kilocalories). In multivariable analysis, FI was associated with higher hemoglobin A1c (0.34%, p < 0.001), but neither HEI-2015 (p = 0.90) nor energy intake (p = 0.11) mediated this association. Similarly, FI was associated with higher mean DBP (1.49 mmHg, p = 0.04) but not significantly mediated by HEI-2015 (p = 0.42) or energy

intake (p = 0.006, 6% mediating effect). FI was also associated with higher BMI (0.94 kg/m^2, p = 0.05) and higher waist circumference (1.59 centimeters, p = 0.06) but did not reach statistical significance. There was no association of FI with SBP (p = 0.08), HDL (p = 0.34), or triglycerides (p = 0.31) in multivariable analyses.
Conclusion: FI is associated with worse metabolic health in MASLD. However, overall diet quality and total energy intake are not the main underlying drivers of this association. Future studies should investigate the role of individual dietary components, psychosocial factors (i.e. stress, depression), and other social determinants of health that may present in the context of FI.

THU-382-YI
Exploring the interplay between sarcopenia, liver and cardiovascular damage in non-cirrhotic MASLD patients: a genetic perspective
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Background and aims: Sarcopenia is associated with advanced liver fibrosis, and bioelectrical impedance analysis (BIA) reliably assesses muscle mass. Both metabolic-dysfunction associated steatotic liver disease (MASLD) and sarcopenia increase cardiovascular (CV) risk. Genetic variants like PNPLA3, TM6SF2, and HSD17B13 influence MASLD risk, but their roles in sarcopenia and CV damage are unexplored. Aim: To assess the impact of sarcopenia and genetic variants on liver and CV damage in non-cirrhotic MASLD patients.
Method: We enrolled 841 MASLD patients from three Liver Units. Fibrosis was assessed by liver stiffness measurement (LSM) (LSM ≥8 kPa for advanced fibrosis) and steatosis by controlled attenuation parameter (CAP) at Fibroscan (CAP >280 dB/m for severe steatosis). Sarcopenia was defined by the lowest tertile of skeletal muscle index (SMI = skeletal muscle mass/height^2) at BIA. CV risk was assessed using SCORE2 and SCORE-OP; CV damage markers included carotid intima-media thickness (cIMT) ≥0.9 mm, carotid plaques, epicardial fat thickness (EFT) ≥5.2 mm. Increased waist circumference (WC) >102/88 cm in men/women. Genetic polymorphisms in PNPLA3, TM6SF2, and HSD17B13 were assessed in 424 patients.
Results: Mean age was 51 ys, 63% male. 43% were obese, 65% had increased WC. 50% were dyslipidemic, 25% diabetic. 24% had advanced fibrosis, 71% severe steatosis. 71% had higher high CV risk, 22% had increased cIMT, 35% had carotid plaques, 83% had increased EFT. Sarcopenia (SMI < 10.35/7.75 kg/m^2 in men/women) was linked to older age (54 vs 48 ys, p < 0.001), lower BMI (27 vs 33.4 kg/m^2, p < 0.001), WC (99 vs 110 cm, p < 0.001), CAP (293 vs 317 dB/m, p < 0.001), and LSM (4.9 vs 6.4 kPa, p < 0.001) compared to non-sarcopenic. Sarcopenic also had higher dyslipidemia (56% vs 46%, p = 0.03), increased cIMT (28% vs 18%, p = 0.01), and EFT (85% vs 77%, p = 0.05). At adjusted multivariate analysis, sarcopenia remained associated with low BMI (OR 0.61; 95% CI 0.5–0.7, p < 0.001), WC (OR 0.92; 95% CI 0.8–0.97, p = 0.001), female sex (OR 2.21; 95% CI 1.2–4.0, p = 0.008), and increased cIMT (OR 2.1; 95% CI 1.1–3.97). In sarcopenic, PNPLA3 CG/GG variant was linked to increased LSM (OR 1.82, 95% CI 1.1–3.1, p = 0.03) but lower cIMT (OR 0.39, 95% CI 0.15–0.96, p = 0.04). TM6SF2 wild-type allele was associated with increased cIMT (OR 3.4, 95% CI 1.3–5.8, p = 0.004), and WC (OR 2.3, 95% CI 1.4–3.6, p = 0.001). No differences were seen in HSD17B13 variant.
Conclusion: Sarcopenia independently correlates with atherosclerosis markers in non-cirrhotic MASLD, though liver damage is less common, possibly due to lower visceral fat. In sarcopenic patients, the PNPLA3 variant correlated with increased liver damage but lower subclinical atherosclerosis, while TM6SF2 polymorphism showed a protective role against CV damage. Combining imaging and genetic data is required to clarify the role of sarcopenia in liver and CV damage in non-cirrhotic MASLD.

THU-383
Muscle fat content quantified by L3-PDFFPsoas is strongly associated with fibrosis in patients with metabolic dysfunction-associated steatotic liver disease
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Background and aims: The relationship between muscle fat content and metabolic dysfunction-associated steatotic liver disease (MASLD) has not been well investigated. Here, we aim to elucidate the association between muscle fat content quantified by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and MASLD severity.
Method: Cross-sectional and longitudinal studies were conducted in this research. The cross-sectional study enrolled 500 participants,

including 446 patients with MASLD and 54 healthy volunteers. Among the patients with MASLD, 164 underwent liver biopsy. A total of 136 MASLD patients was subjected to a 24-weeks follow-up in longitudinal study. All subjects underwent abdominal MRI, and general, biochemical, and imaging parameters were collected. The muscle fat content was measured in the psoas muscle at the level of the 3rd lumbar vertebra by PDFF (L3-PDFFPsoas). L3-PDFFPsoas response was defined by Cohen's d (responding group, Cohen's d ≥0.2).
Results: MASLD patients exhibited higher L3-PDFFPsoas compared to healthy volunteers [median (IQR): 4.8(1.6) % vs. 6.6(2.6) %, P < 0.001]. L3-PDFFPsoas was higher in metabolic dysfunction-associated steatohepatitis (MASH) than in MASL (P = 0.0048) and increased with the severity of MASH (early MASH, fibrotic MASH, and MASH cirrhosis) (P = 0.013). Subjects with more severe ballooning or fibrosis had higher L3-PDFFPsoas (all P < 0.05). Also, in total participants, L3-PDFFPsoas was significantly related to FIB-4 score and liver stiffness measurement (LSM), respectively (r = 0.349 and 0.264, all P < 0.05). After adjustment for multiple confounders, L3-PDFFPsoas was robustly associated with liver fibrosis (odds ratio = 1.320, 95% CI: 1.039–1.678, P = 0.023), while L3-PDFFPsoas was not significantly associated with MASLD and MASH. After 24-weeks follow-up, there are significant reductions in L3-PDFFPsoas (all P < 0.05) in patients with a 30% relative decrease in MRI-PDFF, 17 IU/L decrease in alanine aminotransferase (ALT) or over 2 kPa decrease in LSM. Between-group analysis showed greater reduction in MRI-PDFF, ALT and LSM in favor of L3-PDFFPsoas responders (all P < 0.05).
Conclusion: Muscle fat content is significantly correlated to MASLD, especially liver fibrosis. Alterations in muscle fat content correspond with MASLD improvement. These data underscore the potential utility of muscle fat content as a biomarker in the diagnostic and management of MASLD.

THU-384

Cardiovascular risk screening in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. Patients with MASLD are at higher risk of developing cardiovascular diseases (CVD), which are associated with increased mortality rates. However, the management of CVD screening in MASLD patients is still unknown. Therefore, our aim was to assess the CVD risk and develop a CVD risk stratification protocol for MASLD patients.
Method: Between 2007–2024, 251 reclassified NAFLD/MASLD patients (126 females – 125 males) were recruited in two hepatology units of Semmelweis University, Hungary. The reclassification of recruited patients was performed according to the latest guidelines based on the modified multisociety Delphi consensus statement. We used Framingham risk score and Atherosclerotic Cardiovascular Disease (ASCVD) score for CVD risk stratification. Among non-invasive fibrosis markers, fibrosis-4 index (FIB-4) and aspartate aminotransferase to platelet ratio index (APRI) were calculated to identify the high CVD risk patients with MASLD and the most common CVD complications.
Results: There was an increased CVD risk in 21% of MASLD patients (51/247). Stroke was the most prevalent CVD complication. Compared to Framingham risk score, ASCVD was significantly (p < 0.05) associated with higher occurrence of CVD complications. Liver cirrhosis was developed in 13% of MASLD patients (32/247) during the follow-up period, which was associated with higher CVD risk. Regarding median values of FIB-4 and APRI, FIB-4 ≥1,36 MASLD patients were at significantly (p < 0.05) higher risk of developing CVD complications in the low CVD risk patients with MASLD (ASCVD<10%).
Conclusion: ASCVD had a better predictive value in CVD risk screening. MASLD patients were vulnerable to disease progression and consequently more severe clinical outcomes. FIB-4 ≥1,36 was significantly associated with higher CVD risk, regradless of ASCVD levels. FIB-4 and ASCVD scores should be routinely employed for CVD risk assessment in MASLD.

THU-385-YI

Association between polycystic ovary syndrome, steatotic liver disease in pregnancy, and adverse pregnancy outcomes: results from the prospective fatty liver in pregnancy cohort

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Background and aims: Polycystic Ovary Syndrome (PCOS), often associated with insulin resistance (IR), is one of the strongest predictors of steatotic liver disease (SLD) in women, which in turn has been associated with adverse pregnancy outcomes (APOs). We evaluated the relationship between PCOS and SLD in pregnancy, the role of IR, and its influence on APOs.
Method: We leveraged the prospective "Fatty Liver in Pregnancy" cohort to evaluate the prevalence of PCOS by medical record and SLD by liver ultrasound performed between 18–26 weeks gestation. PCOS patients were stratified by evidence of IR, defined as history of diabetes mellitus (DM) or gestational diabetes (GDM) in a prior pregnancy. History of pre-pregnancy SLD, SLD during pregnancy, and prevalence of APOs were compared between the groups and to a control population without SLD/PCOS.
Results: Of 1,148 patients enrolled from 2019–2024, 73 (6%) had PCOS; 211 (18%) had evidence of SLD. Patients with PCOS were more likely to be Hispanic (60% vs 54%, p = 0.04), have hypertension (20% vs 8%, p = 0.00), have taken Metformin previously (4% vs 0.3%, p = 0.00) or Aspirin during pregnancy (50% vs 35% p = 0.02), and were on average older (31% vs 29%, p = 0.01) with higher pre-pregnancy BMIs (31% vs 28%, p = 0.00). The PCOS group had higher rates of prior GDM as well as DM (17% vs 5%, p = 0.01; 9% vs 3%, p = 0.01), as did those with SLD (13% vs 6%, p = 0.00; 8% vs 3%, p = 0.00). In those with both SLD and PCOS, rates were higher than in either group alone compared to controls (36% p = 0.00; 19% p = 0.00). PCOS patients had a higher incidence of preeclampsia (21% vs 13%, p = 0.05), which more than doubled in those with PCOS and IR (47% vs 13%, p = 0.00). There was an increased incidence of preterm birth and current GDM in those with PCOS and IR (33% vs 14%, p = 0.03; 29% vs 11%, p = 0.04). The PCOS cohort had a higher prevalence of diagnosed pre-pregnancy SLD (4% vs 1% p = 0.01), which was increased in those with PCOS and IR (13% vs 1%, p = 0.00). Those with PCOS and IR also had an increased incidence of SLD in pregnancy (43% vs 20%, p = 0.03). In a multivariate analysis adjusted for age and BMI, PCOS with IR was associated with SLD in pregnancy (OR 3.11, CI: 1.02–9.45; p = 0.05).
Conclusion: SLD was seen in 26% of pregnant patients with PCOS. Although PCOS is a known risk factor for SLD, only PCOS with IR was associated with SLD in pregnancy. PCOS with IR also plays an important role in the development of some APOs, necessitating the consideration of PCOS phenotypes when evaluating risk of both SLD in pregnancy and pregnancy outcomes.

THU-386

Both high intensity and moderate intensity exercise interventions improve steatotic liver disease: a prospective randomized trial

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Background and aims: Steatotic liver disease (SLD) is the most common liver disease worldwide. Lifestyle modification including exercise intervention is recommended to reduce hepatic steatosis, but the effectiveness of different exercise patterns and adherence remains unclear.
Method: This prospective single-center study was conducted at National Taiwan University Hospital (NTUH) from August 2020 to December 2023, just during the COVID-19 pandemic period. After diagnosing SLD, individuals were assessed with baseline cardiometabolic profile and imaging examination composed of transient elastography with controlled attenuation parameter (CAP), magnetic resonance imaging (MRI) with proton density fat fraction (PDFF), and magnetic resonance spectroscopy (MRS). Then the subjects were separated into control (N = 20) and exercise (N = 95) cohorts (randomized into moderate-intensity continuous [MCT], N = 49; and high-intensity interval training [HIIT] groups, N = 46) at baseline. Finally, 80 and 20 in the exercise and control groups completed the 24-week trial assessment and analysis with the primary outcome of a decrease of PDFF >10% and secondary outcome of a decrease of PDFF >30%.
Results: In the intention-to-treat analysis, exercise (odds ratio [OR]: 3.783, 95% confidence interval [CI]: 1.251–11.439, p = 0.018), HIIT pattern (OR: 3.666, 95% CI: 1.162–11.562, p = 0.027), and adherence (OR: 1.044, 95% CI: 1.025–2,063, p < 0.001) were the most important predictors of achieving a decrease of PDFF >10% in multivariate analysis. By per-protocol analysis of the exercise group, adherence (OR: 1.025, 95% CI: 1.004–1.047, p = 0.019) was the only factor to predict a decrease of PDFF >10% by multivariate analysis. Similar findings were obtained regarding secondary outcome of a decrease of PDFF >30%. Exercise significantly decreased CAP, PDFF, and MRS (all p < 0.001) values.
Conclusion: Exercise was an effective intervention in patients with SLD. High-intensity pattern and adherence played the most important roles in achieving a decrease in hepatic steatosis.

THU-387

Analysis of body composition in patients with metabolic dysfunction-associated steatotic liver disease and its relationship with liver fibrosis

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Background and aims: Type 2 diabetes mellitus (T2D) and obesity are key risk factors for the development of metabolic dysfunction-associated steatotic liver disease (MASLD). Lifestyle modification is essential for managing this condition, and body composition serves as a primary indicator of overall health and nutritional status. However, the impact of body composition changes on MASLD progression remains unclear. This study aims to investigate the correlation between body composition and advanced liver fibrosis in T2D patients.
Method: This cross-sectional observational study was conducted in a tertiary care hospital between October 2023 and April 2024. Data collection included clinical and epidemiological information, transient elastography (FibroScan™ and Smeda-New Life™), and dual-energy X-ray absorptiometry (DXA, Hologic A™). A total of 172 patients aged 18 years or older were initially enrolled. Seven participants were excluded due to an interquartile range (IQR) ≥30, five due to unfeasible examinations, 44 with type 1 diabetes mellitus, and five with latent autoimmune diabetes in adults. The final analysis included 111 participants, all diagnosed with T2D, of whom 54 underwent DXA. Statistical analysis was performed using univariate logistic regression with the Stata software.
Results: The analysis revealed that among the 77 patients without advanced liver fibrosis (G1), 18.2% were male and 81.8% were female, with a mean age of 60 years (±13.93). Among the 34 patients with advanced liver fibrosis (G2), 41.2% were male and 58.8% were female, with a mean age of 64 years (±12.22). Compared to G1, G2 patients exhibited a larger waist circumference (97 ± 13.08 cm vs. 106 ± 10.65 cm; p = 0.001) and a higher body mass index (29.9 ± 5.46 vs. 32.15 ± 4.75; p = 0.021). Among the 54 patients who underwent DXA, 33 (61.1%) were classified as having no advanced liver fibrosis (G3), while 21 (38.9%) had advanced liver fibrosis (G4). G4 patients showed a higher trunk-to-leg fat ratio compared to G3 (1.14 ± 0.18 vs. 1.018 ± 0.18; p = 0.024). Additionally, the android-to-gynoid fat ratio exceeded one in both groups, with averages of 1.06 ± 0.15 in G3 and 1.15 ± 0.16 in G4 (p = 0.078). Other variables measured by DXA, such as lean mass and fat mass, did not show statistically significant differences.
Conclusion: Patients with advanced liver fibrosis demonstrated a higher body mass index, an increased trunk-to-leg fat ratio, and a greater waist circumference compared to those without advanced liver fibrosis.

THU-388

Early-onset cancer risk in young adults with metabolic dysfunction-associated steatotic liver disease

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Background and aims: The incidence of early-onset cancers, typically defined as cancers diagnosed in adults <50 years of age, has increased. Metabolic dysfunction-associated steatotic liver disease (MASLD) extends beyond the liver to affect cardiovascular disease and various extrahepatic cancers. In this study, we investigated the association between MASLD and cancer in young adults.
Method: This study included adults aged 20–39 years who underwent health screening examinations between 2009 and 2012 based on the Korean National Health Insurance Service database. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of cancer were analyzed using Cox proportional hazards models.
Results: During the median 10.6 years of follow-up, MASLD was observed in 1,447,148 (25.4%) of the 5,690,033 participants. According to the age- and sex-adjusted model, the risk of all cancers was increased in the MASLD group compared with the no steatosis group (HR: 1.26, 95% CI, 1.24–1.28). After multivariable adjustment, the risk of all cancers was 1.11 (95% CI: 1.09–1.23)-times greater in individuals with MASLD than in those without steatosis. When stratified by various subgroups, the increased risk for cancer in the MASLD group was prominent in individuals under 30 years of age, males, current smokers, and those who consumed alcohol (all *P* values for interactions <0.05).
Conclusion: In young adults, MASLD was associated with an increased risk of developing cancer. These findings highlight the need for early intervention in patients with MASLD before they reach middle age to mitigate cancer risk.

THU-389

The severity of MASLD is associated with chronic kidney disease in patients with type 2 diabetes and/or obesity

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Background and aims: An association between metabolic dysfunction associated steatotic liver disease (MASLD) and chronic kidney disease (CKD) has been reported, but the link between MASLD severity and CKD has not been well explored. Therefore, we assessed the association between CKD and advanced fibrosis in patients with type 2 diabetes (T2D) and/or obesity and MASLD prospectively enrolled in a systematic screening for the presence of advanced fibrosis (AF).
Method: A cross-sectional analysis was conducted on 787 patients with T2D and/or obesity (classes 1 & 2) and MASLD, aged 40–80 years. These patients were prospectively recruited from four diabetology departments in France (2020–2024) to assess the risk of AF. All participants underwent a comprehensive liver assessment using Fibrotest®, FibroMeter®, ELF™, FIB-4 and transient elastography (TE) and controlled attenuation parameter (CAP) with FibroScan. If clinically indicated a liver biopsy or magnetic resonance elastography (MRE) was performed to assess the risk of AF. High risk of AF was defined by a hierarchical composite criterion depending on availability: 1. liver biopsy ≥F3, 2. MRE ≥3.62 kPa or overt imaging diagnosis of cirrhosis 3. TE ≥12 kPa. CKD was defined by a decrease of estimated glomerular filtration rate by CKD-EPI formula (eGFR) <60 ml/min/1.73 m^2 or urinary albumin-to-creatinine ratio (uACR) >3 mg/mmol.
Results: Among the 787 participants (mean age: 59.9 ± 9.7 years; mean BMI: 32.7 ± 4.4 kg/m², mean eGFR: 81.3 ± 15.6 ml/min/73 m^2 , mean uACR: 14.0 ± 45.4 mg/mmol; 86.1% with T2D and 73.7% with obesity), 35.6% had CKD and 8.9% had high risk of AF. Liver stiffness measurement by TE were significantly higher in patients with CKD: 6.1 versus 5.5 kPa, p < 0.001. CAP value was also significantly higher in patients with CKD: 321 versus 311 db/m, p = 0.01. All non-invasive blood-based biomarkers of fibrosis (Fibrotest®, Fibrometer®, ELF™, and FIB-4 scores) were also significantly higher in the presence of CKD compared to patients without CKD (all p < 0.001). The proportion of CKD increased with fibrosis severity: 33.1% (low), 38.8% (intermediate), and 54.3% (high), p for trend = 0.002. Participants at high-risk of AF had a significant increased risk of CKD compared to those with low/intermediate risk of AF: Odds ratio (OR): 2.33, [95% confidence interval (CI): 1.42–3.82], p < 0,001. This higher risk of CKD remained significant after adjustment for age, sex, HbA1c and BMI: adjusted OR: 1.84 [95%CI: 1.08–3.14], p = 0.025. This association was also observed in the subgroup with T2D: adjusted OR for age sex and BMI: 1.71 [95%CI: 1.004–2.910], p = 0.048.
Conclusion: In patients with T2D and/or obesity, the presence of MASLD-related AF was associated with CKD, independently of age, sex, HBA1c and BMI.

THU-390

Genetic risk accentuates the impact of lifestyle on progression hepatic steatosis and fibrosis: insights from a population-based cohort

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Background and aims: Genetic factors and lifestyle choices both play a role in the risk of developing hepatic steatosis and fibrosis. However, the impact of gene-lifestyle interactions on these conditions has not been fully explored.
Method: This cohort study involved 724 MASLD patients, all of whom completed two follow-up visits at least one year apart. Lifestyle factors from the past month, including sedentary behavior, soft drink intake, and physical activity levels (PA; categorized as low, moderate, or high per WHO guidelines), were recorded through questionnaires. Liver fat content (LFC) and fibrosis severity (LSM) were measured via MRI-PDFF and FibroScan, respectively. Diagnoses adhered to EASL standards, with Mod-Sev steatosis defined as LFC >14.1%.Genetic analysis of blood samples from 272 participants included an Asian Screening Array and additional susceptibility SNPs (e.g., PNPLA3, HSD17B13, RASGLP1). Following quality control, genotyping data for 260 samples across 475,787 SNP loci were obtained. A genetic risk score (GRS) based on the top 10 SNPs associated with LFC was computed. Gene-lifestyle interactions were examined for their effects on steatosis and fibrosis progression using R.
Results: Mod-Sev steatosis was observed in 38.1% (N = 276) of patients. Risk factors included low PA, frequent soft drink consumption (>1 time/week), and prolonged sedentary behavior (>6 hours/day), with odds ratios (ORs) of 4.0 [3.1–5.3], 2.4 [1.7–3.3], and 1.7 [1.2–2.3], respectively. Genetic variants in PNPLA3 and HSD17B13, along with a high GRS, were significantly associated with Mod-Sev steatosis, with ORs of 1.6 [1.1–2.2], 2.5 [1.6–3.8], and 2.9 [1.9–4.2]. Among individuals sedentary >6 h/day, those with the PNPLA3 GG genotype (N = 34) had an 82% prevalence of severe steatosis compared to 50% in CC carriers (N = 33). For soft drink consumption, prevalence was 57% in GG carriers (N = 37) versus 38% in CC carriers (N = 28). The interaction of the PNPLA3 G allele with soft drink consumption increased LFC by 1.6-fold compared to soft drink consumption alone. Similarly, its interaction with sedentary behavior resulted in a 2.2-fold higher effect than sedentary behavior alone. The HSD17B13 A insertion mutation amplified the effect of low PA by 3.6 times. Significant interactions were also observed between a high GRS and both low PA and soft drink consumption. Among individuals with weight loss over one year (N = 127), those with the RASGRP1 (rs7403531) TT genotype showed a significantly greater association between weight change and changes in LSM (gene-weight interaction β: 0.98, P = 0.005) and experienced a larger reduction in LSM compared to CC/CT carriers (−1.90 kPa vs. −0.06 kPa).
Conclusion: The effects of lifestyle on LFC and LSM were markedly enhanced in patients with higher genetic risk for MASLD, suggesting that lifestyle interventions could be particularly effective in these individuals.

THU-391

Impact of metabolic dysfunction-associated steatotic liver disease (MASLD) on serological milestones of chronic hepatitis B patients

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Background and aims: Chronic hepatitis B (CHB) affect over 254 million people globally, contributing to liver-related complications and mortality. The natural history of CHB can be predicted and classified into three distinct milestones such as seroclearance of HBeAg, HBV DNA, and HBsAg. Fatty liver disease (FLD), now termed

metabolic dysfunction-associated steatotic liver disease (MASLD), affects one-third of the global population and contributes to liver disease progression. MASLD includes patients with chronic viral hepatitis and metabolic risk factors. Although MASLD has been linked to changes in liver function, its specific impact on the natural history of CHB remains unclear. This study investigates how MASLD influences HBV's progression and serological outcomes in CHB patients.

Method: The REVEAL-HBV cohort in Taiwan included 3,653 HBV-infected individuals without hepatitis C. Those with baseline cirrhosis or missing fatty liver data were excluded (n = 1,067). MASLD diagnosis required hepatic steatosis detected via ultrasound and at least one metabolic criterion: (1) BMI ≥23 kg/m² or waist circumference ≥90 cm (men) or ≥80 cm (women); (2) fasting glucose ≥100 mg/dL, two-hour glucose ≥140 mg/dL, or HbA1c ≥5% or (3) triglycerides ≥150 mg/dL. Patients with one metabolic criterion were classified as mild MASLD; those with two or more as moderate MASLD. Clinical outcomes included HBeAg, HBV DNA, and HBsAg seroclearance. Kaplan-Meier analysis estimated cumulative incidence rates, and Cox regression calculated hazard ratios (HR).

Results: Baseline BMI (22.77 ± 2.65 vs. 26.18 ± 3.38 vs. 26.96 ± 2.90) and triglycerides (101.32 ± 66.39 vs. 106.64 ± 60.63 vs. 247.56 ± 193.42) differed significantly across non-fatty liver, mild MASLD, and moderate MASLD groups. HBeAg seroclearance rates showed no significant difference between mild or moderate MASLD and non-fatty liver groups (adjusted HR = 0.86 [95% CI: 0.59–1.26] and 1.13 [0.73–1.76], respectively). However, moderate MASLD was associated with higher HBV DNA undetectability (HR = 1.54, 95% CI: 1.17–2.03) and HBsAg seroclearance (HR = 1.70, 95% CI: 1.31–2.21). Cumulative incidence analysis shows no significant difference in the clearance in HBeAg seroclearance among the groups (p-value = 0.34), while MASLD groups exhibit higher cumulative incidence of HBV DNA undetectability and HBsAg seroclearance than the non-fatty liver group (p-value = 0.00029 and 0.00011).

Conclusion: This study demonstrates that concurrent MASLD in CHB patients is associated with significantly higher HBV DNA and HBsAg seroclearance rates, suggesting reduced viral replication and potentially slower disease progression. However, no significant differences were observed in HBeAg seroclearance among the groups, consistent with previous findings that steatosis does not affect HBeAg clearance. These results highlight MASLD's influence on HBV serological outcomes, particularly in enhancing viral clearance.

THU-392

Changes in liver stiffness and controlled attenuation parameters of transient elastography according to weight change in metabolic dysfunction-associated liver disease

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Background and aims: The Controlled attenuation parameter (CAP) and the liver stiffness (LS) of transient elastography (TE) are widely used to measure the degree of fatty liver and liver fibrosis. We investigated whether there were significant changes in CAP and LS according to the amount of weight loss in patients with metabolic dysfunction-associated liver disease (MASLD).

Method: The patients with MASLD at Jeju National University Hospital in Korea who had TE tests more than once while losing body weight were analyzed. CAP and LS were compared between the time of the first test and the time of the weight was most lost during the follow-up.

Results: A total of 410 patients were analyzed and 74.6% of patients lost body weight during the follow-up period. The mean age was 51.97 years (standard deviation (SD): 15.10), the mean body mass index (BMI) was 28.71 (SD: 4.21). Patients who lost weight were divided into 5 groups according to the amount of weight loss (WL), and all groups showed significant CAP change (−25.62 in the 0 to 3% WL group, −21.52 in the 3 to 5% WL group, −41.92 in the 5 to 7% WL group, −32.79 in the 7 to 10% WL group, −74.16 in the more than 10% WL group, all p-values <0.05). The mean LS change by group was +0.75 in the 0 to 3% WL group, −0.30 in the 3 to 5% WL group, +0.40 in the 5 to 7% WL group, −0.40 in the 7 to 10% WL group, −1.31 in the more than 10% WL group, and was significant only in the more than 10% WL group (p = 0.002). In multivariable analysis, weight change percentage, baseline BMI, and weight loss duration were significantly associated with CAP change, and weight change percentage, baseline BMI, and weight loss duration were significantly associated with LS change.

Conclusion: In patients with MASLD, there was a significant correlation between weight loss and CAP, and LS decreases significantly when weight loss is greater than 10% of baseline body weight.

THU-397

Clinically meaningful fatigue is associated with the presence of systemic inflammation, lower erythrocyte count and haemoglobin level, and decreased muscle strength in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Fatigue is a significant issue in metabolic dysfunction-associated steatotic liver disease (MASLD) and may hinder increased physical activity and lifestyle modifications, which are the cornerstone of MASLD therapy. Although the pathogenesis of fatigue in MASLD remains poorly understood, potential mechanisms may involve several extrahepatic factors. This study aimed to evaluate the association between laboratory data, muscle strength, and the presence of clinically meaningful fatigue in patients with MASLD.

Method: A total of 116 MASLD patients were included in the study. MASLD was diagnosed based on ultrasonography findings, the absence of other liver disease etiologies (based on laboratory data), and the presence of at least one cardiometabolic risk factor. Fatigue was evaluated using the Fatigue Assessment Scale (FAS). An overall score of ≥22 points was indicative of clinically meaningfull fatigue. Grip strength (GS) was measured using a mechanical hand dynamometer (ZAO "NTMIZ" Russia). Patients were instructed to squeeze the dynamometer with maximum force three times using their dominant hand, with a 60-second rest between trials. The maximum value was registered. GS <27 kg in men and <16 kg in women were used as thresholds for decreased GS. Relative GS (rGS) value was calculated as GS devided by body mass index (BMI). To assess leg muscle strength, a 5-times chair stand test (CST) was performed. A time of >15 s was used as the threshold for decreased muscle strength.

Results: The median age of patients was 57 years (interquartile range: 46.3–64 years), and 60.3% were female. The median BMI was 32.8 kg/m² (IQR: 29.6–36.4). All patients had arterial hypertension and dyslipidemia. Dynapenia, defined as decreased GS or a CST time >15 s for 5 rises, was observed in 20 (17.2%) and 14 (12.1%) patients, respectively. Patients with a FAS score ≥22 had significantly higher ESR and CRP levels (p < 0.001 and p = 0.001, respectively) and significantly lower erythrocyte counts, hemoglobin levels, and rGS values (p < 0.001, p = 0.001, and p = 0.019, respectively). Additionally, these patients required substantially more time to perform the CST (p = 0.016) compared to those with a FAS score <22. The areas under the ROC curve (AUROCs) (± standard errors (SEs)) were 0.654 (±0.06) for the CST, 0.721 (±0.057) for CRP, and 0.751 (±0.055) for ESR in confirming the presence of fatigue, and 0.646 (±0.06) for rGS in excluding the presence of clinically meaningful fatigue.

Conclusion: Our findings demonstrate that fatigue, a troubling symptom common in MASLD patients, is associated with systemic inflammation, lower erythrocyte count and haemoglobin level (suggesting hypoxemia), and dynapenia. This suggests that the pathogenesis of fatigue in MASLD is complex. In addition, it can be hypothesized that in MASLD, a vicious cycle is formed in which dynapenia simultaneously acts as a factor associated with fatigue and as a consequence of hypodynamia, one of the possible causes of which may be fatigue itself.

THU-398

Endothelial dysfunction and metabolic dysfunction-associated steatotic liver disease: is there a relationship?

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Background and aims: It is currently considered that metabolic dysfunction-associated steatotic liver disease (MASLD) is a risk factor for liver cirrhosis, liver cancer, diabetes and cardiovascular disease. The presence of cardiovascular complications of MASLD worsens its course and prognosis for patients. In recent years, researchers have focused on the features of intercellular interaction and endothelial dysfunction (ED) as a factor in vascular damage in patients with MASLD, but endothelial dysfunction has not been studied enough. The aim - to evaluate the relationship between markers of systemic inflammation, degree of liver fibrosis and endothelial dysfunction in patients with MASLD.
Method: We examined 241 patients and determined the level of inflammatory mediators, endothelin (ET-1), the activity of the Willebrand's factor (vWF), the thickness of the intima-media complex, presence atherosclerotic plaque and stenosis of the carotid arteries, index HOMA-IR. The ratio between the content of adiponectin and leptin was represented as log A/L. The anthropometric survey, measured levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), the degree of liver fibrosis using elastography (FibroScan), ECG and echocardiography were conducted.
Results: Correlation analysis revealed a direct correlation between HOMA-IR and leptin ($r = 0.8$; $p = 0.00166$) and inverse correlation between HOMA-IR and adiponectin ($r = -0.66$; $p = 0.0033$) and index log A/L ($r = -0.71$; $p = 0.0000$) It is evident that the decrease in the concentration of adiponectin with a parallel increase in the content of leptin increases IP. A comparative analysis of the level of CRP inflammation marker in obese patients showed a direct relationship with HOMA-IR ($r = 0.58$; $p = 0.05$), glucose ($r = 0.44$; $p = 0.0045$) and insulin ($r = 0.66$; $p = 0.0001$) in the blood. The patients with MASLD by obesity showed a reduction in endothelium-dependent vasodilation, indicating the presence of endothelial dysfunction. The concentration of proinflammatory cytokines such as TNF-α and IL-6 in patients with MASLD was 3–7 times higher than the similar parameters of patients with a similar degree of obesity but without evidence MASLD. The concentration of ET-1 in the blood plasma of patients with MASLD has a strong direct correlation with the degree of cardiovascular risk and cognitive deficit in surveyed patients. It is found that many inflammatory mediators (TNF-α, IL-1, IL-6) and markers (C-reactive protein, fibrinogen) highly correlate with the degree of obesity, the concentration of ET-1, vWF and markers of insulin resistance a predictor for cardiovascular risk.
Conclusion: The development of MASLD is associated with the development of endothelial dysfunction, increasing levels of leptin and markers of systemic inflammation, decreasing levels of adiponectin in patients with MASLD.

THU-399

The relationship between insulin resistance, thyroid gland dysfunction and bacterial overgrowth syndrome in the development of vascular complications in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: It is well known that MASLD is closely associated with obesity, insulin resistance, and cardiovascular diseases. Today, it is relevant to clarify the pathogenetic chains of MASLD formation. Many studies in recent years consider hypothyroidism as a condition specifically associated with MASLD. Modern scientific data indicate that there is a close relationship between the intestinal microbiota and lipid-associated pathologies. The aim of the study was to assess the relationship between atherogenic dyslipidemia, thyroid function of bacterial overgrowth syndrome and adipokines, degree of obesity and insulin resistance in patients with MASLD.
Method: 204 patients with MASLD and 42 healthy individuals were examined. The age of the subjects ranged from 26 to 73 years with a median of 55 years (interquartile range Q1-Q3 from 40 to 61 years). The level of inflammatory mediators (TNF-α, IL-1, IL-6), markers (high-sensitivity C-reactive protein, fibrinogen), HOMA-IR index were determined. An anthropometric examination was performed, the levels of AST, ALT, GGT, the degree of liver fibrosis were determined using elastography (FibroScan), ECG and EchoCG.
Results: Bacterial overgrowth syndrome was detected in 78% of the population. Correlation analysis revealed a direct correlation between HOMA-IR and leptin concentration ($r = 0.8$, $p = 0.0017$) and an inverse correlation between HOMA-IR and adiponectin concentration ($r = -0.66$, $p = 0.0033$) and log A/L index ($r = -0.71$, $p < 0.0001$). A decrease in adiponectin concentration with a parallel increase in leptin content increased IR. Comparative analysis of the level of the inflammatory marker hsCRP in obese patients showed a direct relationship with HOMA-IR ($r = 0.58$, $p = 0.05$), glucose ($r = 0.44$, $p = 0.0045$) and insulin ($r = 0.66$, $p = 0.0001$) in the blood. Positive correlations were found between alanine aminotransferase (ALT) and FT3 ($r = 0.333$, $p = 0.008$), and negative correlations were noted between TSH and BMR ($r = -0.731$, $p < 0.010$). After adjusting for all factors, insulin, FT4, and TSH were identified as significant independent risk factors for MASLD in univariate analysis.
Conclusion: The presence of hypothyroidism, hyperinsulinemia and bacterial overgrowth syndrome were associated with increased body mass index, elevated hs-CRP, insulin resistance, and increased cardiovascular disease in patients with MASLD.

THU-400

Characterization and validation of regional variation in fibrosis within traditional fibrosis stages

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Background and aims: Histological assessment has anchored the field of metabolic dysfunction-associated steatotic liver disease (MASLD) as a measure of the "ground truth." However, variability in human staging of fibrosis has driven the development of digital pathology approaches to improve the fidelity of the histological assessments. Second harmonic generation/two-photon excitation

fluorescence (SHG/TPEF) imaging is such a method which generates a quantitative fibrosis (qF) score and has provided deep insights into regional differences in fibrosis evolution and during resolution in MASH. This approach has not however been independently validated. The current study represents an independent validation of this method by the NIDDK NASH Clinical Research Network (CRN).

Method: A curated set of 100 paired liver biopsies, separated by a median of 4 years, was selected from the CRN histological database. Of these, 45% demonstrated fibrosis progression, 10% showed no change, and 45% exhibited regression. SHG/TPEF imaging was performed as previously described. Overall qF scores and zonal qF scores (zones 1, 2, 3, central vein, and portal areas) were also independently reported. A prespecified statistical plan and strict data chain of custody ensured study integrity and independence. Concordance with conventional fibrosis staging and zonal changes associated with fibrosis progression versus regression were assessed.

Results: The overall mean qF score increased progressively with fibrosis stage: Stage 0 (1.272, n = 16), Stage 1 (1.562, n = 29), Stage 2 (1.990, n = 19), Stage 3 (3.143, n = 29) and Stage 4 (5.056, n = 4). Spearman's correlation between overall qF scores and CRN staging was strong (rs = 0.75). Portal, zone 1, and zone 3 qF scores increased with advancing fibrosis, while interestingly zone 2 fibrosis scores were lower in cirrhosis compared to stage 3 (p = 0.023). Baseline qF scores in F2 patients were higher in those with fibrosis progression compared to regression in zone 1 (0.29 vs 0.25), zone 2 (0.57 vs 0.35), zone 3 (0.35 vs 0.2), and the central vein (0.17 vs 0.08). With progression to advanced fibrosis (stage 3 or 4), there was a greater increment in portal tract and zone 3 scores compared to other regions. Regression was primarily observed in patients participating in treatment trials. Differential changes, relative to placebo, were noted in various regions in response to three different treatments with varying mechanisms of action.

Conclusion: qF scores strongly correlate with NASH CRN fibrosis stages. Within those with stage 2 fibrosis, qF analysis revealed differential responses to various therapeutic agents compared to placebo, supporting the ability of SHG/TPEF microscopy and qF scores to provide deeper insights into the complexities of fibrosis progression and regression in clinical trials.

THU-401

Liver stiffness and MACE development: an intricate relationship

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Background and aims: Patients with metabolic dysfunction associated steatotic liver disease (MASLD) are known to be at risk of developing hepatic complications which is driven by liver fibrosis, however large observational studies proved that the main risk of death in unselected patients with MASLD is cardiovascular disease (CVD). The relationship between liver fibrosis and the development of major adverse cardiovascular events (MACE) has already been explored but not fully elucidated, therefore we aimed to verify whether liver stiffness according to two dimensional shear wave elastography (2D-SWE) was associated to the development of MACE in a cohort of unselected MASLD patients.

Method: Retrospective study conducted on a consecutive prospective cohort of MASLD patients from a tertiary liver disease center in Bologna. All patients underwent baseline liver stiffness measurement and attended follow-up visits every 6–12 months. Patients with less than 6 months follow-up, unavailable baseline 2D-SWE or prior decompensating events were excluded. The primary endpoint was the development of MACE, defined as the occurrence of either stroke, cardiovascular death, unstable angina, hearth failure or hospitalization for a cardiovascular event.

Results: From 2017 to 2023 we recruited 352 patients meeting inclusion criteria.

After a median follow-up period of 31.2 months, we observed the occurrence of MACE in 28 patients (8.0% of the whole cohort). Comparing patients with significant liver fibrosis (LSM ≥7.37 kPa, corresponding to F3 or F4) to those with non-significant fibrosis (LSM <7.37 kPa, corresponding to F1 or F2), we found that subjects in F3-F4 were older (median 63.4 years vs 53.8 years, p < 0.001), more frequently comorbid, with a higher prevalence of hypertension (82.1% vs 63%, p < 0.001), a higher prevalence of diabetes (54.7% vs 16%, p < 0.001) and lower levels of total serum cholesterol (187 vs 201, p < 0.007) vs and compared to patients in the F1–F2 group, while no difference was observed in terms of sex distribution (55% of male in the F1–F2 group vs 51.6% in the F3–F4 group, p = 0.540).

The incidence of MACE was comparable between the two groups (7,0% in F1–F2 vs 10,4% in F3–F4, p = 0.275).

Conclusion: In our cohort of unselected MASLD patients, an increased liver stiffness was not clearly associated to an increased incidence of MACE after three years of median follow-up. This result underlines the necessity of an holistic evaluation of patients with MASLD not solely based on LSM, in particular to evaluate the risk of MACE which are the main cause of death in this group of patients.

THU-402-YI

Real-world practice using liver stiffness measurement through two-dimensional shear wave elastography (SuperSonic Imagine) as a predictive tool for hepatocellular carcinoma risk in non-cirrhotic MASLD patients

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Background and aims: Hepatocellular carcinzma (HCC) commonly develops in patients with liver cirrhosis; however, non-cirrhotic metabolic dysfunction-associated steatotic liver disease (MASLD) also presents a significant HCC risk. Developing effective screening protocols for MASLD-HCC necessitates identifying "at-risk" patients for targeted surveillance. Liver stiffness measurement (LSM) using two-dimensional shear wave elastography (2D-SWE) and clinical and demographic parameters could enhance MASLD-HCC risk stratification. This study evaluated the utility of LSM performed with the SuperSonic Imagine (SSI) ultrasound machine to predict HCC risk and guide screening strategies in MASLD patients.

Method: A retrospective study was conducted on a consecutive prospective cohort of MASLD patients from a tertiary liver disease center in Bologna. All patients underwent baseline LSM-SSI and attended follow-up visits every 6–12 months. Patients with less than 6 months follow-up, unavailable baseline 2D-SWE, or prior HCC were excluded. LSM-SSI cut-offs based on recent meta-analysis data were applied. The primary endpoint was the incidence of de novo HCC, with liver decompensation events and portal vein thrombosis (PVT) considered as competing risks. Univariate competing-risks regression (CRR) models, using Fine and Gray's proportional subhazards method, identified HCC risk predictors.

Results: Among 352 patients (mean follow-up: 38 ± 26 months), the average age was 56.4 ± 13.4 years, and the BMI was 29.6 ± 4.4 kg/m². At baseline, 73% of patients had LSM-SSI <7.37 kPa, 27% ≥7.37 kPa, and 8% >15.59 kPa. All patients with liver events had baseline LSM-SSI ≥7.37 kPa. Among these, 9.5% developed HCC, 6.3% had their first liver

decompensation, and 2.1% developed PVT. For non-cirrhotic patients (LSM-SSI ≤15.6 kPa), baseline LSM-SSI was significantly associated with HCC risk (HR 1.542, 95% CI 1.269–1.875, p < 0.0001). Using a significant fibrosis cut-off of 8.28 kPa, LSM-SSI demonstrated 66.7% sensitivity, 88.1% specificity, and 99.6% negative predictive value for HCC (AUROC: 0.770) and a number needed to diagnose (NDD) of 25.2. Multivariate analysis identified LSM-SSI (HR 1.052, 95% CI 1.030–1.075, p < 0.001), type 2 diabetes mellitus (HR 4.555, p = 0.038), and gamma-glutamyl transferase (HR 1.004, p = 0.003) as independent predictors of MASLD-HCC.
Conclusion: For non-cirrhotic MASLD patients, an LSM-SSI <7.37 kPa effectively rules out the need for HCC screening, whereas patients with significant fibrosis may benefit from HCC surveillance strategies based on elevated LSM-SSI and other identified risk factors.

THU-403

Liver disease severity and cardiovascular risk in steatotic liver disease with different alcohol exposure - a nationwide study in Taiwan

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Background and aims: Recent nomenclature of steatotic liver disease (SLD) stratify subjects based on the cardiometabolic risk factors (CMRFs) and alcohol consumption. SLD subjects carrying CMRFs and with moderate alcohol consumption are named as MetALD, whereas those with heavy alcohol consumption are viewed as having alcoholic liver disease (ALD) regardless CMRF carriage. The study aims to address the prevalence, liver disease severity and cardiovascular risk in SLD patients with different alcohol exposures and CMRF carriage in Taiwan.
Method: Eligible subjects were those retrieved from a nationwide-based health check-up system in Taiwan from 1997 to 2019. SLD was evaluated by sonography and/or having hepatic steatosis index greater than 36. Alcohol consumption was judged by questionnaires and transformed into daily exposure. Liver disease severity was evaluated by fibrosis-4 index (FIB-4) and the cardiovascular risk was calculated by Framingham risk score (FRS).
Results: A total of 501,863 subjects were recruited, and 162,689 (32.4%) subjects had SLD (mean age 44.0 years, male: 63.6%). Of the SLD subjects, the proportion of subjects without alcohol use or with social drinking (Group A), moderate alcohol consumption (Group B) and heavy alcohol consumption (ALD, Group C) was 93.3% (n = 151,747), 4.0% (n = 6,597) and 2.7% (n = 4,345), respectively. The proportion of CMRF carriage was 96.0% (MASLD), 98.1% (Met-ALD) and 97.9% among the 3 groups, respectively. The FIB-4 value progressively increased from Group A (0.85 ± 0.58), Group B (0.96 ± 0.80) to Group C (1.20 ± 1.13) (Ptrend <0.001). While subjects were divided by the CMRF carriage, those with CMRF carriage had a significantly higher FIB-4 than those without in each subgroup (All P value <0.001). Group A subjects without CMRF had the lowest FIB-4 value (0.71 ± 0.36) whereas Group C subjects with CMRF had the highest FIB-4 value (1.21 ± 1.14). Logistic regression analysis revealed that factors independent associated with significant fibrosis (FIB-4 > 2.6) included alcohol exposure (Odds ratio [OR]/95% confidence intervals [CI]: 2.00/1.91–2.11, P < 0.01 for Group B; OR/CI: 2.61/2.46–2.77, P < 0.01 for Group C, compare to Group A) and CMRF carriage (OR/CI: 4.94/4.27–5.71, P < 0.01 for 1–2 CMRF carriage; OR/CI:27.78/24.03–32.09, P < 0.01 for >3 CMRF carriage, compared to no any CMRF carriage). Coincidently, FRS progressively increased from Group A (6.95 ± 7.08), Group B (9.60 ± 8.56) to Group C (10.79 ± 9.33) (Ptrend <0.001). Alcohol exposure was independently associated with a higher cardiovascular risk (OR/CI: 1.64/1.53–1.75, P < 0.01 for Group B; OR/CI: 1.74/1.60–1.90, P < 0.01 for Group C, compared to Group A).
Conclusion: Despite the classification of Met-ALD and ALD takes CMRF carriage into consideration, almost all the SLD subjects with moderate or heavy alcohol consumption carried at least one CMRF. Both alcohol exposure and CMRF carriage were independently associated with liver disease severity and cardiovascular risk in Taiwanese SLD subjects.

THU-404

Genome-wide association study of noninvasive scores of fibrotic MASLD in an italian population

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Background and aims: Metabolic Associated Steatotic Liver Disease (MASLD) is the most prevalent chronic liver disease. It can progress to metabolic steatohepatitis (MASH), resulting in cirrhosis and hepatocellular carcinoma. A large fraction of MASLD heritability remains unexplained, and few genomic data are available in the Italian population. Genome-wide association studies (GWAS) offer a powerful method to identify genetic risk variants for risk stratification and therapeutic strategies.
Method: The Milano BioBank is a multi-center effort which is gathering genomic and phenotypic data of Italian individuals enriched for the presence of metabolic dysfunction and MASLD (currently n = 5,875). Global Screening Array 3.0 (Illumina) and Michigan Imputation Server (GRCh38 TOPMed freeze 5) were used for SNP detection and imputation. We considered as main outcome the Fibrosis-4 Index (FIB-4) and secondary the Fibrotic NASH Index (FNI) and liver enzymes, as first-line clinical tests to identify at-risk MASLD (quantitative traits) adjusting the REGENIE regression models for age, sex, BMI, ethnicity.
Results: We confirmed a genome-wide significant association of *PNPLA3* locus with FIB-4 and FNI (rs738409 p.I148M; beta = 0.132, p = 3.06*10–22 and beta = 0.233, p = 3.59*10–16 respectively) and with circulating ALT (rs3747207; beta = 0.145, p = 2.64*10–16), AST (rs738408; beta = 0.186, p = 1.48*10–23), and GGT (rs738409; beta = 0.109, p = 1.28*10–11) levels. Additionally, *HAPLN4-TM6SF2* locus was associated with FNI (current top hit rs150641967 intronic variant; beta = 0.374, p = 5.55*10–10), *ERLIN1* locus was associated with circulating ALT (rs10883451; beta = -0.099, p = 2.64*10–9) while *GGT1* (rs2073397, beta = 0.157, p = 4.21*10–22), *RORA* (rs339969, beta = 0.108, p = 5.84*10–11) and *EXOC3L4* (rs944002, beta = 0.108, p = 8.22*10–10) loci associated with GGT.

Conclusion: We confirmed that single nucleotide polymorphisms in genes involved in hepatic lipid retention are the main genetic determinants of at risk of MASLD in the Italian population. These findings reinforce the role of *PNPLA3* as a key genetic determinant of MASLD, suggest the possible presence of additional contributors to liver disease at the *TM6SF2* locus and support the use of FNI to detect fibrosing MASH.

THU-405

Impact of ultra processed foods on metabolic dysfunction-associated steatotic liver disease: limitations of the NOVA classification

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Background and aims: The rise in consumption of ultra-processed foods (UPFs) has become an increasing concern in facilitating the metabolic syndrome. Subsequently, the relationship between MASLD and UPFs needs to be explored. The NOVA classification system categorizes foods into four groups based on their level of processing. This study aims to investigate UPF consumption, as classified by NOVA, in MASLD patients, and examine the impact of UPF intake on disease severity.
Method: A total of 315 MASLD patients were prospectively included (01/21–09/24) in a multi-center study. At baseline, all patients completed a food frequency questionnaire including 53 food groups to assess UPF consumption using the NOVA system. Clinical data, including controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were available for each patient. Follow-up (FU) nutritional and clinical data were obtained for 42 patients. Statistical analyses were performed using SPSS.
Results: Slightly more men (54%) than women (46%) were included with a mean age of 54y and a mean BMI of 32.5 kg/m². UPFs (NOVA 4) accounted for a significant proportion (34.7%) of total caloric intake in MASLD patients. Gender-specific dietary patterns were observed, with men consuming a significantly higher percentage of UPFs (37.2% ♀ vs 30.4% ♂, $p < 0.001$). Although no overall associations were found between UPF consumption (NOVA 4) and liver enzymes, CAP, or LSM, specific UPFs showed notable effects. Soft drink consumption was significantly associated to higher LSM, particularly in men, regardless of sugar content. Fast-food intake correlated with higher ALT levels, again more prominently in men. Conversely, patients consuming more unprocessed foods (NOVA 1) had significantly lower CAP levels (326 dB/m vs. 346 dB/m; $p < 0.024$). A reduction in processed meat intake during follow-up was associated with significantly lower CAP values, while increased consumption of salty fast foods correlated with higher LSM over time.
Conclusion: UPFs contribute to a large component of the diet in MASLD patients, particularly in men. While the NOVA food classification system offers a framework for categorizing UPFs, it provides limited insights into the effects of specific UPFs on MASLD. This study underscores the importance of dietary interventions to improve liver health, promoting increased consumption of unprocessed or minimally processed foods and reduced intake of soft drinks, fast foods, and processed meats.

THU-406

Life-style factors of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) – data from the german SLD-registry

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects more than 18 million individuals in Germany. Life-style choices including alcohol, coffee and smoking are frequent among these patients but prospective data on the combinatorial effects are rare. Real-world data help to better characterize the natural history of disease and to guide targeted lifestyle intervention.
Method: The German SLD-Registry aims to describe clinical characteristics and observe outcomes in secondary and tertiary care. Detailed data on life-style choices are prospectively collected. Advanced fibrosis was defined as liver stiffness (LS) >9.6 kPa.
Results: Baseline data of 903 patients were analysed. 40% (363/903) reported low grade alcohol consumption (mean 1.4 g/day, 60% male). The alcohol subgroup had higher levels of ferritin (152 vs. 205 ng/ml) but less frequently high-risk fibrosis scores (FIB-4 > 2.67 8.5 vs. 15%; NFS > 0.675 9.3 vs. 17%) or LS values > 9.6 kPa (25 vs. 73%; OR 0.546 [0.41–0.73], $p < 0.001$). Smokers (current 83/544, former 136/544) were more frequently male than never smokers (325/544) and had a trend towards higher CAP values (326 and 314 vs. 305 dB in never smokers). No association of smoking to LS > 9.6 kPa or cirrhosis stage could be observed (OR 0.94 [0.62–1.43], $p = 0.78$). Former smokers had more frequently coronary heart disease, hypercholesterolemia and hypertension. Coffee consumers (1–2 cups/day 229/464, 3–4 cups/day 117/464, > 5 cups/day 36/464) more frequently had high-risk fibrosis scores compared to non-consumers (FIB-4 > 2.67 17, 16, 14% vs. 9.8%; NFS > 0.675 18, 13, 19 vs. 7.9%). LS > 9.6 kPa tended to be more frequent in non-consumers (45% vs. 36, 23 and 28%). CAP values were not different between these groups. The OR for coffee drinkers was reduced (0.58 [0.97–0.34]; $p = 0.04$) with a significant dose dependency ($p < 0.003$). Physical activity was associated with a decreased risk of LS > 9.6 kPa (OR 0.63 [0.42–0.96], $p = 0.031$). No interaction of alcohol, coffee consumption and smoking could be detected.
Conclusion: Alcohol and coffee consumption is frequent among MASLD patients. Low grade alcohol and any degree coffee consumption were associated with a decreased risk of advanced liver fibrosis. For smoking, no such association to fibrosis but a trend towards

higher steatosis grade could be detected. Our data may confirm the beneficial effects of coffee and indicate that very low alcohol consumption may at least not exert relevant unfavourable effects of fibrosis progression.

THU-407-YI

Assessing muscle function in non-cirrhotic patients with steatotic liver disease : a cross-sectional study

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Background and aims: Muscle function decay and frailty are prevalent in cirrhosis whatever the cause. However, muscle function evaluation in non-cirrhotic patients is lacking, as well as data by etiology, including steatotic liver disease (SLD). Our aim is to determine if muscle function already decays in non-cirrhotic SLD and if the SLD subtype impacts muscle function.

Method: SLD patients were prospectively recruited and classified according to the recent SLD subtype categories. Liver disease was assessed by transient elastography (Fibroscan®). Cirrhotic patients were excluded. Controls were defined by the absence of liver steatosis on controlled attenuation parameter (<215 dB/m). Muscle function was assessed by isokinetic dynamometer (Cybex®). All patients and controls also underwent the three tests used to calculate the liver frailty index (LFI): handgrip strength, sit-to-stand test and balance test. SLD patients and controls were classified based on the LFI as robust (LFI <3) or pre-frail/frail (LFI ≥3). Results are expressed as means ± SD.

Results: One hundred and thirty-seven patients with SLD were included: 69 with alcohol-related liver disease (ALD) and 66 with metabolic dysfunction-associated steatotic liver disease (MASLD), and compared to 30 healthy controls matched for sex and age (controls: 47.8 years ± 14.1, ALD: 50.2 ± 10.8, MASLD: 52.5 ± 10.4; p = 0.16). The groups differed for several parameters, such as alanine aminotransferase (controls: 18.4 IU/L ± 10.2, ALD: 74.8 ± 53.2, MASLD: 48.3 ± 29.5; p < 0.0001), liver stiffness (controls: 4.4 kPa ± 1, ALD: 8.9 ± 3.5, MASLD: 9 ± 3.9; p < 0.0001) and body mass index (controls: 22.1 kg/m² ± 2, ALD: 26.3 ± 5, MASLD: 33.3 ± 6.4; p < 0.0001). LFI negatively correlated with right knee extension evaluated by isokinetic dynamometer in all SLD patients (N = 137, r = –0.53; p < 0.0001). LFI was higher in all SLD subgroups compared to controls (controls: 2.2 ± 0.8, ALD: 3.2 ± 0.8, MASLD 3.1 ± 0.7; p < 0.0001) without any difference between MASLD and ALD patients (p = 0.67). 56.5% of ALD patients and 58.5% of MASLD patients were considered pre-frail or frail (p = 0.81) compared to only 10% of control patients (p < 0.0001). LFI negatively correlated with right knee extension evaluated by isokinetic dynamometer in all SLD patients (N = 137, r = –0.53; p < 0.0001).

Conclusion: LFI is an accurate method to assess muscle function. Muscle function assessed by the LFI declines in non-cirrhotic SLD patients compared to age-matched controls. Frailty severity is not influenced by the SLD subtype. This highlights the concept of a muscle-liver axis already in the early stages of SLD.

THU-408

The impact of first and further decompensation in patients with metabolic-dysfunction associated compensated advanced chronic liver disease

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Background and aims: The first and further decompensation mark the natural history and the risk of mortality in patients with cirrhosis. We assessed the cumulative incidence of first and further (acute and non-acute) decompensation and evaluated their impact on both liver-related death (LR-D) in patients with compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD).

Method: Consecutive patients with clinical (LSM > 10 kPa) or biopsy-proven (F3-F4 fibrosis) diagnosis of cACLD due to MASLD were included. First and further decompensation were defined according

to Baveno VII criteria. Competing risk analysis and cumulative incidence functions were assessed by Fine and Gray. Cause-specific Cox models with baseline and time-dependent variables were applied. Multistate model was built to better assess the clinical course of cACLD due to MASLD.
Results: The cumulative incidence of the first decompensation was 3.5% at 5 years, increasing 20-fold the risk of LR-D at cause-specific Cox analysis; the cumulative incidence of further decompensation was 44% at 5 years among patients with first decompensation, additionally increasing 1.6-times the risk of LR-D. Ascites, followed by variceal bleeding, were the most common events in both first and further decompensation. Hepatocellular carcinoma (HCC) further independently increased the risk of LR-D of 3.2-times and 1.6-fold, respectively, in the whole cohort of cACLD due to MASLD and in those who experienced first decompensation.
Conclusion: The first and further decompensations represent tipping points in the clinical course of patients with cACLD due to MASLD, increasing 20-times and additionally 1.6-times the risk of LR-D. HCC is an independent predictor of LR-D in patients with cACLD due to MASLD, resulting in an additional risk of LR-D when associated with both first and further decompensation.

THU-413
Metabolic-dysfunction associated steatotic liver disease in inflammatory bowel disease: prevalence and progression
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Background and aims: Prevalence of MASLD in patients with Inflammatory Bowel Disease (IBD) has been reported 24.4% in a recent metaanalysis and 21.6% in a previous cross-sectional study from our center. However, data on the progression of MASLD in IBD patients are scanty. We aimed to investigate the prevalence and the progression of MASLD, diagnosed by non-invasive tools, in a homogeneous cohort of patients with IBD followed in our referral center.
Method: Consecutive IBD patients without known chronic liver disease were retrospectively enrolled and prospectively followed between 2020 and 2024. MASLD was defined as Controlled Attenuation Parameter (CAP) according to EASL criteria. Significant fibrosis was defined as Liver Stiffness (LSM) ≥8 kPa by FibroScan. Demographic, metabolic and biochemical data were collected at baseline and at the last follow-up visit. All patients were genotyped for PNPLA3 rs738409 C > G by Taqman assay. Univariate logistic regression analysis was performed to identify risk factors associated with the prevalence of MASLD and its progression.
Results: 230 patients (mean age was 46.1 ± 13.4 years, 49.2% were males, 50.8% had Crohn's disease, mean disease duration was 9.4 ± 7.5 years) were recruited. 14.8% of them were obese (BMI > 30 kg/m^2), 9.8% diabetic. 49.2% were PNPLA3 rs738409 CG/GG. 62 out of 230 patients had complete metabolic and biochemical assessment at follow-up. Mean follow-up time was 4 years. At baseline, according to EASL criteria, 31.1% (19/62) had MASLD. 19.1% (8/42) of patients without steatosis at baseline, developed steatosis at follow-up; while 42.1% of those having steatosis at baseline, did not show steatosis at follow-up. Two patients without fibrosis assessed by LSM at baseline developed significant fibrosis, while two patients with fibrosis at baseline experienced fibrosis regression. 13.5% developed obesity. Obesity was significantly associated with the prevalence of MASLD both at baseline ($p = 0.01$) and on follow-up ($p = 0.01$) and was a predictor of steatosis progression ($p = 0.01$); no association was found in relation to sex, PNPLA3 polymorphism, disease characteristics and the use of biologics. Diabetes was not significantly associated with MASLD in our cohort, but the number of patients was low.
Conclusion: One third of IBD patients had MASLD and obesity was the main predictor of its prevalence and progression, highlighting the relevance of active surveillance of MASLD and appropriate nutritional and lifestyle counselling especially in obese IBD patients. The use of biologics to control inflammation seems to have no influence on MASLD progression but data need further confirm in larger cohorts.

THU-414
Rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD)-associated hepatocellular carcinoma: a comparative analysis of clinical features and outcomes
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Background and aims: The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has been increasing worldwide. The prevalence of hepatocellular carcinoma (HCC) caused by MASLD is also increasing. Studies have shown that the clinical features and outcomes of MASLD-associated HCC differ from those of HCC due to viral and other etiologies; however, the results are conflicting. We aimed to compare the clinical features and outcomes of MASLD-associated HCC with those of other non-MASLD HCC.
Method: Between 1/1/2009 and 1/1/2024, we retrospectively identified patients (n = 174) diagnosed with HCC in our hospital and divided them into two groups: MASLD HCC and non-MASLD HCC. (1) Patient demographic and clinical characteristics, (2) tumor characteristics, (3) treatment modalities, and overall survival outcomes were compared between the two groups.
Results: The primary etiology was MASLD in 34 (19.5%) of the 174 patients with HCC included in the study. Most patients had a viral etiology (n = 121, 69.5%). The MASLD HCC group was less likely to be male than the non-MASLD HCC group (61.8% vs. 78.6%, $p = 0.042$), the median BMI was higher (31.5 kg/m^2 vs. 27.7 kg/m^2, $p < 0.001$), and the prevalence of diabetes was higher (91.2% vs. 32.9%, $p < 0.001$). The median alpha-fetoprotein levels, FIB-4 scores, ALBI scores, ECOG scores, BCLC stages, maximum tumor diameters, and baseline cirrhosis percentages were similar between the groups. Patients were divided into two groups according to their primary etiological diagnosis: before and after January 2019, a significantly higher proportion of MASLD HCC patients (88.2%) was diagnosed after January 2019 than non-MASLD HCC patients (67.9%) ($p = 0.018$). The median overall survival (OS) of non-MASLD HCC median OS was 46 and 41 months, respectively. MASLD HCC compared to non-MASLD HCC, hazards ratio was 0.98 (95% CI: 0.56–1.71, $p = 0.938$). There was no significant difference in the OS between the two groups.
Conclusion: The prevalence of HCC in the MASLD setting has significantly increased in recent years. There was no difference in overall survival between patients with HCC due to MASLD and HCC due to other etiologies.

THU-415
Comparison of clinical characteristics and outcome of HCC patients with and without MASLD underwent surgical resection – experience from an asian tertiary center
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) may influence the outcomes of patients with hepatocellular carcinoma (HCC). This study aimed to compare the clinical characteristics and outcomes of HCC patients with and without MASLD who underwent surgical resection and identify risk factors associated with poor overall survival (OS) and recurrence-free survival (RFS).
Method: This retrospective study included 946 HCC patients who underwent surgical resection as their initial treatment at Taipei Veterans General Hospital between 2016 and 2022. Patients with combined HCC and cholangiocarcinoma (n = 35) and those with insufficient pathological data (n = 5) were excluded, leaving 906 patients for analysis. Based on the latest MASLD diagnostic criteria, patients were categorized into the MASLD group (n = 410) and the non-MASLD group (n = 496). The primary endpoint was OS, while the secondary endpoint was RFS. Baseline demographics, serum biochemistry, imaging features, and pathological findings from hepatectomy specimens were analyzed. Independent risk factors for poor OS and RFS were identified using Cox proportional hazards models. Kaplan-Meier survival analyses were performed to compare outcomes between groups.
Results: HCC Patients with MASLD were less likely to have cirrhosis, and had earlier tumor stages, lower histological grades, lower rates of microvascular invasion, and lower serum alpha-fetoprotein (AFP), aspartate aminotransferase (AST) levels and lower platelet counts, and higher serum albumin levels, compared to the non-MASLD cohort. After a median follow-up of 59.2 months, 195 patients died, and 385 experienced recurrences. The 5-year OS rate was significantly higher in the MASLD group (78.3%) than in the non-MASLD group (67.1%) (p = 0.006). Similarly, the 5-year RFS rate was higher in the MASLD group (50% vs. 45%, p = 0.019). Cox proportional hazards models identified age, serum albumin, serum creatinine, serum AST, serum AFP, tumor size, and histological grade, but not MASLD, as independent risk factors for poor OS.
Conclusion: HCC patients with MASLD demonstrated better OS and RFS compared to non-MASLD patients. However, MASLD itself was not an independent risk factor for poor OS or RFS.

THU-416

Risk assessment for carotid atherosclerosis in asymptomatic patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Cardiovascular disease remains a leading cause of mortality in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). This study evaluated the association between subclinical carotid atherosclerosis (SCA) and MASLD or MASLD and increased alcohol intake (MetALD) in asymptomatic individuals.
Method: This cross-sectional study analyzed 56,889 adults who underwent health check-ups at a tertiary hospital in South Korea between January 2015 and December 2020. Hepatic steatosis was diagnosed via sonographic findings, and SCA was assessed using duplex ultrasound to measure carotid intima-media thickness or detect plaques. Liver fibrosis was evaluated using the Fibrosis-4 index and point-shear wave elastography. The study population included 13,969 patients with MASLD and 3,854 with MetALD.
Results: Among the participants, 7,679 (13.5%) were diagnosed with SCA. MASLD was significantly associated with SCA after adjustment (adjusted odds ratio [aOR] 1.26; 95% confidence interval [CI] 1.19–1.33, p < 0.001), as was MetALD (aOR 1.43 [1.30–1.58], p < 0.001). The association between MASLD and SCA increased with the severity of hepatic steatosis and liver fibrosis. MASLD patients with a hepatic steatosis index ≥36, Fibrosis-4 ≥1.3, and liver stiffness ≥5.6 kPa had adjusted odds ratios of 1.70 [1.53–1.88], 1.23 [1.14–1.33], and 1.78 [1.05–3.01], respectively, for SCA risk compared to individuals without MASLD. A similar trend was observed for MetALD, with adjusted odds ratios of 1.83 [1.51–2.23], 1.49 [1.30–1.70], and 1.29 [0.52–3.19], respectively.
Conclusion: MASLD and MetALD are strongly associated with an elevated risk of SCA, particularly in the presence of liver fibrosis. These findings underscore the importance of carotid ultrasound screening in patients with MASLD and MetALD accompanied by liver fibrosis.

THU-417

Influence of cardiometabolic risk factors and alcohol consumption on liver stiffness in MASLD patients: a multicenter study in Colombia

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Background and aims: To better characterize steatotic liver disease, a new nomenclature has recently been proposed, aiming to group patients based on the disease's etiology. The metabolic dysfunction-associated steatotic liver disease (MASLD) category includes all patients with steatosis who present at least one cardiometabolic risk factor (CMRF). However, significant differences exist in how each factor influences disease progression. Alcohol consumption thresholds for MASLD diagnosis were arbitrarily chosen, risk of chronic liver disease seems to increase even with values below current limits. It is possible that alcohol's interaction with different cardiometabolic risk factors, or even the interaction between the risk factors themselves, could contribute to disease progression. This study aims to compare elastographic values in MASLD patients based on the number of CMRF and determine the effect of interactions between CMRF themselves and these risk factors and alcohol consumption on liver stiffness.
Method: Patients diagnosed with MASLD from four cities in Colombia who underwent transient elastography were included. Other causes of chronic liver disease were ruled out. Patients with significant alcohol consumption were excluded. Cardiometabolic risk factors were defined according to ATP III criterio. Alcohol consumption was calculated using the number of standard drink units per week. Interaction terms between CMRF themselves, and between CMRF and alcohol consumption were included in a multivariate linear regression analysis where liver stiffness was the dependent variable.
Results: A total of 284 patients were included, 57.4% were female. The prevalence of hypertension, diabetes, dyslipidemia, and overweight was 50.4%, 27.1%, 64.8%, and 92.3%, respectively. Patients with 1, 2, 3, and 4 cardiometabolic risk factors represented 25.4%, 27.8%, 33.8%, and 13%, with progressively increasing elastographic values of 6.4 KPa, 6.9 KPa, 7.9 KPa, and 8.5 KPa, respectively. However, there were no statistically significant differences in elastographic values between patients with 1 or 2 (3.5 KPa vs. 4.7 KPa; p = 0.47), 2 or 3 (6.9 KPa vs. 7.9 KPa; p = 0.39), or 3 or 4 (7.9 KPa vs. 8.5 KPa; p = 0.66) CMRF. Multivariate linear regression analysis identified diabetes (b = 0.2, 95% CI: 1.1 to 4.3; p = 0.001) and the interaction between diabetes and dyslipidemia (b = –0.32, 95% CI: –7.8 to –1.7; p = 0.003) as the only independent predictors of liver stiffness. Diabetic patients had higher elastographic values than their counterparts (9.6 KPa vs. 6.7 KPa, p = 0.017). No interaction terms between alcohol

consumption and cardiometabolic risk factors were associated with elastographic values.
Conclusion: The MASLD category encompasses a heterogeneous spectrum of disease severity. Diabetes and its interaction with dyslipidemia appear to be the main determinants of liver stiffness but this data needs further validation. No association was found between mild alcohol consumption and elastographic values.

THU-418
The effect of a fast-food meal on endothelial function in people with metabolic dysfunction-associated steatotic fatty liver desease
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Background and aims: For people with metabolic dysfunction-associated steatotic fatty liver disease (MASLD), cardiovascular disease (CVD) is the leading cause of death. Although the association between the two diseases is strongly established, the underpinning mechanisms are not clearly defined. Elevated consumption of dietary fat combined with metabolic dysfunction may contribute to the burden of CVD on people with MASLD by inducing endothelial dysfunction. Therefore, this study aimed to investigate the acute response in endothelial function and circulating blood lipids and glucose to a fast-food meal (breakfast burger) in participants with and without MASLD.
Method: Participants with (n = 8, 68 ± 7 years, 50% male) and without MASLD (n = 9, 62 ± 8 years, 44% male) attended two experimental sessions separated by at least 7 days. The participants with MASLD were non-cirrhotic and had a liver stiffness between 8–12 kPa. During experimental sessions, participants consumed either a fast-food meal (3579 kj, 45 g of fat) or a 50 mL glass of water (control) in a randomized cross-over design. Outcome measures included brachial artery flow mediated dilation (FMD) for analysis of endothelial function and venous blood samples for blood glucose and lipid concentrations, taken prior to meal/water consumption and then hourly for six hours.
Results: During the water control visit, there was no change in FMD, blood triglycerides, or blood glucose concentration for either group, however, after consumption of the meal there was a reduction in FMD in both groups. When expressed relative to baseline, the percentage change in FMD was greater in the MASLD group after the test meal compared with the healthy control group (−61 ± 12% vs −41 ± 23%, p = 0.046). Blood triglyceride concentrations were elevated after the test meal for both groups. However, the absolute change in triglyceride levels from baseline to peak elevation was greater in the MASLD group compared with the healthy control group (+1.41 ± 0.58 mmol·L^{-1} vs +0.72 ± 0.56 mmol·L^{-1}, p = 0.043). Blood glucose concentration was elevated after the test meal in the MASLD group, while it did not change in the healthy control group.
Conclusion: The novel finding from this study is that postprandial endothelial dysfunction is exacerbated in people with MASLD compared with sex- and age-matched healthy participants. In MASLD, exaggerated elevations in blood triglycerides and blood glucose postprandially may aggravate endothelial dysfunction. These findings suggest that reducing intake of dietary fats and glucose should be a treatment target to decrease both the risk and the burden of CVD on the MASLD population.

THU-419
Differences in quality of life and coping strategies between patients with metabolic dysfunction-associated steatotic liver disease and liver transplant recipients. A comparison with the general spanish population
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and liver transplantation are closely associated with a psychosocial risk profile, including impaired quality of life (QoL) and maladaptive coping strategies. However, evidence of differences in QoL and coping strategies between these two groups of patients has not yet been reported. We therefore sought to analyze the differences in QoL and coping strategies between MASLD patients and liver transplant recipients, using QoL data from the general Spanish population in (GSP), and determine the coping strategies predicting QoL in these two groups.
Method: The total sample of 480 patients was evaluated using the SF-12 and Brief COPE and divided into two groups balanced for age and gender: 240 biopsy-proven MASLD patients (G_1) and 240 liver transplant recipients (G_2). The independent samples *t*-test was used to compare QoL and coping strategies between these two groups and with the GSP. Stepwise multiple linear regression was used in both groups of patients to analyze what coping strategies predicted QoL. Cohen's d was used to measure effect size.
Results: Patients with MASLD (G_1) had better scores in physical functioning ($p < 0.006$, $d = 0.25$), role-physical ($p < 0.001$, $d = 0.36$), social functioning ($p < 0.001$, $d = 0.46$) and role-emotional ($p = 0.011$, $d = 0.23$), and worse scores in general health ($p < 0.001$, $d = –0.62$) and vitality ($p = 0.008$, $d = -0.24$) than liver transplant recipients (G_2). Both MASLD patients (G_1) and liver transplant recipients (G_2) had worse scores in physical functioning ($p < 0.001$, $d = –0.56$, G_1; $p < 0.001$, $d = –0.82$, G_2), role-physical ($p < 0.001$, $d = –0.38$, G_1; $p < 0.001$, $d = –0.74$, G_2), bodily pain ($p < 0.001$, $d = –0.25$, G_1; $p = 0.002$, $d = –0.21$, G_2), vitality ($p < 0.001$, $d = –0.50$, G_1; $p < 0.001$, $d = –0.26$, G_2), role-emotional ($p < 0.001$, $d = –0.31$, G_1; $p < 0.001$, $d = –0.55$, G_2) and physical component summary ($p < 0.001$, $d = –0.47$, G_1; $p < 0.001$, $d = –0.47$, G_2) than the GSP. Lastly, active coping ($p < 0.001$, beta = 0.31), denial ($p < 0.001$, beta = –0.24), positive reframing ($p = 0.004$, beta = 0.20), self-blame ($p < 0.001$, beta = –0.21) and acceptance ($p = 0.024$, beta = 0.16) predicted QoL in MASLD patients (G_1). Self-distraction ($p < 0.001$, beta = –0.23), acceptance ($p = 0.004$, beta = 0.19), active coping ($p < 0.001$, beta = 0.27), self-blame ($p = 0.009$, beta = –0.17) and religion ($p = 0.015$, beta = –0.15) predicted QoL in liver transplant recipients (G_2).
Conclusion: QoL was mostly lower in liver transplant recipients than MASLD patients, although self-perceived health was worse in MASLD. Both groups of patients showed greater decline in QoL, mainly physical, than the GSP. Coping strategies such as active coping, positive reframing or acceptance predicted better QoL, while denial, self-blame, self-distraction and religion predicted worse QoL. QoL and coping strategies should be considered important at all stages of liver disease, from MASLD to liver transplantation.

THU-420

10 years progression of metabolic risk factors, diet quality and degree of steatosis and fibrosis in a general population cohort - ECOR liver study

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Background and aims: Relationship between diet quality, inflammation, and metabolic health is key to understanding non-communicable diseases such as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). This study evaluates dietary patterns, anthropometric parameters, and the degree of steatosis and fibrosis in a Portuguese cohort over 10 years, correlating outcomes with the Healthy Eating Index (HEI).
Method: Assessments were conducted at two time points, with a mean 10-year interval. Participants consulted with a hepatologist, dietitian, nurse and underwent physical exams, blood tests, liver elastography (Fibroscan®) measuring CAP (steatosis), LSM (liver stiffness), and nutritional parameters (BMI, waist circumference - WC, dietary intake). HEI was calculated based on consumption of specific food groups. Higher consumption of dairy, protein foods, fruits, whole fruits, whole grains, vegetables, greens, beans and seafood/plant proteins contributed positively to the score, while higher intake of refined grains, sodium, added sugars, and saturated fats contributed negatively. HEI was analyzed as a continuous variable and by quartiles based on the sample distribution.
Results: The cohort of 92 individuals (53.3% male, baseline age 47.5 ± 16.2 years) showed a significant increase in steatosis prevalence from 29.3% to 47.8% ($p = 0.014$). Mean LSM decreased slightly from 5.1 ± 1.4 to 4.9 ± 1.8 kPa (NS), while moderate fibrosis (> 8 kPa) rose from 3.3 to 5.6% (NS). Weight (73.7 ± 14.1 to 77 ± 15.9 kg, $p < 0.001$), BMI (26.7 ± 3.6 to 28.2 ± 4.4 kg/m², $p < 0.001$), and WC (89.1 ± 12.5 to 93.9 ± 14.1 cm, $p < 0.001$) increased significantly. Caloric intake reduced from 2469 ± 805 to 1874 ± 672 kcal ($p < 0.001$), with reductions in protein (110.8 ± 34.7 to 88.1 ± 31.8 g, $p < 0.001$), carbohydrates (292.5 ± 111.6 to 194.9 ± 78.9 g, $p < 0.001$), and fiber (29.1 ± 12.1 to 20.4 ± 8.6 g, $p < 0.001$). Total HEI improved from 53.1 ± 7.9 to 59.8 ± 9.7 ($p < 0.01$). Significant HEI decreases for whole grains ($p < 0.01$), saturated fats ($p < 0.01$), greens and beans ($p = 0.027$), and whole fruits ($p < 0.01$). HEI for added sugar ($p = 0.001$) and sodium ($p < 0.01$) improved. Individually, HEI inversely correlated with BMI ($r = -0.297$, $p < 0.01$) and weight ($r = -0.267$, $p < 0.05$). Lower HEI quartiles link to poorer fatty acid profiles, while higher quartiles show better refined grain scores ($p < 0.03$ to $p < 0.001$). Whole grains, vegetables, fruits, and greens and beans intake improves with higher HEI scores ($p < 0.05$ to $p < 0.001$).
Conclusion: Despite improvements in diet quality, including reduced added sugar, sodium intake and lower caloric consumption, these changes did not significantly reduce weight, WC, or steatosis prevalence. Liver stiffness remained stable, suggesting reduced caloric expenditure, lower physical activity, or reporting bias. Nutritional interventions are crucial to further improving diet quality and promote weight control.

THU-421

10 year progression of metabolic risk factors - correlation with steatosis and fibrosis degree in a general population cohort

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Background and aims: There is evidence that aging is associated with an increase in the number of metabolic risk factors potentially increasing prevalence and degree of hepatic steatosis. Aiming to evaluate which factors could predominantly be associated, we studied a group of individuals from the general population that had been previously evaluated, comparing risk factors, as well as hepatic steatosis and fibrosis grade after a 10-year interval.
Method: From 220 participants initially included, it was possible to re-evaluate 92 with a similar methodology, single visit to a multidisciplinary consultation: hepatologist, dietitian and nurse. A physical examination, blood panel and liver elastography (Fibroscan®) with assessment of CAP (for steatosis), LSM (for liver stiffness) and a nutritional evaluation (BMI, waist circumference-WC, dietary intake) were carried out.
Results: 53.3% of the participants were male, with an average baseline age of 47.5 ± 16.2years. Steatosis prevalence increased from 29.3 to 47.8% ($p = 0.014$). Prevalence of moderate fibrosis increased from 3.3 to 5.6% (NS), but none of the current fibrotic patients presented fibrosis at baseline. Eighty percent of those with steatosis at baseline, now had moderate fibrosis. Average weight was 73.7 ± 14.1 kg at baseline vs. 77.6 ± 15.9 kg ($p < 0.001$) currently, implicating an increase in the average BMI from 26.7 ± 3.6 at baseline to 28.2 ± 4.4 kg/m² ($p < 0.001$). Average WC also increased: (89.1 ± 12.5 vs. 93.92 ± 14.1 cm: $p < 0.001$). The proportion of overweight participants has risen from 69.7% to 81.4% ($p = 0.035$), obese prevalence increased from 15.7 to 27.9% ($p = 0.001$). Mean systolic blood pressure increased from 122.9 ± 18.6 mmHg to 130.9 ± 20.7 mmHg ($p < 0.001$). Participants with steatosis, had higher BMI: 28.1 ± 3.2 vs. 25.6 ± 3.4 kg/m² ($p = 0.001$) and WC: 94.8 ± 10.6 vs. 84.4 ± 11.8 cm ($p < 0.001$) compared to baseline. From univariate analysis, the BMI ($p = 0.002$), ALT ($p = 0.012$), GGT ($p < 0.001$) and HDL ($p = 0.010$), at baseline significantly correlate with the presence of steatosis 10 years later. However, in multivariate analysis only GGT remained significantly associated (OR: 1.043 [1.002–1.086]: $p = 0.038$).
Conclusion: We confirmed aging to associate with increased prevalence of overweight/obesity as well as waist circumference, with potential increase in visceral fat, a significant risk factor for metabolic diseases. As expected, the prevalence of steatosis and moderate fibrosis also increased. These findings highlight the need for interventions with an emphasis on preventing weight gain, that besides promoting cardiovascular and metabolic health, can mitigate the progression of liver diseases. Interestingly, elevation of GGT in the baseline was the best predictor of steatosis development.

THU-422-YI

Hepatic mitochondrial reductive stress predicts major adverse liver-related outcomes and is modifiable by common medications and diet

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, which can progress to life-threatening cirrhosis and liver failure. Clinical studies have shown that the severity of MASLD associates with a high plasma beta-hydroxybutyrate-to-acetoacetate ratio (bOHB/AcAc), a well-established marker of hepatic mitochondrial reductive stress. Here, we aimed to investigate whether bOHB/AcAc predicts major adverse liver-related outcomes (MALO) in a large prospective cohort. Additionally, we sought to identify medications and dietary factors that associate with bOHB/AcAc.
Method: In the UK Biobank data (~500,000), plasma bOHB and AcAc concentrations were determined using the Nightingale NMR metabolomics platform. We excluded participants with liver disease at baseline or chronic viral hepatitis at any time, and constructed registry-based prospective models restricted to a 15-year follow-up. We conducted multivariable Cox regression analyses to evaluate the associations between baseline bOHB/AcAc and MALO. The analyses were adjusted for age, sex, waist-to-hip ratio, BMI, and alcohol consumption. We utilized linear regression to evaluate the associations of bOHB/AcAc with self-reported medication use and dietary factors based on repeated 24-hour dietary recalls. We validated medication associations in vitro by assessing their effects on HepG2 cell viability after 24-hour incubations in 300 uM palmitate.
Results: High baseline bOHB/AcAc predicts the risk of hospitalization due to both non-alcohol-related and alcohol-related cirrhosis (K70.3 or K74.6) and chronic hepatitis (K73) (HR = 1.12–1.51 per 1-SD, $p < 0.05$, for all). Furthermore, bOHB/AcAc predicts mortalities related to cirrhosis (K70.3 and K74.6) and liver failure (K70.4 and K72) (HR = 1.24–1.50 per 1-SD, $p < 0.05$ for both). Multiple commonly used medications associated with bOHB/AcAc, including statins, whose users had 10.8% lower bOHB/AcAc compared to non-users (FDR <0.0001). Atorvastatin and simvastatin improved HepG2 viability dose-dependently ($p \leq 0.0001$, for both). Regarding dietary factors, high fat intake was associated with high bOHB/AcAc (effect size 2.4% per 1-SD, FDR <0.01). Conversely, intakes of vitamins B1, B2, B3, B5, B6, B9, and B12, as well as zinc, exhibited an inverse association with bOHB/AcAc (effect sizes ranging from −1.7% to −2.5% per 1-SD, FDR <0.01).
Conclusion: Plasma bOHB/AcAc predicts both metabolic dysfunction-associated and alcohol-related MALO. High dietary fat intake associates with increased bOHB/AcAc, while statin use and intake of nutrients necessary for mitochondrial energy metabolism, such as B vitamins and zinc, associate with decreased bOHB/AcAc. These data suggest that mitochondrial reductive stress contributes to the development of MALO, and may be modifiable by medications and dietary factors.

THU-423

All-cause and disease-specific mortality in young adults with metabolic dysfunction-associated steatotic liver disease: a nationwide cohort study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a major cause of chronic liver disease globally, particularly among young adults. This study aimed to analyze all-cause and disease-specific mortality in young adults with MASLD.
Method: In this nationwide cohort study, we analyzed data from the Korean National Health Insurance Service, focusing on individuals aged 20 to 39 years who underwent health screenings between 2009 and 2012. The participants were categorized into two groups: those with MASLD and those without steatotic liver disease (SLD). SLD was defined by a fatty liver index ≥30. Mortality risk was analyzed via Cox proportional hazards models.
Results: MASLD was present in 25.3% of the study participants. During a median follow-up of 10.6 years (interquartile range, 9.5–11.2), individuals with MASLD had a significantly greater risk of all-cause mortality than did those without steatosis (adjusted hazard ratio [aHR], 1.17; 95% confidence interval [CI], 1.13–1.21). The MASLD group also had an increased risk of mortality related to cardiovascular disease, liver cancer, and liver disease, whereas the risk of extrahepatic cancer related mortality did not significantly differ between the two groups. Compared with men with MASLD, women with MASLD had higher risks of all-cause mortality, cardiovascular mortality, extrahepatic cancer mortality, and liver disease-related mortality, although the risk of liver cancer-related mortality was similar between the sexes.
Conclusion: Young adults with MASLD are at a significantly increased risk of all-cause and disease-specific mortality. These findings underscore the importance of early detection and intervention to mitigate the long-term outcomes of MASLD in young adults.

THU-424

Patient preferences for metabolic-dysfunction associated steatotic liver disease: moving towards patient centred care

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Background and aims: Considerable variability exists among MASLD care pathways. There is an important, unmet need to identify patient preferences for MASLD care for prevention, screening, risk stratification, follow-up and management. Understanding patient preferences is integral to the improvement and innovation process and can optimise clinical outcomes, improve engagement and treatment adherence. This study aimed to explore patient preferences for MASLD care.
Method: In-depth qualitative interviews and focus groups were conducted with adults in the UK who have MASLD, managed in primary or secondary care, and with those at risk of MASLD. An interview guide was co-developed by the multidisciplinary research team and patient and public involvement representatives and was updated in an iterative manner. Thematic analysis of the data was performed.
Results: Thirty-three adults aged between 31 and 78 years participated (30% male, 70% female; 85% White, 12% Black, 3% Asian). Twelve participants were managed in primary care, twelve in secondary care and nine were identified as being at risk of MASLD. The absence of MASLD public health campaigns negatively influenced participants understanding of its importance. This was compounded by the lack of information provided by healthcare professionals at diagnosis. All participants wished to be screened for MASLD, primarily as they felt a diagnosis would encourage lifestyle changes. Emphasis was placed on clear communication of the diagnosis, including information about disease stage, trajectory and reversibility. Participants were receptive to multiple non-invasive testing to determine disease stage and were not concerned by potential false positive results providing the possibility was clearly explained. Participants strongly desired more information on weight

management and suggested that individualised support would be most effective. When asked to rank preferences of care, clear explanation of liver disease stage and test results was deemed a priority, compared to access to clinical trials and treatment for weight loss.
Conclusion: In this first qualitative study to explore patient preferences for MASLD care, clear communication emerged as the dominant theme across the patient journey for people at risk of, and living with, MASLD. Incorporating such patient preferences into MASLD care pathways will potentially improve patient satisfaction and clinical outcomes.

THU-425-YI
Clinical and genetic predictors of steatotic liver disease in lean individuals: a cohort study of risk factors and fibrosis prediction
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Background and aims: Steatotic liver disease (SLD), characterized by fat accumulation exceeding 5% in the liver, can progress to cirrhosis due to cardiometabolic conditions, genetic predisposition, or alcohol consumption. Lean SLD, a rare phenotype, presents unique challenges as the balance of metabolic and genetic risk factors remains unclear. Although non-invasive tools like the Fib-4 score and polygenic risk score are validated for the general population, their utility in lean individuals is underexplored. This study aimed to characterize clinical and genetic factors influencing SLD and advanced fibrosis in lean patients (BMI ≤25 kg/m²).
Method: We used natural language processing, search tools, and manual chart review to identify lean SLD patients and match lean controls without SLD from two large healthcare biobanks. We also performed cross-sectional comparisons with overweight/obese SLD patients (BMI > 25 kg/m^2). SLD diagnosis was confirmed through radiology, pathology, or biopsy review. Data on clinical variables, laboratory values, and genetic variants (in *PNPLA3, TM6SF2, GCKR*, and *MBOAT7*) were analyzed using univariate and multivariate statistical methods.
Results: Among 188 lean SLD patients, 694 lean controls, and 3090 overweight/obese SLD patients, lean SLD patients had fewer metabolic comorbidities than their overweight/obese counterparts but more than lean controls. Diabetes emerged as the strongest predictor of lean SLD (OR 2.42, 95% CI 1.43–4.08, p < 0.001). Coronary artery disease and hypertension showed a trend without reaching statistical significance. Genetic variants in the main genes associated with SLD polygenic score were not significantly associated with SLD or fibrosis in lean patients. The Fib-4 score demonstrated moderate accuracy in identifying advanced fibrosis in lean individuals (AUC 0.76, 95% CI 0.64–0.89, p < 0.001).
Conclusion: Metabolic factors, particularly diabetes, are primary predictors of SLD in lean individuals, while genetic variants did not contribute significantly to disease risk or progression. The Fib-4 score proved to be an effective tool for assessing advanced fibrosis risk in this population, supporting its role in early diagnosis and targeted management strategies for lean SLD patients.

THU-429
Volatile organic compound metabolites in urine are associated with MASLD and fibrosis: an environmental health study
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Background and aims: Exposure to volatile organic compounds (VOCs) through inhalation, ingestion, and dermal contact has increased over the past decades, raising concerns about their impact on environmental health. VOCs are mostly metabolized by the liver into various compounds which are subsequently excreted in urine. While VOC exposure has been linked to impaired metabolic health, the associations between VOCs and metabolic dysfunction-associated steatotic liver disease (MASLD) as well as fibrosis due to steatohepatitis or a direct toxic effect remains unclear.
Method: We used data from the NHANES 2017–2020 cycle, a United States population-based cohort with data on controlled attenuation parameter (CAP) and liver stiffness measurements (LSM). Participants with viral hepatitis, excessive alcohol consumption or missing data on urine creatinine were excluded. MASLD was defined as CAP ≥275 dB/m together with metabolic dysfunction and fibrosis as LSM ≥8 kPa. To account for co-linearity between the 15 individual urine VOC metabolites, least absolute shrinkage and selection operator (LASSO) analysis was used to identify urine VOC metabolites that were most associated with MASLD and fibrosis. Weighted quantile sum (WQS) analysis was performed to quantify the associations of the LASSO-selected parameters. Analyses were adjusted for age, sex, smoking and alcohol consumption.
Results: The cohort included 2,279 participants (median age 51 [34–64], 48% male), with 41.4% having MASLD and 9.6% fibrosis. LASSO identified CEMA, MA, 3HPMA and DHBMA as a predictor of increased steatosis and/or fibrosis risk, while PGA, SBMA, CYMA, 2-HPMA and ACTA were linked to reduced steatosis and/or fibrosis risk. WQS analysis generated weighted quantile mixtures of the LASSO-selected VOCs both in positive and negative directions of effect. For steatosis, a non-significant increased risk was observed (aOR 1.13 per quartile, 95%CI 0.97–1.32; 75% accounted for by CEMA), while a significant decreased risk was found (aOR 0.66 per quartile, 95%CI 0.53–0.83; 38% by PGA, 33% by CYMA). For fibrosis, a non-significant increased risk (aOR 1.37 per quartile, 95%CI 0.86–2.17; 31% by MA, 25% by DHBMA, 24% by 3-HPMA) and a significant decreased risk (aOR 0.61 per quartile, 95%CI 0.40–0.93; 48% by PGA, 21% by 2-HPMA) were found.
Conclusion: Urinary metabolites of VOCs are associated with MASLD and fibrosis in the general population. Both positive and negative associations were observed. Notably, MA, a metabolite of styrene and ethylbenzene, is further metabolized by alcohol dehydrogenase into PGA. In this study, higher levels of MA were linked to an increased risk of fibrosis, while higher levels of PGA were associated with a decreased risk of fibrosis. These contrasting associations raise the possibility that impaired metabolism of ethylbenzene and styrene could lead to intra-organic accumulation, potentially contributing to fibrosis risk.

THU-430
Weight loss was associated with risk reduction of MASLD, at-risk MASH and fibrosis with ongoing effects beyond the current recommendations
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Background and aims: Weight loss varying between 3–10% is recommended in individuals with MASLD, dependent on whether there is only steatosis or also signs of metabolic dysfunction associated steatohepatitis (MASH) or fibrosis. These recommendations originate from experiences post gastric bypass surgery. However, improved insulin resistance is observed in individuals after gastric bypass even before substantial weight loss has occurred. We therefore investigated the associations between weight loss and risk of MASLD, MASH and fibrosis in a general population setting.
Method: A United States population-based cohort, NHANES 2017–2020, was used. Participants aged 18–80 years, with data on controlled attenuation parameter (CAP) and/or liver stiffness measurements (LSM) were selected. Exclusion criteria were BMI <18.5, excessive alcohol consumption, viral hepatitis, ALT > 100 and missing data on weight history. Weight change was based on self-reported weights. Current MASLD status was defined as CAP ≥275 dB/m together with metabolic dysfunction, at-risk MASH based on the Fibroscan AST (FAST) score ≥0.35 and fibrosis as LSM ≥8 kPa. Risk reduction attributed to weight loss was quantified using logistic regression analysis, adjusted for age, sex, race, education, smoking, alcohol consumption and BMI (either 10 years or 1 year ago, depending on the analysis). Non-linearity was assessed by restricted cubic splines among those with either weight loss or stable weight.
Results: We included 6753 individuals (aged 48 yr [33–62], 48.7% male), of whom 29% gained >3% weight, 44% remained stable, and 28% gained >3% weight over the last year. Weight change was between −14% and +14% for 90% of the population. At the current study visit, 42.0% had MASLD, 5.9% at-risk MASH and 8.9% fibrosis. Compared to stable weight, weight increase was associated with an increased risk of MASLD (OR 1.76; 95%CI 1.52–2.04), at-risk MASH (OR 1.96; 95%CI 1.48–2.58) and fibrosis (OR 1.55; 95%CI 1.23–1.96). Similarly, weight loss was associated with reduced risk for MASLD (OR 0.52; 95%CI 0.45–0.61), at-risk MASH (OR 0.73; 95%CI 0.54–0.98) and fibrosis (OR 0.59; 95%CI 0.46–0.75). Among those with stable weight or weight loss, each 5% reduction in weight was associated with lower risk of MASLD (OR 0.66; 95%CI 0.62–0.70), at-risk MASH (OR 0.85; 95%CI 0.74–0.95) and fibrosis (OR 0.79; 95%CI 0.71–0.90). There was no evidence of significant non-linearity for these outcomes. Results were consistent for 10-years weight change or when focusing on BMI changes.
Conclusion: In this general population study, the observed risk of MASLD, MASH and fibrosis decreased with self-reported weight loss. Higher reported weight loss was associated with lower observed risks in a linear fashion, indicating that weight loss beyond the currently recommended targets could further reduce the risk of advanced liver disease.

THU-431

Influence of cardiometabolic risk factors on HCC risk in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Emerging data suggest that cardiometabolic risk factors (CMRFs) are major risk factors for hepatocellular carcinoma (HCC). However, it is unclear that which CMRFs are significantly associated with HCC development in metabolic dysfunction-associated steatotic liver disease (MASLD). We investigated the influence of five CMRFs, the criteria of MASLD definition, on the risk of HCC development in patients with MASLD.
Method: Between 2004 and 2023, this multicenter retrospective cohort study recruited 73,599 patients with MASLD from 5 medical centers in South Korea. The index date was defined as the date of the first diagnosis of MASLD and the primary outcome was HCC development. A time-varying Cox proportional analyses was performed for risk factor of HCC development, which handled the duration of each CMRF in each patient as a time-dependent variable. Significant liver fibrosis was defined as the fibrosis-4 index (FIB-4) > 2.67 or liver stiffness (LS) by vibration-controlled transient elastography ≥8 kPa.
Results: The mean age was 53.3 years, and male gender predominated (n = 43,440, 59.0%). During a median follow-up period of 5.0 years (interquartile range, 2.5–9.0 years), 142 (0.2%) patients developed HCC (0.32 per 1,000 person-years). Among fiver CMRFs, Overweight/obesity or central obesity (CMRF 1; adjusted hazard ratio [aHR] = 2.20, 95% CI = 1.26–3.85, p = 0.006) and pre-diabetes/diabetes (CMRF 2; aHR = 1.90, 95% CI = 1.20–3.00, p = 0.006) were independently associated with the risk of HCC development in time-varying Cox multivariable analysis, along with age, gender, platelets. Patients with CMRFs 1 and 2 had a significantly higher risk of HCC development than those with other CMRFs in the subgroup with FIB-4 <2.67 (aHR = 3.18, 95% CI = 1.46–6.93, p = 0.004). In contrast, the risk of HCC development was statistically similar between patients with CMRFs 1 and 2 and those with CMRFs 1 and 2 who additionally had other CMRFs (p = 0.119). Similar results were identified in the subgroups with FIB-4 ≥2.67, LS <8 kPa, and LS ≥8 kPa. Among patients with MASLD having CMRFs 1 and 2 at baseline (n = 29,453), the risk of HCC development was significantly lower in those who improved CMRF 2 at 2 years (n = 7,453 [25.3%], p = 0.004) compared to that in patients who consistently had CMRFs 1 and 2 (n = 18,930, 64.3%). No HCC developed in patient who improved both CMRFs 1 and 2 at 2 years (n = 1,319, 4.5%).
Conclusion: The influence of five CMRFs on the HCC risk significantly differed in MASLD. Overweight/obesity or central obesity and pre-diabetes/diabetes with fibrotic burden were significantly associated with the increased risk of HCC development in patients with MASLD.

THU-432

Impact of metabolic dysfunction-associated steatotic liver disease on post-surgical outcomes in HBV-related hepatocellular carcinoma

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Background and aims: The impact of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic risk factors on post-surgical outcomes for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) remains unknown.
Method: A retrospective cohort study was conducted on 2,485 consecutive patients with very early or early-stage HBV-related HCC who underwent curative resection between 2010 and 2018 at a tertiary center in Korea. We collected baseline data on the presence of histologic steatosis and metabolic risk factors, including obesity, hypertension, dyslipidemia, and diabetes. The risks of intrahepatic HCC recurrence and overall mortality were analyzed based on MASLD status and metabolic risk profile.
Results: Among the 2,485 patients, 1,050 (42.3%) had MASLD. Patients with MASLD had more metabolic comorbidities, a higher prevalence of cirrhosis, lower alpha-fetoprotein levels, and less microvascular invasion compared to those without MASLD. During a median follow-up of 4.9 years, 1,087 (43.7%) cases of recurrence and 475 (19.1%) deaths were recorded. Patients with MASLD showed a

significantly higher risk of intrahepatic HCC recurrence compared to those without MASLD (adjusted hazard ratio [aHR], 1.16; 95% confidence interval [CI], 1.03–1.32), with a clear trend of increasing risk as the number of metabolic risk factors increased, ranging from 8% for one factor to 24% for three or more factors. However, MASLD was not significantly associated with overall mortality (aHR: 1.07; 95% CI: 0.88–1.30). Subgroup analysis revealed that the impact of MASLD on the risk of intrahepatic HCC recurrence was more pronounced in non-obese patients (aHR, 1.55; 95% CI, 1.15–2.09) compared to obese patients (aHR, 1.11; 95% CI, 0.95–1.28; *P* for interaction = 0.02), implying that the interplay between MASLD and metabolic risk factors may vary depending on obesity status.
Conclusion: MASLD is associated with an increased risk of intrahepatic HCC recurrence following curative resection for HBV-related HCC, particularly among non-obese patients and those with multiple metabolic risk factors, underscoring the need for tailored post-surgical surveillance and management strategies based on obesity status and metabolic risk profiles.

THU-433-YI

The impact of cardiopulmonary fitness on metabolic dysfunction-associated steatotic liver disease in a combined lifestyle intervention for adolescents with obesity

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Background and aims: The interplay between liver and muscle health is incompletely understood, especially in adolescents. Cardiopulmonary exercise testing (CPET) evaluates cardiopulmonary fitness. Its association with metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD evolution during a lifestyle intervention is poorly characterized.
Method: Adolescents aged 12–18 years old living with (severe) obesity who received a structured, combined lifestyle intervention in a residential setting were prospectively followed for 6 months. CPET was performed at the start using a step-wise load increasing protocol. Raw data were analyzed, and the maximal parameters were obtained. Lean mass was obtained by DEXA scanning. MASLD was defined as a CAP value > 248 dB/m, and resolution as a CAP <248 dB/m at 6 months when baseline CAP values were > 248 dB/m.
Results: 119 adolescents (60 boys) with obesity were included, with a median (interquartile range) age of 16 (15–17) years. The median (IQR) BMI z-score was 2.87 (2.51–3.17). 85 adolescents (71.4%) had MASLD, of which 58.8% were boys. Maximal cardiopulmonary fitness (expressed as the percentage of the predicted VO2max; VO2max%) was significantly lower in adolescents with MASLD, with a median (IQR) of 42.8 (35.7–52.1) vs. 53.5 (46.1–58.5) % in adolescents without MASLD ($p < 0.001$). Strikingly, VO2max/kg did not differ between groups, whereas VO2max on lean mass was significantly lower in patients with MASLD: 35.5 (30.3–40.3) vs. 39.5 (33.9–44.8) ml/kg/min ($p = 0.036$). This highlights the importance of fat-free mass on cardiopulmonary fitness and MASLD. Next, data on resolution of baseline MASLD after 6 months intervention were available for 66 patients, of whom 33 (50.0%) had resolution. Interestingly, a higher VO2max/kg and VO2max% at baseline were associated with steatosis resolution, respectively 19.7 (16.6–22.1) vs. 16.1 (13.9–19.2) ml/kg/min ($p < 0.001$) and 45 (41–54) vs. 36 (29–52) % ($p = 0.006$). Moreover, this was also observed for VO2max on lean mass: 37.7 (33.8–43.6) vs. 32.9 (27.8–37.2) ml/kg/min ($p = 0.003$). These results remained significant when including weight z-scores at 6 months and gender in a binary logistic regression model. As a sensitivity analysis, MASLD was defined by the presence of liver steatosis on ultrasound, and the results remained significant.
Conclusion: Cardiopulmonary fitness is associated with liver health. Baseline cardiopulmonary fitness, independent from (fat) mass, in adolescents with obesity is associated with MASLD and could be an important contributor to MASLD resolution during a combined lifestyle intervention.

THU-434

Liver phenotypes in a multicentric PCOS cohort: prospective analysis including steatotic liver disease-associated genetic variants

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Background and aims: Polycystic ovary syndrome (PCOS) is frequently associated with advanced steatotic liver disease (SLD). However, there are numerous knowledge gaps in our understanding of genetic architecture of MASLD and its severity in women with well characterized PCOS. In this study, we aim to evaluate the role of genetic variants in shaping SLD phenotypes in women with PCOS, using non-invasive methods for quantification of hepatic fibrosis and steatosis.
Method: A total of 797 females with PCOS were recruited from Poland (n = 343), Germany (n = 42), USA (n = 264), and Brazil (n = 148). Liver status was assessed using SWE for patients from Poland, and Fibroscan with CAP for patients from Germany, the USA, and Brazil. All participants were genotyped for SLD-related variants, including *PNPLA3* p.I148M, *MBOAT7* p.G17E, *HSD17B13 rs72613567*: TA, *MTARC1* p.A165 T, *PIS*, *PIZ* and *PSD3* p. L186 T, using TaqMan assays. Steatosis was defined as CAP > 285 db/m, clinically significant fibrosis (CSF) as LSM > 8.5 kPa, and advanced fibrosis (AF) as LSM > 10.3 kPa.
Results: Among recruited patients with liver stiffness measurements (median: 4.8 kPa, range: 2.1–66.3 kPa), 8.3% had CSF and 4.8% met criteria for AF. CAP > 285 db/m was observed in 46.5% of patients with available CAP data (median: 279, range: 100–400 db/m). The median ALT was 17 I/UL (range: 4–253 I/UL), the median AST was 19 IU/l (range: 9–238 IU/L), and the median bilirubin was 0.5 mg/dl (range: 0.1–4.3 mg/dl). Only two patients had bilirubin levels exceeding 2 mg/dl. Minor allele frequencies (MAF) for genotyped variants were: *PNPLA3* p.I148M - 0.24, *MBOAT7* p.G17E - 0.40, *HSD17B13 rs72613567*: TA - 0.23, *MTARC1* p.A165 T - 0.26, *PIS* - 0.02, *PIZ* - 0.01 and *PSD3* p.

L186 T - 0.29. The *PNPLA3* polymorphism significantly modulated serum ALT (P = 0.002), AST (P = 0.049), CAP (P = 0.033) and liver stiffness (P = 0.013), with the highest values detected among carriers of the *PNPLA3* p.148MM genotype. Heterozygotes for the *PIS* had higher liver stiffness (P = 0.032). Carriers of the *PNPLA3* p.148M allele were at increased risk of CAP > 285 db/m (OR 1.71, 95% CI 1.16–2.52, P = 0.006).
Conclusion: SLD is common among females with PCOS, whereas advanced liver fibrosis is less frequent. Common genetic variants, particularly the *PNPLA3* p.I148M, significantly influence liver status in females with PCOS.

THU-435
Obesity-related cognitive problems are not related to liver disease severity and remain unchanged after metabolic restoration
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Background and aims: Obesity with metabolic dysfunction is associated with cognitive impairments in up to 40% of cases, primarily affecting reaction time stability, short-term, and long-term memory. The etiology of these cognitive issues is unclear, possibly linked to metabolic dysfunction associated steatotic liver disease and steatohepatitis (MASLD and MASH), or resulting from premature brain aging due to neuroinflammation, oxidative stress, and neurodegeneration. This study investigates whether cognitive dysfunction improves with weight loss post-bariatric surgery, suggesting a metabolic origin.
Method: Individuals with obesity (BMI > 35 kg/m²) underwent evaluations including liver biopsies, biometric assessment, and multidomain cognitive tests: the Continuous Reaction Time Test (CRT), Portosystemic Encephalopathy Syndrome Test (PSE), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Abnormal results were defined using validated cut-offs: CRT (<1.9), PHES (<-4), RBANS (<79). One-third underwent bariatric surgery (BS) after baseline visit, and all participants, including controls, had serial liver biopsies. Changes in test scores and their correlation with weight or liver histology improvements were analysed.
Results: Among 110 patients (67% female, age 48 ± 13 years, weight 126 kg ± 23), 24% had type 2 diabetes. At baseline, 19% had no-MASLD, 51% had MASLD, 30% had MASH, fibrosis staging was 74% (F0-F1), 19% F2, and 7% F3-F4. At follow-up (2.7 years ± 0.43 years), BS patients (n = 35) lost 40.7 kg (±14.5), while the no-surgery group (n = 73) remained weight stable (−2.8 kg, SD 8.4). No significant changes were observed in the proportions of participants with abnormal CRT, PHES, and RBANS performances: 68% vs. 68%, 11% vs. 8%, and 39% vs. 30% respectively. Cognitive improvements occurred in both groups, with no significant changes in CRT index (0.17 ± 0.67 vs. 0.03 ± 0.52), PHES score (0.52 ± 1.5 vs. 0.79 ± 2.9), or RBANS index (9.2 ± 16.3 vs. 7.8 ± 14.9). Improvements in liver histology (≥1 grade fibrosis or inflammation/ballooning) did not correlate with cognitive improvements.
Conclusion: Cognitive impairments, affecting reaction time and memory, were present in 40% of this obese cohort at baseline and persisted nearly 3 years post-bariatric surgery despite MASLD and metabolic improvements. These deficits may be congenital or indicate irreversible damage, potentially reflecting premature brain ageing.

THU-436
Histologic severity on liver biopsy is identical between normal weight and overweight adults with metabolic dysfunction associated steatotic liver disease: is it time to revise the definition of lean MASLD?
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Background and aims: While higher body weight is closely associated with histologic severity in MASLD, lean MASLD (i.e., MASLD in normal weight individuals) is a distinct phenotype which has received considerable attention. However, there are knowledge gaps in our understanding of the interplay among weight categories, *PNPLA3* genotype, and severity of liver histology. We examined clinical, *PNPLA3* genotypic, and histological characteristics of MASLD across several BMI categories in adult participants of the NASH CRN.
Methods: We categorized MASLD in the adult NASH CRN participants into normal weight (BMI <25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), class 1 obesity (BMI 30–34.9 kg/m^2) and ≥ class 2 obesity (BMI ≥35 kg/m^2). These weight categories were adjusted for Asian participants according to the WHO criteria. Definite NASH, NAFLD Activity Score (NAS), advanced fibrosis (≥ F3) and cirrhosis (F4) were histological outcomes of interest.
Results: There were 107 adults with normal weight (mean BMI 23.2 kg/m^2), 744 with overweight (mean BMI 27.7 kg/m^2), 1128 with class 1 obesity (mean BMI 32.3 kg/m^2), and 1407 with class ≥2 obesity (mean BMI 40.5 kg/m^2) MASLD. The prevalence of metabolic syndrome increased across 4 weight groups - normal weight: 25%, overweight: 45%, class I obesity: 64%, and ≥ class 2 obesity: 72% ($p < 0.001$). The prevalence of *PNPLA3* G-allele did not differ - normal weight: 74%, overweight: 75%, class I obesity: 70%, and class ≥2: 73%. The mean NAS increased across categories: normal weight: 4.1, overweight: 4.1, class 1 obesity: 4.4, and class ≥2 obesity: 4.4 ($p < 0.001$), as did the proportion of definite NASH: normal weight: 50%, overweight: 50%, class 1 obesity: 59%, and class ≥2 obesity: 63% ($p < 0.001$). The prevalence of advanced fibrosis increased across 4 weight groups: normal weight: 24%, overweight: 24%, class 1 obesity: 30%, and class ≥2 obesity: 37% ($p < 0.001$), as did cirrhosis: normal weight: 8%, overweight: 8%, class 1 obesity: 10%, and class ≥2 obesity: 13% ($p < 0.001$). When normal weight MASLD with and without advanced fibrosis were compared, individuals with normal weight with advanced fibrosis were older (58.5 vs 49.8 years, $p = 0.005$), more likely to have diabetes (48% vs 19%, $p = 0.003$) and metabolic syndrome (46% vs 19%, $p = 0.009$) and be homozygous for *PNPLA3* G allele (44% vs 17%, $p = 0.02$). The histologic severity was identical between normal and overweight MASLD groups (mean NAS 4.1, 50% definite NASH, 24% advanced fibrosis, and 8% cirrhosis in both groups).
Conclusion: One in 4 normal weight adults with MASLD have advanced fibrosis and one in 12 normal weight adults with MASLD have cirrhosis. Interestingly the rates of advanced fibrosis and cirrhosis are similar in patients with normal weight and overweight MASLD, and their histological severity worsens only after BMI > 30 kg/m^2. These data call for revising definition of lean MASLD as a distinct entity.

THU-437

Association of alpha-1 antitrypsin Pi*Z allele and disease severity in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Alpha-1 antitrypsin deficiency is a known cause of cirrhosis specifically in Pi*Z allele homozygotes (serpin family A member 1 [*SERPINA1*] rs28929474). However, studies have suggested that patients with Z allele heterozygosity have increased risk of liver injury and cirrhosis as well. The impact of Pi*Z allele in metabolic dysfunction-associated steatotic liver disease (MASLD) is unclear; therefore, we aimed to evaluate the frequency of *SERPINA1* Pi*Z allele in an ongoing prospective registry of patients with well characterized MASLD cohort and examine its association with disease severity.
Methods: A total of 915 patients in the Indiana University MASLD cohort who underwent SERPINA1 genotyping and Vibration Controlled Transient Elastography (VCTE) assessment were included in this analysis. *SERPINA1* rs28929474 was genotyped via TAQMAN genotyping assay (C is the ancestral allele whereas T is the minor allele). The outcomes of interest were liver stiffness measurement (LSM) and CAP measurement by VCTE in all patients and NAFLD Activity Score (NAS 0–8) and fibrosis score (F0–4) in patients with liver histology available (n = 419).
Results: There were 864 patients (94%) with CC genotype (65% female, 93% Caucasian, mean BMI 35.6 kg/m^2) and 51 patients (6%) with CT genotype (53% female, 96% Caucasian, mean BMI 35.2 kg/m^2). There were no individuals with homozygosity for T allele. There appears to be an enrichment of *SERPINA1* rs28929474 T allele in this cohort relative to population controls (6% in our cohort vs 2–3% in general population). The mean CAP measurement in the CC genotype group was 319 dB/m and it was 310 dB/m in the CT genotype group (p = 0.28). The mean LSM was 14 kPa in CC group and 15 in CT group (p = 0.77). The prevalence of LSM ≥12 kPa was 36% CC group and 37% CT group (p = 0.87). Of the 915 patients included in this analysis, 419 patients had liver histology assessment on biopsy. The mean NAS score was 3.7 ± 1.6 in both CC and CT genotype groups (p = 0.94) with a NAS score ≥4 in 56% of CC genotype and 65% of CT genotype participants (p = 0.45). The mean fibrosis score was 2.1 ± 1.4 in the CC group and 2.0 ± 1.3 in the CT group. The prevalence of advanced fibrosis (F≥3) was 42% and 35% respectively in CC and CT groups (p = 0.52). The prevalence of cirrhosis was 20% and 15% respectively in CC and CT groups (p = 0.56).
Conclusion: The minor allele frequency for *SERPINA1* rs28929474 (Pi*Z) in a large cohort of Caucasian individuals with well characterized MASLD was 6%. While this MAF is higher than in general population, Pi*Z carriers did not have worse liver disease by VCTE or by liver histology.

THU-438

Altered C-fiber function and neuropathic changes in metabolic syndrome and MASLD indicate early peripheral nerve dysfunction

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Background and aims: Sensory neuropathic symptoms are frequently overlooked in patients with metabolic syndrome (MetS), especially compared to Type 2 Diabetes Mellitus (T2DM). The mechanisms underlying small nerve fiber damage in MetS remain poorly understood. Reactive carbonyl species (RCS), such as methylglyoxal (MGO), by-products of glucose and lipid metabolism, are implicated in diabetic peripheral neuropathy, neuropathic pain, and liver steatosis-associated damage. This study evaluates small nerve fiber function in hepatological patients with MetS, including metabolic-associated steatotic liver disease (MASLD), and T2DM, correlating findings with RCS levels, nerve histopathology, and microneurography.
Method: Patients were recruited from a tertiary hepatology outpatient clinic. Clinical assessments included liver ultrasound, elastography, neuro-electrophysiology, pain/neuropathy questionnaires, and systemic MGO measurements. Small nerve fiber function was evaluated via quantitative sensory testing (QST) and selective C-fiber electrical stimulation. Skin biopsies from upper and lower legs were analyzed for intraepidermal nerve fiber density (IENFD) and MGO-derived glycation markers (MG-H1). Direct C-fiber recordings via microneurography were performed to objectively assess the extent of pathological C-fiber changes.
Results: MetS patients showed significant alterations in skin nerve fiber function compared to healthy controls, despite the absence of overt clinical neuropathy. Reduced IENFD correlated with elevated MG-H1 and MGO levels and diminished pain responses to C-fiber stimulation. Electrical stimulation induced dose-dependent pain in both groups, but MetS patients demonstrated a lack of pain adaptation during longer-lasting sinusoidal wave stimulation, a pattern typically seen in healthy controls. Women reported overall higher pain ratings than men. Direct microneurography recordings revealed abnormal C-fiber activity in MetS patients, indicating early pathological changes in peripheral nerve function.
Conclusion: Small nerve fiber dysfunction, including altered C-fiber functionality, is detectable in Mets/MASLD patients even in the absence of clinically evident neuropathy, highlighting the need for early diagnostic and preventive strategies. These findings suggest potential interactions between small nerve fibers and other MetS-affected organ systems, such as the liver or vasculature, possibly mediated by neuropeptides facilitating bidirectional signaling. Correlation of RCS levels with C-fiber changes may reveal early metabolic and functional biomarkers for neuropathy development.

THU-439-YI

Impact of a multidisciplinary clinic for metabolic dysfunction-associated steatotic liver disease on cardiovascular risk and liver health

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Background and aims: Cardiovascular disease (CVD) is the leading cause of mortality in metabolic dysfunction-associated steatotic liver disease (MASLD) patients. Guidelines recommend a multidisciplinary approach, but real-world data are limited. This study aimed to assess the efficacy of a multidisciplinary MASLD clinic in optimising control of metabolic comorbidities and liver injury markers.
Method: We conducted a retrospective analysis of 465 patients seen in a multidisciplinary MASLD clinic from June 2014 to June 2024. All participants were evaluated by both a hepatologist and an expert in cardiovascular disease. Patients were referred directly from primary care or through the Camden and Islington MASLD Pathway (London, UK), which involved a FIB-4 and, if needed, an ELF score. Each patient received a comprehensive hepatological assessment, cardiovascular risk assessment and management, and, where required, dietary counselling by a dietician. Diagnostic criteria for comorbidities, including hypertension, type II diabetes, dyslipidaemia, and obesity, were based on recognised clinical guidelines. Cardiovascular risk was assessed using the QRISK-3 Score, with statins recommended for patients with a ≥10% 10-year CVD risk or a history of cardiovascular events. Baseline and follow-up data on anthropometry, blood pressure, and laboratory values were collected. Primary endpoints were changes in liver injury markers (transaminases, LSM) and metabolic comorbidities (e.g., blood pressure, HbA1c, lipid profile, and QRISK-3 Score).
Results: The mean age of 465 patients was 57 ± 12 years, 56% were males, and 54% Caucasian. Hypertension, diabetes, and dyslipidaemia were present in 66%, 56%, and 84% of patients, respectively. At baseline, 65% had abnormal ALT, while LSM, measured in 95% of patients, had a median of 7.9 kPa. Of 190 liver biopsies, 79% showed steatohepatitis, with bridging fibrosis in 29% and cirrhosis in 14%. At a 15-month median follow-up, 61% of patients remained under secondary care, with significant improvements observed in ALT ($p < 0.001$), AST ($p < 0.001$), GGT ($p < 0.001$), total cholesterol ($p < 0.001$), LDL-c ($p < 0.001$), TG ($p = 0.007$), systolic and diastolic blood pressure ($p < 0.001$ and $p = 0.001$), weight ($p < 0.001$), BMI ($p < 0.001$), LSM ($p = 0.020$), and QRISK-3 Score ($p = 0.002$). Waist circumference decreased significantly in obese patients, with 12% achieving ≥10% weight loss. Therapy adjustments improved metabolic markers, notably HbA1c, blood pressure, and lipid profile in patients with diabetes, hypertension, and dyslipidaemia, respectively.
Conclusion: A multidisciplinary approach to MASLD effectively improves liver and CV risk markers. Long-term collaboration between primary and secondary care is crucial to achieve and maintain these health improvements.

THU-440
The paradox of low hepatic fat content in steatotic liver disease: insights from an MRI-PDFF study

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Background and aims: The pathophysiological mechanisms of hepatic fat loss in late steatotic liver disease (SLD) are enigmatic, and the impact of low hepatic fat content (LHF) on prognosis in advanced chronic liver disease (ACLD) is remains unclear. Proton density fat fraction (PDFF) measured by MRI can non-invasively and accurately quantify hepatic fat content. In the present study, we investigated these issues using MRI-PDFF measurements.
Method: This is a single-center retrospective study of 657 patients with CLD excluding alcohol-related liver disease in which MRI-PDFF and liver stiffness (LS) on MRE were measured. 46 patients with HCC were included. Patients were divided into two groups according to the etiology of their disease: SLD (group S) and other etiologies (group O). We examined the trends and interrelationships of PDFF, ALT, and ALBI score in five stages of LS progression (<2.5, 2.5–3.5, 3.5–4.5, 4.5–5.5, and ≥5.5 kPa). We defined LHF as PDFF ≤2.7%, and analyzed the relationships between variables using multivariate analysis and the prognosis of ACLD patients using the Cox proportional hazards model.
Results: 1) Analysis of PDFF: There was a significant difference in the mean PDFF (12.8% and 5.3%) between Group S (n = 232) and Group O (n = 425) ($P < 0.05$). In the multivariate analysis, Group S ($\beta = 0.26$), BMI (0.25), ALT (0.22), triglyceride (0.14) and ALBI score (-0.18) were independent associated factors of hepatic PDFF (each $P < 0.01$). 2) Analysis of the five groups (without HCC): In the group S, the PDFF was 12, 14, 15, 18, 7 (%) and the ALT was 45, 69, 85, 73, 49 (U/l), and it turned from an increase to a decrease at 5.5 kPa. Then, the ALBI score (−2.95, −2.97, −2.96, −2.73, −2.18) significantly worsened at ≥5.5 kPa ($P < 0.01$). In addition, in Group O, there was a significant correlation between the progression of LS and the ALBI score, and the PDFF (5, 6, 7, 6, 3%) decreased at ≥5.5 kPa ($P < 0.05$). 3) Study in ACLD (LS ≥3 kPa): In both the S and O groups, a significant inverse correlation was observed between the ALBI score and PDFF ($r = -0.588$ and -0.341, $P < 0.01$). In addition, the incidence of LHF increased with progression of ALBI grade ($P < 0.01$). In the prognosis analysis with a median observation period of 36 months and 33 cases of liver-related death, ALBI score (HR: 4.3), HCC (4.4), and LHF (6.2) were independent associated factors ($P < 0.01$).
Conclusion: This study showed that the increase in hepatic PDFF, a factor in liver inflammation and fibrosis in SLD, begins to decrease at 5.5 kPa and is associated with worsening liver reserve function. Hepatic PDFF may serve as a dynamic biomarker reflecting liver pathophysiology, and LHF is an important independent factor that predicts the prognosis in all ACLD patients. These results suggest that a decrease in liver fat content in the advanced stage of SLD does not necessarily indicate a good prognosis, and it is important to continuously monitor hepatic fat content in patient management.

THU-445
Subgroup definition and monitoring of liver fibrosis evolution in patients with MASH bridging fibrosis based on objective measurements of septa parameters using digital pathology with artificial intelligence analyses

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Background and aims: Metabolic Dysfunction-Associated Steatohepatitis (MASH) with bridging fibrosis (stage F3) is a critical, yet very broad category, in steatotic liver disease encompassing subjects with potential progression to cirrhosis or regression to milder stages. Second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy with artificial intelligence (AI) provides sensitive and objective quantification of liver fibrosis. This study aimed to identify subsets of the MASH F3 population by quantitative septa evaluation.
Method: Paired liver biopsies from 57 patients, all with bridging fibrosis, part of the FLIGHT-FXR trial (NCT02855164): placebo (PLB, n = 17), tropifexor (TXR, n = 40) were included. Unstained sections were analyzed by SHG/TPEF microscopy with quantification of 12 septa parameters at baseline (BL) and end of treatment (EOT) biopsies. Septum width measurement of 93 randomly selected septa was used to differentiate thick (mean width 167 µm) from thin septa (mean width 41 µm) with a cutoff of 88.5 µm, as determined by the Youden's index. The ratio between the thick septa area to total septa area per biopsy identified 2 subgroups: predominantly thin septa

(F3a) (mean ratio 13%, range 0–48%) or predominantly thick septa (F3b) (mean ratio 71%, range 51–97%).
Results: At BL, 27 of 57 F3 patients were categorised as F3a (PLB, n = 9; TXR, n = 18) and 30 were F3b (PLB, n = 8; TXR, n = 22). The average septa area in F3b patients was 3-fold larger (21820 ± 3383 μm²) than in F3a patients (6752 ± 7219 μm², p < 0.001). Importantly, septa area measurements revealed significant imbalance between those randomised to receive PLB or TXR (p = 0.027). From BL to EOT, intra-stage changes F3a to F3b and vice versa were observed in 5 of 11 PLB and 10 of 28 TXR cases with unchanged F3 stage by the ordinal scoring. The placebo cohort showed no consistent trend in septa area dynamics across F3a or F3b subgroups, while the TXR cohort, especially F3b subgroup, showed a notable reduction in the septa area, though not statistically significant.
Conclusion: SHG/TPEF microscopy with AI offers precise insights into fibrosis dynamics in MASH F3 patients, revealing details not detectable by conventional methods. Its use in clinical trials can optimise patients' selection and stratification, as well as dose-response analyses. These findings highlight the potential of digital pathology for an objective subgroup separation of F3 stage, informing future studies.

THU-446

Risk stratification of liver-related complications through unsupervised partitioning clustering of alanine aminotransferase (ALT) levels and trajectories in patients with type 2 diabetes (T2D)

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Background and aims: ALT is commonly used in clinical practice to screen for and monitor liver disease in patients with T2D. We aimed to characterise common ALT levels and trajectories and examine their impact on the risk of liver-related complications including hepatic decompensation, hepatocellular carcinoma, and liver-related death in T2D.
Method: A territory-wide retrospective cohort of patients with T2D from 2000–2016 was identified in Hong Kong. Patients with type 1 diabetes, chronic viral hepatitis, excessive alcohol use, or liver-related complications before baseline or follow-up <5 years were excluded. Unsupervised partitional clustering was applied to identify trajectories by testing the number of clusters (k) from 1 to 6. Various distance measures with centroid calculation were employed, including Euclidean distance, dynamic time wrapping (DTW) and move-split-merge (MSM) with arithmetic mean, DTW with DTW barycenter averaging (DBA), and MSM with MSM barycenter averaging (MBA). Cluster validity indices were summarised to determine the optimal k and the best-performing algorithm. The association between ALT levels and trajectories with liver-related complication risk was evaluated using cause-specific hazard models, with non-liver-related death as competing risk. ALT trajectories were quantified by linear mixed models.
Results: Of 240,076 patients with T2D (age 61 ± 13 years, 48.7% females, 1.9% cirrhosis, HbA_{1c} 8.0 ± 2.2%, ALT 23 [17–35] U/L), 2,859 (1.2%) developed liver-related complications at a median follow-up of 12.0 (9.3–15.0) years. MSM-MBA identified 4 robust ALT trajectories in the first 5 years after T2D diagnosis: U-shaped, inverted U-shaped, increasing and decreasing. Considering the limited clinical significance and shallow pattern differences between the U-shaped and inverted U-shaped trajectories, the two groups were merged, resulting in 3 trajectories: stable (n = 149,520 [62.3%]), increasing (n = 54,593 [22.7%]) and decreasing (n = 35,963 [15.0%]). Compared to a stable trend, patients with decreasing ALT had a lower risk (adjusted hazard ratio [aHR], 0.63 [95% CI, 0.55–0.71]), while those with increasing ALT had a higher risk (aHR, 1.15 [95% CI, 1.05–1.27]). Compared to a stable trajectory with ALT <upper limit of normal (ULN; 35 U/L for male and 25 U/L for female), patients with baseline ALT <ULN with an increasing trend or 1–2×ULN with either a stable or increasing trajectories had higher risks of liver-related complications (aHR [95% CI], 1.12 [1.01–1.24], 1.36 [1.22–1.51], and 1.84 [1.49–2.28], respectively); while patients with baseline ALT ≥2×ULN demonstrated higher risks across all trajectories: decreasing (aHR, 1.29 [95% CI, 1.09–1.52]), stable (aHR, 2.69 [95% CI, 2.28–3.17]), and increasing (aHR, 3.76 [95% CI, 2.46–5.75]). Higher HbA_{1c}, older age and cirrhosis were associated with higher liver risk.
Conclusion: Lower ALT levels and decreasing ALT over time are associated with a lower risk of liver-related complications in T2D.

THU-447

Impact of metabolic dysfunction-associated steatotic liver disease on fatigue and pruritus in primary sclerosing cholangitis: a U.S. single-center cross-sectional study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of liver disease in the United States and frequently coexists with other liver diseases, including viral hepatitis, autoimmune hepatitis, and primary sclerosing cholangitis (PSC). Despite growing interest in MASLD overlap syndromes, the presence of MASLD in PSC patients remains underexplored. Consequently, data on patient-reported outcomes, particularly pruritus and fatigue, are limited. This study aimed to assess the prevalence and characteristics of the MASLD-PSC overlap syndrome, with a specific focus on patient-reported outcomes such as pruritus and fatigue.
Method: A cross-sectional study used data from a single visit of PSC patients enrolled between January 2018 and November 2024 in the Autoimmune Liver Diseases Registry at Beth Israel Deaconess Medical Center (Boston, MA, USA). Steatosis was defined as: (i) > 5% hepatocyte steatosis on liver biopsy per NASH CRN criteria, (ii) CAP (controlled attenuation parameter) > S1 (248 dB/m), or (iii) hyperechogenic liver parenchyma on ultrasound. Patient-reported outcomes, including fatigue and pruritus, were assessed using the Chronic Liver Disease Questionnaire (CLDQ) and 5D Itch Scale. Ordinal logistic regression evaluated the association between MASLD overlap and fatigue severity. Continuous variables were analyzed with the Wilcoxon rank-sum test, categorical variables with Fisher's exact test, and results were summarized as medians (IQR) or percentages. Statistical significance was defined as p < 0.05.
Results: A total of 103 patients with PSC were included in this analysis, 33% of whom had overlap with MASLD. Patients with PSC/MASLD were significantly older (median age: 55 vs. 46 years, p < 0.006), had a higher body mass index (BMI) (median: 30 vs. 25 kg/m², p < 0.001), and were more likely to have bile duct involvement (43% vs. 12%, p = 0.002) compared to those with PSC alone. No significant differences were observed in gender, race, or inflammatory bowel disease prevalence. In the ordinal logistic regression analysis, pruritus intensity (odds ratio [OR]: 2.64; 95% CI: 1.51–4.61, p = 0.001), DM (OR: 4.48; 95% CI: 1.05–19.10, p = 0.043), and BMI (OR: 1.08; 95% CI: 1.01–1.16, p = 0.018) were associated with higher fatigue levels. MASLD overlap was linked to lower fatigue intensity (OR: 0.37; 95% CI: 0.16–0.85, p = 0.020).
Conclusion: PSC patients with MASLD overlap present with distinct clinical features, including older age, higher BMI, and greater bile duct involvement. Interestingly, MASLD overlap is associated with reduced fatigue intensity, suggesting a possible influence of altered

inflammatory or metabolic pathways. Further research is needed to elucidate the mechanisms underlying this relationship and its clinical implications.

THU-448

Impact of anthropometric and body composition on response to lifestyle intervention in patients living with MASLD

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Background and aims: Weight loss intervention often raise concerns about the preservation of muscle mass given its critical role in preventing sarcopenia. This study evaluates the relationship between anthropometric and body composition on response to lifestyle intervention combining exercise and a Mediterranean Diet.

Method: Patients with MASLD (n = 96) underwent a 6-month lifestyle intervention. Baseline and a 6-month follow-up with MRI including PDFF and MRE, VCTE, liver ultrasound and assessments of metabolic and liver function. Muscle function was assessed by muscle elastography and stiffness at external Vastus in leg. Data were reported as delta between baseline and six months intervention. Statistical analyses included t-student, U-Mann-Whitney and logistic regression performed with SPSS 29.0.

Results: Regarding to MASLD responses, fibrosis regression correlated with an increase in muscle stiffness (7.31 ± 5.50 in responders vs −4.68 ± 9.64 in non-responders, n = 23) and a decrease in fat-free mass (−4.48 ± 5.93 vs −1.59 ± 3.24, n = 47), muscle mass (−4.69 ± 6.21 vs −1.59 ± 3.10, n = 47) and basal metabolism (−122.34 ± 156.70 vs −42.79 ± 85.07, n = 47), but not with delta BRI and delta BMI. after multivariate analysis, no variable remains as independent associated to fibrosis. MASH resolution was associated with an increase in muscle stiffness (0.10 ± 7.86 vs −6.70 ± 12.72, n = 44) and a decrease in BMI (−1.60 ± 1.35 vs. −0.73 ± 1.75, n = 89). Age (p = 0.042; OR 1.06; CI95% 1.00–1.13) and muscle stiffness (p = 0.085, OR 1.08, CI95% 0.99–1.17) remained as independent variables associates to MASH resolution after a backward LR analysis. Steatosis response correlated with a decrease in BMI (−1.76 ± 1.73 vs −0.61 ± 1.62, n = 65); in fat-free mass (−4.62 ± 5.07 vs −1.11 ± 2.62, n = 65); in muscle mass (−4.14 ± 5.24 vs −1.41 ± 2.71, n = 65) and in basal metabolism (−111.19 ± 132.98 vs −39.36 ± 75.45, n = 65). Backward LR identified free-fat mass as the only independent variable associated to steatosis response (p = 0.003, OR 0.254, CI95% 0.575–0.892).

Conclusion: Weight loss correlated with steatosis response and MASH resolution. Increased muscle stiffness and decreased muscle mass correlated with fibrosis regression and MASH resolution. Future interventions should prioritize not just weight loss but also muscle preservation to mitigate sarcopenia risks and optimize metabolic health outcomes.

THU-449-YI

Steatosis in cirrhosis: a prognostic marker for liver related outcomes in metabolic-dysfunction associated steatotic liver disease

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Background and aims: The association between fibrosis and liver-related outcomes is well established. However, the predictive utility of histological components have not been well studied. We aim to study the utility of the qFIBs and its components (qfibrosis, qInflammation, qBallooning, qSteatosis) in predicting risk of Liver Related Events (LRE) in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).

Method: 108 liver biopsy images were retrieved and the composite LREs of liver-related death, hepatic encephalopathy (HE), ascites and hepatocellular carcinoma (HCC) were studied with the Non-alcoholic Steatohepatitis Clinical Research Network (NASH-CRN) score and qFIBs. Firth-corrected Cox regression was performed due to the occurrence of few events, together with log-rank tests and Kaplan-Meier analysis.

Results: LREs (liver-related deaths = 5, HE = 4, HCC = 4, ascites = 8) occurred in 12% of the cohort (n = 13/108). There was a median follow up of 7.83 years. Patients with more advanced fibrosis had a six-fold risk of developing LREs (qF3/4 vs qF0/1/2, HR 6.41, 95% CI 1.10–37.23), compared to a seven-fold risk with NASH-CRN (F3/4 vs F0/1/2, HR 7.19, 95% CI 1.74–29.82). A lower qSteatosis showed a twenty-three fold increased risk of developing LREs (HR 23.51, 95% CI 1.23–448.16). On further analysis, it was found that majority of the patients with lower steatosis were also cirrhotic. Interestingly, among the cirrhotic group (n = 33), a lower steatosis grade, rather than being a protective factor, correlated with poorer outcomes (qS0/1 = 24 vs qS2/3 = 9, 100% of LREs occurred in the qS0/1 group), likely due to the reduction of steatosis in dynamic fat changes in end stage liver disease. This is further substantiated by the finding that samples with lower percentages of macrovesicular steatosis had a significantly higher risk of developing LREs compared to samples with more macrovesicular steatosis (18% vs 30%, p = 0.013). In addition, patients with lower zone 2 steatosis had higher risk of LREs (HR 6.86, p = 0.001, 95% CI 1.79–26.33). Though the difference was not significant, fat distribution was also more azonal in the LRE group (zone 3: 18%, p = 0.886; azonal 64%, p = 0.901). Ballooning was positively associated with higher risk of LREs (HR 3.20, p = 0.042, 95% CI 1.02–10.03).

Conclusion: Lower steatosis and inflammation grades in cirrhosis correlate with the occurrence of LREs and reiterates the natural history of MASLD - as fibrosis progresses, steatosis regresses. On histology, steatosis was less likely to be macrovesicular and more likely to be azonal in distribution. Our findings open up exciting new channels for validation with larger cohorts and exploration of the process of steatosis fluxes and how it reflects the underlying pathogenesis of MASLD progression to decompensation and LREs.

THU-450

Cryptogenic cirrhosis in Brazil: much beyond burned-out metabolic associated steatohepatitis

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Background and aims: Cryptogenic cirrhosis is now considered a consequence of metabolic associated steatohepatitis (MASH) in European and North-American centers. Little is known about the frequency of MASH in subjects with cryptogenic cirrhosis from other populations. The purpose of the present study was to evaluate clinical and histological signs of MASH as well as traditional histological markers of other liver diseases in patients submitted to liver transplantation (LT) due to cryptogenic cirrhosis (CC) in Brazil.
Method: All patients who underwent LT in four different Brazilian centers due to CC were retrospectively reviewed. Type 2 diabetes and/or overweight or obesity were arbitrarily defined as clinical risk factors for MASH. Only patients with histopathological findings of the explants were included in the study. Burned-out MASH was considered in the presence of cirrhosis without proper histological markers in subjects with clinical risk factors for MASH.
Results: 3775 patients were included in the study. Only 511 (14%) (309 males, mean age: 56+14 years) had a diagnosis of CC before LT. After analysis of explants and clinical and/or laboratory reassessment, diagnosis of MASH and burned-out MASH were observed in 147 (29%) and 111 (22%) patients, respectively. Diagnosis of CC remained unchanged in 129 (25%) patients. Other diagnoses were elicited in the 124 remaining patients including biliary cirrhosis compatible with adult-onset familiar progressive intrahepatic cholestasis (PFIC) (n = 34), porto-sinusoidal vascular disorder (PSVD) and/or schistosomiasis (n = 23) and non-HFE hemochromatosis (n = 19).
Conclusion: MASH or burned-out MASH was shown to be responsible for at least ½ of the cases of CC requiring LT in Brazil, but other diagnosis could be elicited in ¼ of the remaining patients including biliary cirrhosis resembling adult-onset PFIC and PSVD.

THU-451

Long-term outcomes of metabolic dysfunction associated steatotic liver disease (MASLD) patients in a prospective, german real-world cohort

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Background and aims: Metabolic Dysfunction-associated steatotic liver disease (MASLD) is the most frequent liver disease, but longitudinal data of clinical outcomes in Germany are lacking. Aim of this study is to analyse long-term outcomes in a prospective, German real-world cohort.
Method: A total of 310 MASLD patients, diagnosed via histology or liver stiffness/CAP, were prospectively included and followed from 2012 to 2023. Liver-related outcomes and mortality were analyzed using SPSS.
Results: 310 MASLD patients were followed for a median of 36 ± 16 months (56.8% male, mean age 52.3 years, mean BMI 32.5 ± 6.4 kg/m²), 40% had T2DM, 58% arterial hypertension and 36% hypercholesterinemia. 36% were diagnosed histologically (of those 36.9% F2-F4) and 59% staged by elastography (12% LS 8–12 kPa, 21% > 12 kPa). Long-term follow-up showed that patients with cirrhosis had significantly more liver-related outcomes compared to those without (HR 3.501 (95% CI 1.835–6.682)) and a higher mortality (HR 11.572 (95% CI 3.030–44.194)). Patients with F2–F3 in histology had a higher rate of liver-related outcomes compared to F0–F1 (HR 3.638 (95%-CI 1.345–9.840)). Stratified by liver stiffness, the highest rate of liver-related outcomes was detected for > 12 kPa (HR 11.738 (95% CI 4.421–31.167)) followed by 8–12 kPa (HR 4.630 (95% CI 1.514–14.160)), both compared to <8 kPa. Mortality was similarly increased for > 12 kPa (HR 13.489 (95% CI 1.622–112.152)) and 8–12 kPa (HR 6.044 (95% CI 0.546–66.876)). In the longitudinal study 3.5% (n = 11) of patients died, three due to liver-related complications.
Conclusion: In this first German longitudinal MASLD cohort, patients with significant fibrosis or cirrhosis have the highest risk for liver-related outcomes and overall mortality. This underscores the need for regular monitoring of at-risk-patients.

THU-452-YI

Intravenous infusions of fatty acids and ethanol induce hepatic mitochondrial reductive stress in humans

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, but the underlying pathophysiology remains unclear. Recent studies have shown that the severity of MASLD associates with a high plasma beta-hydroxybutyrate-to-acetoacetate ratio (bOHB/AcAc), a well-established marker of hepatic mitochondrial reductive stress. Here, we investigated whether intravenous administration of fatty acids and ethanol – two key risk factors of SLD – induce hepatic mitochondrial reductive stress in humans. Furthermore, we tested whether the stable isotope tracer ^{13}C-alpha-ketoisocaproate (^{13}C-KIC), whose catabolism in hepatic mitochondria produces $^{13}CO_2$ and isovaleryl-CoA in a redox-dependent manner, is applicable for studying hepatic mitochondrial reductive stress.
Method: On three separate days after an overnight fast, 8 healthy volunteers (4 female, 4 male, age 29.6 ± 4.7 years, BMI 25.2 ± 2.0 kg/m^2, liver fat 2.4 ± 1.3%) received, in a random order, volume-controlled 240-minute infusions of either: a) a lipid emulsion (Intralipid 20% with heparin, IL/Hep), b) 6% ethanol (EtOH), or c) saline. Breath alcohol concentration (BrAC) was clamped to 60 mg/dl using a breathalyzer and a physiologically based pharmacokinetic model-based algorithm. After 60 minutes from starting the infusions, the participants ingested a tracer dose of ^{13}C-KIC (1 mg/kg) and L-leucine (20 mg/kg). Breath samples were collected for determination of $^{13}CO_2$ production using isotope ratio mass spectrometry. Cumulative $^{13}CO_2$ areas under the curve (AUC) were calculated using the trapezoidal rule. Arterialized plasma samples were taken for colorimetric determination of bOHB/AcAc and for targeted metabolomics using liquid-chromatography mass spectrometry.
Results: IL/Hep infusion increased circulating fatty acid concentration from 0.47 ± 0.06 to 1.47 ± 0.19 mmol/l at 60 minutes and 1.51 ± 0.16 mmol/l at 240 minutes. EtOH infusion increased BrAC to 60 mg/dl in 30 minutes, remaining at a steady state of 61.1 ± 0.3 mg/dl between 30 and 240 minutes. No significant differences in glucose, insulin, pH or bicarbonate were detected during IL/Hep or EtOH compared to saline infusion. Plasma bOHB/AcAc increased by 59%

during IL/Hep (p = 0.002) and by 109% during EtOH infusion (p = 0.01). Compared to saline infusion, $^{13}CO_2$ AUC was 34% lower during IL/Hep (p = 0.0006) and 26% lower during EtOH (p = 0.0028). Both IL/Hep (–24%) and EtOH (–25%) decreased plasma concentration of isovalerylcarnitine, a breakdown product of KIC.
Conclusion: Physiological increases in circulating fatty acids and ethanol induce hepatic mitochondrial reductive stress, as determined by increased plasma bOHB/AcAc and decreased $^{13}CO_2$ production after ingestion of ^{13}C-KIC. ^{13}C-KIC breath test is a useful noninvasive method for the study of hepatic mitochondrial reductive stress.

THU-453
Evaluation of liver steatosis and advanced fibrosis assessed by transient elastography in general population: a prospective study from north-eastern Romania
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Background and aims: Cirrhosis is considered the final stage of liver fibrosis, and it is the leading cause of liver disease-related death worldwide. Viral hepatitis B (VHB) and C (VHC), alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD) have been found to have a major impact on the development of chronic advanced liver disease. Our study's goal was to ascertain the prevalence of liver steatosis and advanced fibrosis and steatosis in Northeastern Romania's general population.
Method: One thousand one hundred and twenty-three adult asymptomatic participants of apparently healthy subjects from Northeastern region of Romania, were selected for this study. Each participant's demographic, clinical, and physiological information was documented once informed consent was obtained. The AUDIT-C questionnaire was filled out by each participant. Transient elastography (TE) was used to evaluate liver fibrosis, controlled atenuation parameter (CAP) was used to assess liver steatosis, and rapid blood tests were used to check presence of VHB and VHC.
Results: We found that 56.7% of the screened participants were males, 48.5% had a smoking habit, and 1.4% had a history of blood transfusions, tattooing, drug use or imprisonment over the years. Moreover, 44.2% of the patients had a body mass index above the normal limit, 3.5% of the participants were positive for the presence of HBs antigen, while 2.1% exhibited HCV antibody positive titer. In addition, approximately one-third of the subjects (35.1%) were diagnosed with metabolic syndrome and according to Audit-C questionnaire we found that 4.8% of the individuals had a history of alcohol consumption. Regarding the prevalence of liver steatosis, 60.5% of subjects included in our study was found with liver steatosis according with CAP values (≥274 dB/m). Advanced liver fibrosis was found in 7.6% of the participants, and liver cirrhosis in 5.3% of the cohort. Furthermore, we observed that more than one-third of the participants with advanced fibrosis or cirrhosis (35.4%) from general population had the criteria for MASLD.
Conclusion: We discovered that a significant portion of Romanians have severe liver fibrosis by screening a cohort of individuals who appeared to be clinically healthy and lived in North-Eastern Romania. These individuals had significant risk factors, including tattooing, increased alcohol consumption, and blood transfusions. This should raise concerns for public health organizations and physicians.

THU-454
Coagulation imbalance is associated with hepatic and vascular complications in patients with MASLD and diabetes: key role of factor VIII
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Background and aims: Metabolic-dysfunction associated steatotic liver disease (MASLD) promotes fibrosis and vascular complications, especially if associated to type 2 diabetes (T2DM), and both diseases present a procoagulant imbalance. Aim: to evaluate the association between hypercoagulability, hepatic and vascular damage in a cohort of MASLD diabetic patients.
Method: 185 MASLD patients with T2DM (mean age 62 ± 11 ys, 59% males) underwent assessment of coagulation factors (fibrinogen, FII, FVIII, protein C and antithrombin; FVIII/PC considered a hypercoagulability index), FibroScan® (LSM > 8 kPa), and assessment of macro/microvascular complications. In 96 patient genotyping for PNPLA3 and thrombin generation assay,) which directly measures thrombin production over time (peak-thrombin: greatest amount of generated thrombin; endogenous thrombin potential (ETP):total amount of generated thrombin), expressed as ratio in presence/absence of added trombomodulin-TM as index of procoagulant imbalance) were also available. In addition, 192 healthy controls were tested for all the coagulation parameters.
Results: MASLD diabetic patients presented higher FVIII/PC (1.36 ± 0.58 vs 1.08 ± 0.31, p < 0.001) and ETP-TM ratio (0.68 ± 0.22 vs 0.60 ± 0.17, p = 0.003) compared to controls. In patients, ETP-TM ratio and FVIII/proteinC increased over LSM quartiles (from 1 to 4: 0.63 ± 0.12 to 0.89 ± 0.42, pANOVA = 0.012; 1.18 ± 0.35 to 1.57 ± 0.68, pANOVA = 0.003) and independently associated with increasing LSM values (b-coefficient, 6.11; CI 95% 3.59–8.64; b-coefficient, 4.80; CI 95% 2.28–7.32). Antithrombin and proteinC independently inversely correlated to LSM > 8kpa (OR 0.92, CI 95% 0.88–0.97; OR 0.97, CI 95% 0.94–0.99). Added to the model, PNPLA3 hampered these associations and remained independently associated with increased peak thrombin ratio (b-coefficient 0.063; CI 95% 0.001; 0.126) and decreased antithrombin (b-coefficient –6.14; CI 95% –11.82; –0.46). Finally, FVIII and fibrinogen levels were independent risk factors for microvascular complications (OR 1.01, CI 95% 1.00–1.02; OR 1.01; CI 95% 1.00–1.01).
Conclusion: MASLD diabetic patients display a procoagulant profile which seems mainly associated with increased FVIII levels and which is independently related to the severity of hepatic fibrosis by Fibroscan and to microvascular complications. A possible interplay between coagulation and PNPLA3 in determining fibrosis has emerged, however further studies are warranted to elucidate this mechanism.

THU-455

Real-world assessment of clinical burden and healthcare resource utilisation among patients with metabolic dysfunction-associated steatohepatitis with additional cardiovascular, renal and metabolic comorbidities in France, Italy, Germany and Canada

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Background and aims: Cardiovascular, renal and metabolic comorbidities are common, clinically relevant conditions associated with metabolic dysfunction-associated steatohepatitis (MASH). As data are limited on the impact of these comorbidities, we aimed to describe the clinical burden and healthcare resource utilisation (HCRU) in patients with MASH.
Method: Data were drawn from the Adelphi Real World MASH Disease Specific Programme™, a cross-sectional survey of physicians and their patients with MASH in France, Germany, Italy, and Canada from January–May 2024. Physicians reported patient demographics, clinical characteristics and HCRU. Patients were grouped by physician-stated fibrosis stage and presence of cardiovascular, renal and metabolic comorbidities: early fibrosis without comorbidities (EFnoC); early fibrosis with ≥1 comorbidity (EFwC); and advanced fibrosis with ≥1 comorbidity (AFwC). EFwC and AFwC groups were compared using pairwise statistics against the EFnoC control group after entropy balancing on patient age and sex.
Results: Overall, 247 physicians reported data for 2675 patients. For EFnoC (n = 170), EFwC (n = 1575) and AFwC (n = 478), respectively, mean ± standard deviation patient age was 50.6 ± 10.8, 54.7 ± 11.3 and 60.4 ± 11.6 years, 46.5%, 40.9% and 37.2% were female. Body mass index was higher for EFwC and AFwC than EFnoC ($p < 0.001$). Compared to EFnoC, AFwC patients had a higher number of symptoms at data collection (1.5 ± 1.8 vs 3.0 ± 3.0; $p < 0.001$) and EFwC and AFwC had more comorbidities (including non-cardiovascular, renal and metabolic; 3.5 ± 2.2 and 4.4 ± 3.1 vs 1.6 ± 1.0; $p < 0.001$). EFwC and AFwC patients also had more diagnostic tests (19.7 ± 11.3 and 23.8 ± 11.9 vs 17.4 ± 10.1; $p < 0.01$). Monitoring required more blood/urine tests in EFwC than EFnoC (3.5 ± 2.5 vs 2.8 ± 1.4; $p < 0.001$), and both EFwC and AFwC had more liver composite tests (2.3 ± 2.0 and 2.9 ± 3.3 vs 1.9 ± 1.3; $p < 0.01$). In the last 12 months, EFwC and AFwC patients visited more healthcare professionals then EFnoC (4.5 ± 3.9 and 4.8 ± 4.0 vs 4.0 ± 3.4; $p < 0.05$). More AFwC patients required ≥1 hospitalisation compared to EFnoC (10.4% vs 24.4%; $p < 0.001$), with a higher mean number of hospitalisations in the last 12 months (0.1 ± 0.4 vs 0.5 ± 2.3; $p < 0.01$). More EFwC and AFwC patients required a caregiver than EFnoC (18.9% and 28.0% vs 7.9%; $p < 0.001$).
Conclusion: Additional cardiovascular, renal and metabolic comorbidities in patients with MASH increased the clinical and HCRU burden of MASH, highlighting the critical need for improved recognition of comorbidities, and appropriate intervention, to improve patient outcomes.

THU-456

The impact of chronic hepatitis B on fibrosis progression in metabolic dysfunction-associated steatotic liver disease

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Background and aims: With the increasing prevalence of obesity and changes in dietary lifestyle, the overlap between chronic hepatitis B (CHB) and metabolic dysfunction-associated steatotic liver disease (MASLD) has been growing. Our study aimed to explore the impact of HBV infection on liver fibrosis progression in patients with MASLD.
Method: We enrolled MASLD patients who underwent liver biopsy at 16 medical centers across China between April 2004 and April 2024. Both univariable and multivariable logistic regression analyses were conducted to examine the association between CHB and significant fibrosis, advanced fibrosis, and cirrhosis. Propensity score matching (PSM) was used to adjust for potential confounders, ensuring a balanced comparison between patients with and without CHB.
Results: A total of 2,787 MASLD patients (Median age 43.5years, 58.9% male) were included in the study, with 1,811 (65.0%) having DM. Multivariate regression analysis suggested that the combination of CHB was an independent risk factor for significant fibrosis (before PSM: OR 1.83, 95% CI: 1.52–2.20, $p < 0.01$; after PSM: OR 1.64, 95% CI: 1.26–2.15, $p < 0.01$), advanced fibrosis (before PSM: OR 1.63, 95% CI: 1.20–2.23, $p < 0.01$; after PSM: OR 1.75, 95% CI: 1.20–2.57, $p < 0.01$), and cirrhosis (before PSM: OR 2.18, 95% CI: 1.32–3.61, $p < 0.01$; after PSM: OR 2.46, 95% CI: 1.40–4.66, $p < 0.01$) in patients with MASLD. In addition, sensitivity analyses were performed in different levels of HBeAg and HBV DNA and in HBV patients not receiving antiviral treatment previously, the conclusions were consistent with previous findings.
Conclusion: Our study demonstrated evidence that the combined CHB was an independent risk factor for significant fibrosis, advanced fibrosis and cirrhosis in patients with MASLD.

THU-461-YI

Genetic risk score correlates with Cytokine expression and risk of HCC and cirrhosis in MASLD patients from Latin America

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Background and aims: Genetic Risk Score (GRS) and cytokine dysregulations have been separately associated with the development of hepatocellular carcinoma (HCC) and cirrhosis in the context of Metabolic Associated Steatotic Liver Disease (MASLD). Latin Americans have elevated rates of HCC attributed to MASLD. However, the relationship between GRS, cytokine expression, and the progression of MASLD-related liver disease has not been explored in this population.
Method: We assessed the SNPs of *PNPLA3* rs738409, *TM6SF2* rs58542926, *MBOAT7* rs641738, and *HSD17B13* rs72613567 in a cohort of 983 individuals from 6 countries in Latin America, consisting of 267 HCC and 716 non-HCC. The four genetic variants were combined to create a genetic risk score for MASLD-related liver disease, including 142 HCC and 364 non-HCC cases. A total of 43 cytokines were measured in a sub-group of these samples (HCC = 107, cirrhosis = 111), categorized by low (0–4) and high (5–8) GRS within each group. Logistic regression was performed to calculate the odds ratios for individual SNPs and the combined GRS. The Mann-Whitney U test was utilized to compare cytokine levels between the low and high GRS groups.
Results: In Latin America, *PNPLA3* GG genotype was associated with a significantly increased risk of MASLD-related cirrhosis (OR: 6.157, 95% CI: 2.997–12.648, $p < 0.0001$) and HCC (OR: 2.629, 95% CI: 1.086–6.368, $p = 0.032$), whereas *HSD17B13* TATA was only associated with MASLD-related cirrhosis (OR: 0.108, 95% CI: 0.022–0.532, $p = 0.006$). No correlation between the SNPs of *TM6SF2* and *MBOAT7* and MASLD-related liver disease was found. When the four SNPs were combined into a GRS, patients with GRS 6–8 had a substantially higher risk of developing MASLD-related cirrhosis (OR: 12.25, 95% CI: 2.125–70.58, $p = 0.005$) and cirrhotic HCC (OR: 4.205, 95% CI: 1.205–14.67, $p = 0.024$) compared to those with GRS 0–2. In MASLD-related cirrhotic HCC, patients with GRS 5–8 exhibited lower expression of CXCL9, TNF, CCL13, CXCL10, CXCL16, CCL2, IFNγ, and CCL8 compared to those with GRS 0–4 ($p < 0.05$). Conversely, in MASLD-related cirrhosis, patients with GRS 5–8 showed higher expression of CCL1, CXCL8, and MMP2 compared to those with GRS 0–4 ($p < 0.05$).
Conclusion: In Latin America, GRS is strongly associated with an increased risk of MASLD-related cirrhosis and cirrhotic HCC, accompanied by opposing and distinct pro-inflammatory cytokine profiles across GRS groups. These findings emphasize the potential of genetic and immune profiling in understanding and stratifying MASLD-related liver disease.

THU-462
The association of Ferritin with subclinical coronary artery calcification is an expression of underlying cardiometabolic risk

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Background and aims: Observations of an association of serum ferritin (SF) and coronary artery calcification (CAC) have revealed conflicting results in the past. The aim of this study was to analyze the impact of SF on risk of subclinical artery disease in a population-based, Central-European cohort with a focus on cardiometabolic risk factors and genetic risk using a polygenic risk score (PRS).
Method: A subset of 1516 individuals of the Paracelsus 10.000 cohort was analyzed. Elevated SF-levels, defined by SF > 200 ng/ml for women and > 300 ng/ml for men, and the association with subclinical CAC were assessed univariate and using multiple regression models adjusted for sex, age, metabolic syndrome (MetS), SCORE 2 and PRS and compared to a model for MetS and CAC adjusted for age, sex and PRS.
Results: In 1516 patients, 12% (n = 182) had hyperferritinemia and 51% (n = 779) were male. Univariate analysis showed a significant association of CAC for ferritin with sex and age (IRR: 1.0003, 95% CI: 1.0000–1.0006, $p = 0.028$), sex and age combined with PRS (IRR: 1.0003, 95% CI: 1.000–1.004, $p = 0.044$), SCORE2 (IRR: 1.0006, 95% CI: 1.0002–1.0009, $p = 0.001$) and SCORE2 combined with PRS (IRR: 1.0006, 95% CI: 1.0003–1.0009, $p = 0.000$). The association was abolished after adjustment for MetS (IRR: 1.0001, 95% CI: 0.9999–1.0005, $p = 0.366$) and MetS combined with PRS (IRR: 1.0001, 95% CI: 0.9998–1.0005, $p = 0.262$). A comparison of the models of SF or MetS with CAC revealed a better fit for the MetS model.
Conclusion: Elevated SF levels and CAC are not independently associated after adjustment for MetS. The higher risk for CAC in people with elevated SF is very likely explained by underlying metabolic disease.

THU-463
Coexistence of fatty acid desaturase 2 (FADS2) and PNPLA3 risk alleles contributes to fibrosis progression in MASLD

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Background and aims: Metabolic-associated steatotic liver disease (MASLD) is triggered by genetic predispositions combined with acquired factors such as overnutrition, aging, and lack of physical activity. A subset of MASLD patients develops liver fibrosis, which can progress to cirrhosis. While the involvement of PNPLA3 single-nucleotide polymorphism (SNP) in MASLD development is well established, the combined effects of multiple genetic factors remain unclear. Our previous animal study suggested that alterations in the expression of fatty acid desaturase (FADS) may influence the progression of steatohepatitis. This study aimed to evaluate the impact of risk alleles of FADS-related SNPs on the progression of MASLD.
Method: This study included 48 biopsy-proven MASLD patients diagnosed between January 2021 and September 2024. Patients were categorized into two groups: non-progressive fibrosis (stage 0–2, n = 32) and progressive fibrosis (stage 3–4, n = 16). DNA was extracted from blood cells, and SNPs of PNPLA3 (rs738409), MBOAT7 (rs641738), TM6SF2 (rs58542926), FADS1 (rs174556), and FADS2 (rs174583) were determined using TaqMan PCR. Group comparisons were performed using chi-square tests or Student's t-tests, and multivariate analysis was conducted using logistic regression.
Results: The mean age tended to be higher in the progressive fibrosis group (60 ± 2 years) compared to the non-progressive group (55 ± 2 years), but the difference was not significant. The male-to-female ratio was 12:20 in the non-progressive group and 8:8 in the progressive group. Comparing SNP frequencies, the PNPLA3 G/G allele was observed in 43.8% vs. 62.5%, the MBOAT7 C/C allele in 43.8%

vs. 43.8%, the TM6SF2 C/T allele in 25% vs. 6.3%, the FADS1 T/T allele in 28.1% vs. 25.0%, and the FADS2 T/T allele in 40.6% vs. 56.3%, indicating that the PNPLA3 G/G and FADS2 T/T alleles tended to be more frequent in the progressive fibrosis group. The proportion of patients carrying both risk alleles (PNPLA3-GG/FADS2-TT) was significantly higher in the progressive group compared to the non-progressive group (12% vs. 43.8%; p = 0.027). Logistic regression analysis, adjusting for age and sex, identified PNPLA3-GG/FADS2-TT as an independent risk factor for fibrosis progression, with an odds ratio of 7.171 (95% CI: 1.284–40.047).
Conclusion: The coexistence of PNPLA3 and FADS2 risk alleles was identified as an independent and significant risk factor for fibrosis progression in MASLD, suggesting a potential synergistic effect. These findings demonstrate the importance of considering combined genetic risk factors, with SNP analysis of PNPLA3 and FADS2 providing a valuable tool for identifying high-risk patients with progressive MASLD.

THU-464
Type 2 diabetes increases the risk of progression to metabolic dysfunction-associated steatohepatitis-related cirrhosis in a real world setting

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Background and aims: In metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes (T2D) confers a higher risk for disease progression, but limited prospective data are available. Thus, we examined the relationship between T2D and the development of cirrhosis in a longitudinal observational study of people with MASLD.
Method: TARGET-NASH is a longitudinal observational cohort comprised of people who are managed for MASLD in hepatology and endocrinology practices in the US. TARGET-NASH previously developed definitions were applied to identify metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis. Diagnosis of T2D was derived from medical history, medication use or HbA1c ≥ 6.5%. People without MASH, with decompensated cirrhosis at index or with other diabetes types than T2D were excluded from the analyses. The index was defined as the earliest date within a 3-year period prior to enrollment when evidence of MASH or cirrhosis was observed. Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS) were calculated to assess fibrosis risk category (low, indeterminate, high). Results for continuous variables are given as median. Hazard ratios were derived from multivariable modeling.
Results: A total of 2415 individuals (1211 with and 1204 without T2D) with MASH (n = 1748) and compensated cirrhosis (n = 667) were included in the analysis. People with T2D were older (58 vs. 55 years), more frequently female (64 vs 54%) and had a higher body mass index (34.3 vs. 30.8 kg/m^2) as well as HbA1c (7.0 vs 5.6%; all p < 0.001) than participants without T2D. At index, people with T2D were more likely to have advanced disease by FIB-4 (high risk category: 33.4% vs 20.9%, p < 0.001) and NFS (44.4% vs 10.2%; p < 0.001). In those with available liver biopsy on or prior to index (n = 402), T2D was associated with a higher prevalence of any fibrosis or advanced (F3/F4) fibrosis (both p < 0.05). People with MASH and T2D had higher hazard ratio (HR) for progression to compensated cirrhosis compared to those without T2D (HR; 95% confidence interval, CI; 2.12 (1.69–2.66)), which remained after adjustment for age and sex (2.05 (1.62–2.58)) and also in the subgroups of different fibrosis risk (high: 1.72 (1.11–2.66); low: HR 2.17 (1.39–3.40)). In contrast, risk of progression from compensated to decompensated cirrhosis was independent of the presence of T2D at index in all individuals (1.15 (CI 0.87–1.52)) and across fibrosis risk groups (high: 1.16 (0.78–1.72); low: 0.92 (0.18–4.67)).
Conclusion: Among people with MASH, the presence of T2D is associated with a higher risk of progression from MASH to cirrhosis, whereas the risk of progression from compensated to decompensated MASH cirrhosis is independent of diabetes status. This underlines the importance of early screening for MASH in people with T2D to reduce the growing individual and societal burden of MASLD-related severe liver disease.

THU-465
Long term outcomes of liver transplantation for patients with metabolic dysfunction and alcohol associated/related liver disease (MetALD) versus alcohol associated liver disease (ALD)

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Background and aims: As per the new nomenclature of steatotic liver disease (previously fatty liver disease), the subcategory of metabolic dysfunction and alcohol associated/related liver disease (MetALD) denotes the co-existence of metabolic and alcohol-associated risk factors. Existing literature shows better post-transplant outcomes after alcohol associated liver disease (ALD) compared to non-alcoholic steatotic liver disease. We assessed the metabolic outcomes & survival of patients of MetALD and ALD who underwent Living donor liver transplantation (LDLT) as there is no existing literature on the same.
Method: This is a retrospective analysis of a prospectively maintained database of LT recipients. 319 patients who underwent LDLT for Alcohol associated liver disease from July 2018 to August 2023 were included in this study. Patients who had at least one Cardio-metabolic risk factor as per the new definition such as Diabetes mellitus, hypertension, and obesity (BMI ≥23 kg/m^2) were reclassified as MetALD. Their pre-transplant characteristics and post-transplant outcomes were compared with patients with ALD.
Results: Of 319 patients, 202 patients had MetALD and 117 had ALD. Patients with MetALD were older [50(25–74) versus 47(25–70) years] and had higher BMI [26.10(18.8–40.8) versus 21.25(15.5–26.6) kg/m^2]. Larger proportion of patients with ALD had weight gain (>10% body weight at 1-year) than MetALD [45 (38%) versus 26 (12%), p = 0.001]. Patients with MetALD had higher incidence of post-transplant steatotic liver disease (SLD) [62(30%) versus 23(19%)]. Incidence of CKD (eGFR <60 ml), post-transplant metabolic risk factors (DM, HTN, Dyslipidemia), coronary artery disease and recidivism were similar in both the groups. There was a trend towards lower survival in patients with MetALD as compared to ALD (1-year survival was 84.2% vs 91.5%), although not statistically significant.
Conclusion: Survival after liver transplantation for patients with MetALD and ALD is comparable. The incidence of post-transplant weight gain is higher in ALD group, probably due to reversal of alcohol & disease associated malnutrition. This group also had equal proportion of metabolic risk factors as of MetALD group.

THU-466
Development of a machine learning model for predicting cardiovascular disease in metabolic dysfunction-associated steatotic liver disease: a prospective cohort study from UK Biobank

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly linked to cardiovascular disease (CVD), the leading cause of death in this population. However, traditional CVD risk models fail to account for MASLD-specific factors such as liver fibrosis and sarcopenia. This study aimed to develop a machine learning model that incorporates these unique characteristics to improve 10-year CVD risk prediction using data from the UK Biobank.
Method: A total of 39,758 participants with MASLD were included in this study. MASLD was defined as the presence of hepatic steatosis, determined by fatty liver index ≥60 in combined with at least one cardiometabolic criterion. CVD outcomes were identified using International Classification of Diseases-10 codes. Predictors included liver-related test results and handgrip strength, alongside established CVD risk factors. Model development and internal validation were performed on the England cohort with an 8:2 training-validation split. The XGBoost algorithm was selected for its superior performance. The Scotland and Wales cohorts served as test sets.
Results: Among study participants, 35,871 individuals from the England cohort and 3,887 from the Scotland and Wales cohorts were diagnosed with MASLD. The mean age was 56.2 years in the England cohort and 55.2 years in the Scotland and Wales cohorts, with male participants comprising 62.2% and 63.6% of each cohort, respectively. The 10-year CVD incidence was 9.4% in the England cohort and 8.1% in the Scotland and Wales Cohorts, respectively. The machine learning model exhibited robust predictive performance for 10-year CVD risk in MASLD participants, an achieving area under the receiver operating characteristic curve (AUROC) values of 0.81 (95% confidence interval [CI]: 0.801–0.821), 0.71 (95% CI: 0.685–0.731), and 0.75 (95% CI: 0.712–0.779) in the training, internal validation, and test sets, respectively. Notably, the model significantly outperformed traditional CVD risk scores such as the atherosclerotic cardiovascular disease (ASCVD) risk score (AUROC 0.69 in the test sets) and the Framingham risk score (AUROC 0.58 in the test sets).
Conclusion: This study indicates that integrating liver-related test results and muscle strength parameters with conventional CVD risk factors improves cardiovascular risk prediction in MASLD participants. Further validation in diverse populations is warranted to confirm its clinical applicability.

THU-467-YI
MASLD and FIB4 are independent predictors of major adverse liver outcomes and cardiovascular events in type 2 diabetes: findings from a single-center cohort using AI-driven machine learning

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Background and aims: MASLD and liver fibrosis are common in type 2 diabetes (T2D), and the FIB-4 index is a widely used non-invasive marker of liver fibrosis. However, data on the specific predictive role of FIB-4 in identifying the risk of major adverse liver outcomes (MALOs) in T2D remain limited.
The primary objective of this study was to evaluate whether the presence of MASLD and elevated FIB-4 predict an increased incidence of MALO in a cohort of patients with T2D, utilizing AI-driven data extraction for analysis. Secondary objectives included assessing whether MASLD and FIB-4 serve as predictors of MACE, and identifying any additional variables associated with MALO and MACE.
Method: This was an observational retrospective cohort study conducted at the outpatient diabetes clinic of the Gemelli Polyclinic in Rome, Italy, from Jan-2016 to Jan-2022. Data were extracted using an AI driven system, which collected comprehensive clinical information. The cohort consisted of adult patients with T2D. MASLD was identified by imaging or the Hepatic Steatosis Index (HSI) and the FIB-4 was calculated. A FIB-4 greater than 2.67 was considered indicative of a high probability of advanced liver fibrosis. The primary outcome was the occurrence of MALO, while a secondary outcome was MACE. To evaluate the predictive role of MASLD and FIB-4 for MALO and MACE, multivariable logistic regression models were developed. Each model was adjusted for clinically relevant covariates, with statistical significance defined as $p < 0.05$.
Results: A total of 1,711 patients were included, of whom 67 (3.9%) experienced a MALO and 203 (11.86%) a MACE. Patients with MASLD had significantly higher odds of experiencing MALO (OR 2.03, 95% CI 1.10–3.77, $p = 0.024$) and MACE (OR 1.40, 95% CI 1.01–1.95, $p = 0.042$). A FIB-4 > 2.67 was strongly associated with an increased risk of both MALO (OR 6.92, 95% CI 4.01–11.96, $p < 0.001$) and MACE (OR 2.39, 95% CI 1.67–3.42 $p < 0.001$). In the second multivariable model, which excluded patients with cirrhosis at baseline, MASLD remained a significant predictor of MALO (OR 2.51, 95% CI 1.04–6.04, $p = 0.040$), and a FIB-4 > 2.67 continued to be associated with an increased risk of MALO (OR 3.02, CI 1.34–6.77, $p = 0.007$). Additionally, HbA1c was a significant predictor in both models (OR 1.02, 95% CI 1.01–1.04, $p = 0.009$).
Conclusion: This study demonstrated that MASLD and elevated FIB-4 are independent predictors of MALOs and MACE in patients with T2D. The findings underscore the importance of routine non-invasive screening for liver fibrosis and MASLD in diabetic populations, as well as the role of HbA1c in predicting adverse outcomes. Early detection and optimal glycemic control could help reduce the risk of both liver and cardiovascular complications. Furthermore, the use of AI-driven data extraction demonstrates the potential for enhancing clinical research and improving patient management in real-world settings.

THU-468
Adverse outcomes and HBsAg seroclearance of chronic hepatitis B complicated with metabolic dysfunction-associated steatotic liver disease: a cohort study

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Background and aims: To explore the influence of MASLD on the risks of adverse events, including cirrhotic complications and hepatocellular carcinoma, and on the HBsAg clearance among patients with CHB.
Method: From January 2015 to January 2024, consecutive patients with CHB and had undergone liver biopsy were enrolled at Ningbo No. 2 Hospital, Ningbo, China. Upon enrolment, participants underwent blood, imaging tests and physical examinations. To assess the presence of MASLD, metabolic dysfunction, steatohepatitis and steatosis in relation to the cumulative incidence of related adverse events (cirrhotic complications and hepatocellular carcinoma) and serum HBsAg clearance.

Results: Our cohort were included 827 patients. The median follow-up time for adverse events as an outcome was 4.62 years (3.08–6.76), and for HBsAg seroclearance, it was 4.72 years (3.23–7.10). There were 81 adverse events, including 13 of hepatocellular carcinoma (HCC) and 68 of hepatic dysfunction, as well as 33 HBsAg antigen-clearance events. The cumulative incidence of 1-, 3-, and 5-year adverse events was 3.3%, 6.1%, and 15%, respectively, in the with MASLD group and 0.7%, 3.9%, and 7.1%, respectively, in the without MASLD group. In multivariable Cox regression models, baseline cirrhosis (corrected hazard ratio [aHR], 9.87; $P < 0.001$), antiviral therapy (aHR, 8.48; $P = 0.031$), lower baseline ALB (aHR, 0.90; $P < 0.001$), higher AST levels (aHR, 1.01; $P = 0.049$), higher ALP levels (aHR, 1.01; $P < 0.001$), and the presence of MASLD (aHR, 2.22; $P = 0.002$) were associated with the incidence of adverse events, whereas a reduction in baseline HBV DNA (aHR, 0.79; $P < 0.001$) was related to adverse events. In the PSM analysis, the presence of MASLD in 151 patients was associated with increased adverse outcomes (PSM-adjusted HR, 2.095), and HBsAg clearance (PSM-adjusted HR, 3.475). In patients with MASLD, the presence of steatohepatitis and metabolic burden ($P > 0.65$) was not associated with adverse outcomes. Compared with the steatosis, activity, fibrosis (SAF) scores <5 group (42.38%), the SAF ≥5 group (57.62%) was significantly associated with adverse event rates (HR: 6.812). Multifactorial analysis demonstrated that aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) were independent risk factors for disease progression in CHB patients with MASLD ($P < 0.05$). The non-invasive diagnostic models, with AST and GGT, developed accordingly were more effective than the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 (FIB-4) in predicting adverse events in patients with MASLD combined with CHB (AUC = 0.700).
Conclusion: The existence of MASLD was related to higher rates of adverse events and HBsAg seroclearance in patients with CHB. In addition to MASLD, metabolic dysfunction can also increase the incidence of adverse events in CHB patients, but there is no cumulative effect. Non-invasive models based on AST and GGT had good accuracy in predicting the risk of adverse events in this population.

THU-469

Long-term clinical outcomes across biopsy-confirmed steatotic liver disease categories: a multicenter prospective cohort study using merged data

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Background and aims: Little has been explored about the long-term outcomes of biopsy-confirmed steatotic liver disease (SLD) and its subcategories. We aimed to investigate the risks of all-cause mortality, liver-related events (LREs), cardiovascular disease, and extrahepatic cancers in biopsy-confirmed metabolic dysfunction-associated steatotic liver disease (MASLD), MetALD, and alcohol-related liver disease (ALD).
Method: This multicenter prospective cohort study included patients who had liver biopsies between 2010 and 2023 at 8 tertiary hospitals in South Korea. SLD was defined as ≥5% macrovesicular steatosis in biopsy specimens. Adjusted hazard ratios (aHRs) for all-cause mortality, LREs, cardiovascular disease, and extrahepatic cancers were estimated using multivariable Cox proportional hazards regression models.
Results: During the median follow-up of 4.8 years, 106 deaths, 118 LREs, 55 cardiovascular diseases, and 94 extrahepatic cancers occurred in 2,543 study populations including MASLD (n = 1,929), MetALD (n = 132), ALD (n = 269), and no SLD (n = 213). Compared with no SLD, MetALD (aHR 8.50; 95% CI, 2.12–33.99) and ALD (aHR 6.93; 95% CI, 1.89–25.42) had higher risks of all-cause mortality. MASLD (aHR 3.64; 95% CI, 1.12–11.87) and ALD (aHR 10.04; 95% CI, 2.82–35.71) had an increased risk of LREs. No significant differences were observed in the risk of cardiovascular diseases or extrahepatic cancers among the subcategories of SLD. Of patients with MASLD, metabolic-associated steatohepatitis (MASH) had an increased risk of all-cause mortality (aHR 2.70; 95% CI, 1.31–5.60) and LREs (aHR 5.02; 95% CI, 2.35–10.74) compared to those without MASH. At-risk MASH (MASH with ≥ F2) showed an increased risk of all-cause mortality (aHR 2.90; 95% CI, 1.52–5.53) and LREs (aHR 9.81; 95% CI, 4.75–20.26) compared to those without.
Conclusion: Using a biopsy-confirmed SLD cohort, this study showed MASLD, MetALD, and ALD had increased risks of all-cause mortality or LREs while little differences were observed with cardiovascular disease and extrahepatic cancers. These findings contribute to deepening the insight into the long-term outcomes of SLD and devising more customized management strategies by the differential risk.

THU-470-YI

Liver-related events are uncommon in patients meeting AASLD criteria for Resmetirom and are not seen in those with a liver stiffness measurement <10 kPa

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Background and aims: Resmetirom, a selective thyroid hormone receptor beta agonist, has been licensed for treatment of MASLD in the USA. AASLD guidelines recommend consideration of Resmetirom for those with a liver stiffness measurement (LSM) between 8 and 15 kPa. Several studies suggest that the risk of liver related events (LRE) is low when LSM <10 kPa, and only moderately increased when between ≥10 kPa and <15 kPa. We sought to evaluate rates of LRE, non-liver related deaths, progression and regression of LSM, amongst MASLD patients meeting AASLD LSM criteria for Resmetirom.
Method: Patients undergoing Fibroscan in a single centre from April 2012 to February 2019 with LSM ≥8 kPa and <15 kPa were identified from an electronic database. Those with an indication recorded as "NAFLD" or "Under Investigation" were selected for case note review. Using recorded alcohol history, patients were included and assigned as having MASLD or MetALD according to current definitions. Those with alternative causes of liver disease were excluded. Data collected included demographic, clinical, and laboratory information. Case notes were reviewed to identify dates of LRE (ascites, jaundice, variceal bleeding, encephalopathy, HCC). Dates of death were identified, and death categorised as liver related if occurring after an LRE. Kaplan-Meier analysis was performed to determine cumulative rates of LRE, censored 01/04/2024. Follow-up LSMs were categorised as improved (<8 kPa), static (≥8 and <15 kPa) or progression (≥15 kPa).
Results: On case note review, 213 of 450 patients meeting LSM and indication criteria were confirmed suitable for inclusion (177 MASLD,

36 MetALD). Median age was 63 (±17) years, with 109 (51.2%) being male. Median follow up was 7.1 (±2.2) years. 179 (84%) patients were obese and 34 (16%) overweight. Hypertension (133, 62.4%), diabetes (107, 50.2%) were the most common metabolic comorbidities. 4 (1.88%) patients experienced LRE (2 HCC and 2 ascites), 2 (0.94%) of whom died. A further 17 (7.98%) experienced non-liver related mortality. No LRE occurred in the 88 (41.3%) of patients with LSM <10 kPa. Cumulative rates of LRE were 0.94% at 5 years and 1.88% at 10 years. Of 127 (61%) patients with a follow up scan, 67 (52.76%) improved, 49 (38.58%) were static, and 11 (8.66%) progressed.
Conclusion: LRE are uncommon in patients meeting AASLD criteria for Resmetirom therapy and were not seen with a LSM <10 kPa. Non liver related mortality was predominant. In an era predating specific drug therapy, a majority of patients undergoing follow up LSM demonstrated improvement. It is likely that a high number of patients would require treatment to prevent one medium term LRE in the suggested treatment population.

THU-472

Sarcopenia is an independent risk predictor for all-cause mortality in individuals with a body mass index less than 25

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent chronic liver metabolic disease characterized by excessive lipid accumulation in the liver. Sarcopenia, a progressive condition involving the decline of muscle mass and function, was traditionally associated with aging. However, recent studies have elucidated a strong connection between sarcopenia and metabolic disorders. Existing literature indicates that MASLD patients with sarcopenia experience more severe disease progression and a higher mortality risk. Nonetheless, there is a paucity of research on the specific subtype known as lean MASLD.
Method: This study included participants from the Third National Health and Nutrition Examination Survey (NHANES III) database who had bioelectrical impedance analysis (BIA) data, with mortality followed up until 2019. MASLD was diagnosed using liver ultrasound data and the presence of overweight, hypertension, diabetes, hyperlipidemia, and low high-density lipoprotein cholesterol. Lean MASLD refers to patients with MASLD and a body mass index (BMI) less than 25. Skeletal muscle mass was calculated and divided by body weight to derive the skeletal muscle index, defined as less than 37% in men and less than 28% in women. Logistic and Cox regression models were used for statistical analysis, with $P < 0.05$ considered statistically significant.
Results: Of the 12316 subjects, 3989 met the MASLD diagnostic criteria. Compared with the MASLD patients without sarcopenia (n = 1709), those with sarcopenia (n = 2,280) had a lower proportion of males but higher BMI, waist circumference, ALP, and triglyceride levels ($P < 0.01$). Multivariate Logistic regression analysis showed that MASLD patients had an increased risk of sarcopenia (OR = 1.14, 95% CI: 1.00–1.29, $P < 0.05$) compared to non-MASLD patients. Among participants, 701 (13.12%) were classified as having sarcopenia in the lean MASLD group, while 3,288 (54.85%) were classified in the non-lean MASLD group. In participants with BMI≥25, sarcopenia was associated with an increased risk of MASLD (OR = 1.28, 95% CI: 1.12–1.46, $P < 0.01$), but not all-cause mortality ($P = 0.89$). Conversely, in participants with BMI<25, sarcopenia was linked to an increased risk of all-cause mortality (HR = 1.27, 95% CI: 1.08–1.49, $P < 0.01$), but not MASLD ($P = 0.49$).
Conclusion: In a nationally representative sample of U.S. adults, MASLD is associated with an increased risk for developing sarcopenia. Among participants with a BMI<25, sarcopenia was linked to an increased risk of all-cause mortality, but not MASLD. Conversely, in participants with a BMI≥25, sarcopenia was associated with MASLD risk, but not all-cause mortality.

THU-475

Ongoing fibrosis quantification in paired liver biopsy samples from MASLD patients using AI-based digital pathology: an international multicenter study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a significant global public health challenge, with liver fibrosis serving as a critical determinant of clinical prognosis. qFibrosis is an automated fibrosis quantification system that combines artificial intelligence with second harmonic/two-photon excitation fluorescence (SHG/TPEF) microscopy imaging. Previous studies suggested that with changes in fibrosis area in the periportal region observed via qFibrosis, we could potentially distinguish patients receiving routine or strengthened lifestyle interventions in the placebo group in the MASH clinical trial. To build on these findings, we expanded the sample size and employed qFibrosis to observe subtle pathological changes in paired liver biopsy specimens.
Method: We initiated an international multicenter study. To date, we have enrolled 308 MASLD patients with paired liver biopsies from 9 medical centers across China, Egypt, India, Italy, Japan, Malaysia, Saudi Arabia and Australia. These patients were managed through lifestyle intervention during follow-up and did not receive resmetirom. Clinical data collation has been completed, while unstained scanning and quantitative fibrosis assessment of their paired liver biopsy samples are ongoing. For comparison, 75 patients from the placebo cohorts in two failed MASLD clinical trials were analyzed.
Results: In the lifestyle intervention group, after a median follow-up of 13 months, 31.5% (97/308) of MASLD patients exhibited fibrosis regression, with significant improvements in fibrosis stage (Δ: -0.1 ± 1.0, $p = 0.011$). Additionally, improvements were observed in steatosis (Δ: -0.3 ± 0.9, $p < 0.001$), lobular inflammation (Δ: -0.2 ± 0.8, $p < 0.001$) and hepatocyte ballooning (Δ: -0.2 ± 0.7, $p < 0.001$). In the placebo group from the clinical trials, 21.3% (16/75) showed fibrosis regression after 24 to 48 weeks of treatment. Significant improvements were observed in the fibrosis stage (Δ: -0.2 ± 0.6, $p = 0.012$) and hepatocyte ballooning (Δ: -0.2 ± 0.6, $p = 0.018$). No significant

difference in fibrosis changes was observed between the two groups (p = 0.687).
Conclusion: Preliminary clinical data analysis revealed significant improvements in liver histological features in both the lifestyle intervention and placebo groups. And the lifestyle intervention group was considered analogous to a placebo group in the real world. We plan to conduct a standardized unstained scan and quantitative fibrosis analysis of paired liver biopsy samples collected globally. Ongoing quantitative fibrosis analysis, focusing on periportal fibrosis dynamics, will further elucidate the differentiation between routine and strengthened lifestyle intervention patients, providing novel insights into fibrosis dynamics and placebo effects.

THU-476
Rising trends in preventable premature MASLD-related deaths: disparities across urban and rural U.S. counties (2011–2021)
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Background and aims: Many MASLD-related deaths in the US occur prematurely and may be preventable. We aimed to evaluate preventable premature MASLD-related deaths and identify associated disparities in the US.
Method: Data from the U.S. National Vital Statistics System (2011–2021) were used to estimate premature preventable death (PPD) defined as deaths exceeding expected numbers based on the death rates of the three states with the lowest premature death (age ≤75 at death) rates. Counties were classified using the Center for Disease Control's (CDC's) urban-rural framework, and county-level demographic, healthcare access, and lifestyle data were obtained from the PLACES dataset. Annual percent changes (APC) were calculated using joinpoint regression models. Mixed-effects linear regression (MELR) models evaluated associations between county-level factors and PPD.
Results: MASLD-related death rates in the U.S. rose from 15.33 to 24.13 per 100,000 between 2011 and 2021 (APC: +4.21%). Of these deaths, ≥84% could be considered PPDs which increased from 13.09 to 20.33 per 100,000 (APC: +3.97%). Rural counties in the US consistently had higher premature MASLD-death rates (16.40 per 100,000 in 2011 to 30.03 in 2021, APC: +6.23%) compared to urban counties (11.56 per 100,000 in 2011 to 16.45 in 2021, APC: +3.48%). The proportion of PPD from MASLD increased more sharply in the urban counties of the US (16.95% in 2011 to 41.49% in 2021, APC: +8.28%) than in rural counties (41.62% in 2011 to 68.41% in 2021, APC: +4.82%). Interestingly, PPD from MASLD in the urban counties in the US surged after 2019 (APC: +18.16%), surpassing rural increases (APC: +6.94%). In fully adjusted MELR models, higher rates of routine checkups (beta = –0.0136 to –0.0138) and cholesterol screenings (beta = –0.0034 to –0.0459) were associated with a lower proportion of PPD from MASLD in both urban and rural counties. Conversely, food insecurity (beta = 0.0154 to 0.0281) and lack of physical activity (beta = 0.0143 to 0.0281) were linked to higher PPD from MASLD. Obesity (beta = 0.0212) contributed to higher PPD in urban counties, while food deserts (beta = 0.0030) were associated with higher PPD in rural counties.
Conclusion: Preventable premature MASLD-related deaths are rising in the U.S. While the rural areas were mostly affected, there is an increase in preventable deaths from MASLD in urban areas since 2019. Components of healthcare access, food insecurity, and physical inactivity are critical drivers of PDP from MASLD in the US.

THU-477
Serum bile acid is associated with clinically significant pruritus in patients with metabolic dysfunction-associated steatotic liver disease
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Background and aims: Although pruritus has been reported in metabolic dysfunction-associated steatotic liver disease (MASLD), its association with serum bile acids is less well established. We assessed the associations of serum bile acids with pruritus in patients with MASLD.
Method: We analyzed clinical, laboratory (including serum bile acid) and CLDQ-NASH data available in MASLD database. All study-related variables were collected after informed consent. The severity of pruritus was assessed using the itch item of CLDQ-NASH, and pruritus was defined as the item score ≤4 on a 1–7 scale (patient troubled by itch at least "some of the time"). In those with follow-up CLDQ-NASH and serum bile acid data available, a significant change in bile acids was defined as a change of ≥20% from baseline; a significant change in pruritus was defined as a change in CLDQ-NASH itch score of ≥2 points from baseline.
Results: We included 2154 subjects: mean (SD) age 57.7 (10.0) years, 42% male, BMI 33.4 (6.8), 66% type 2 diabetes, 25% pruritus. Patients with pruritus had significantly lower HRQL scores in all domains of CLDQ-NASH: up to –1.2 on a 1–7 scale, all p < 0.0001. The correlation of higher serum bile acids with lower itch score was significant (r = –0.12, p < 0.0001), and patients with pruritus had higher levels of bile acids: 12.2 (14.6) µmol/L vs. 10.1 (12.6) µmol/L (p < 0.0001). Among N = 1627 patients with 12-week follow-up data, 14% had their pruritus worsened, 12% improved, and 74% unchanged. Patients with improved pruritus more commonly had a significant decrease in bile acids (34% vs. 24% in pruritus unchanged and 18% pruritus worsened, p = 0.0006). On the other hand, patients with worsened and unchanged pruritus had similar rates of significant bile acids increase (33% vs. 30%, p > 0.05). Among patients with a significant bile acid decrease, there were 17% who had pruritus improved vs. 12% in unchanged bile acids, 9% in increased bile acids groups (p = 0.0009) while no similar association was observed for significant bile acids increase and pruritus worsening (p > 0.05). In multivariate regression analysis, a significant decrease in bile acids was independently associated with higher odds of pruritus improvement (OR = 2.0 (1.3–3.0), p < 0.0001; adjusted for age, sex, BMI, diabetes, history of skin and psychiatric disorders, cirrhosis, baseline history of itch and bile acids levels, baseline ALP, GGT and bilirubin and changes in those). In a round of post hoc cutoff search, significant worsening of pruritus was found to be associated with at least 200% increase in serum bile acids: cross-sectional rates 38% vs. 13%, adjusted OR = 3.70 (1.80–7.59), p = 0.0004.
Conclusion: Among MASLD, higher serum bile acid level is associated with more pruritus. A decrease of ≥20% in bile acids is independently associated with improvement of pruritus, and a three-fold increase in bile acids is associated with pruritus worsening.

THU-478

Metabolic dysfunction-associated steatotic liver disease (MASLD) screening according to EASL guideline is cost-effective

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Background and aims: EASL 2024 guidelines recommend screening individuals with type 2 diabetes (T2D), medically complicated obesity, and elevated liver enzymes to identify those as risk for MASLD. The screening algorithms begin with Fibrosis-4 index (FIB-4), followed by vibration-controlled transient elastography (VCTE) with enhanced liver fibrosis (ELF) as an alternative where VCTE is unavailable. We applied screening algorithm according to 2024 EASL guideline to the primary care setting in the United States.
Method: A Markov-based cost-utility model was developed to evaluate screening strategies. The prevalence of T2D, medically complicated obesity, and elevated liver enzymes in primary care was estimated using nationally representative data. Transition probabilities were aligned with the available national data on liver outcomes (HCC, cirrhosis, and liver transplants) and were adjusted for T2D and obesity. Treatment of co-morbidities (T2D, obesity, etc.) were considered as per standard of care. For those who qualified, treatment with resmetirom was provided according to the FDA approval. Costs for screening, staging, follow-up testing, treatment, and long-term care were sourced from public and private payer data. Incremental cost-effectiveness ratios (ICERs) were calculated over a 20-year horizon, comparing screening strategies to no screening. Sensitivity analyses evaluated the robustness of findings across key parameters.
Results: Screening algorithm recommended by EASL guideline was cost-effective in the U.S., with ICERs ranging from $23,265 to $26,949 per quality-adjusted life year (QALY). Screening reduced the prevalence of advanced fibrosis (24.89%–33.11% vs. 46.70%–48.84%) and cumulative mortality (50.86%–79.60% vs. 61.23%–85.59%) compared to no screening. Sensitivity analyses highlighted treatment effectiveness, fibrosis progression rates, and non-invasive test (NIT) performance as critical determinants of cost-effectiveness. When VCTE access was limited, using ELF as an alternative maintained the cost-effectiveness of screening.
Conclusion: Screening for MASLD following EASL guidelines is cost-effective in the U.S., reducing advanced fibrosis, mortality, and long-term healthcare costs.

MASLD – Diagnostics and non-invasive assessment

TOP-377

The "LITMUS metabolic-dysfunction associated steatotic liver disease intention-to-treat" (LiMITT) score: a machine learning proteomic tool to select patients for therapy

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Background and aims: With the advent of approved MASLD therapies, there remains a critical need for non-invasive tests to accurately triage patients with MASLD for therapy. This study aims to identify proteomic signatures that distinguish between fibrosis stage and disease activity, and to leverage machine learning approaches to develop simple, well-performing models that detect advanced fibrosis and at-risk MASH.
Method: The European SLD Registry (formerly European NAFLD Registry) LITMUS Study Cohort comprises a prospectively recruited histologically characterised international multicentre cohort covering the complete spectrum of MASLD severity. All biopsies were centrally read by expert hepatopathologists using the NASH-CRN system. To assess changes in protein levels across the MASLD spectrum, these were integrated with serum proteomics from a SomaScan panel comprising approximately 7,000 human proteins. Logistic regression models were trained on the prospective LITMUS Study Cohort (1,088 samples). Feature selection utilised XGBoost and recursive feature elimination; best-fitting models were chosen based on AIC. Cases from the LITMUS Metacohort (275 samples) were used

for hold-out independent validation. Additionally, the Cox proportional hazards model was used on a sub-group of 332 patients who had multiple FibroScan-VCTE measurements to identify the proteins linked to fibrosis progression.
Results: Proteomic signatures defining (1) advanced fibrosis and (2) MASLD activity, were identified and used to establish accurate predictive models for clinical application. LiMITT-Fibrosis (comprising ADAMTSL2, COLEC11, CLSTN2, C7, and GDF15) to predict advanced fibrosis (F0-2 vs F3+) when categorised dichotomously, while LiMITT-MASH (comprising ADAMTSL2, AKR1B10, ME1, and UGDH) defined at-risk MASH (MAS ≥4 + F≥2). For LiMITT-Fibrosis, in the training/validation sets respectively, the AUC was 0.92/0.90 (Youden index provided Sensitivity 0.85/0.87, Specificity 0.86/0.80) and outperformed FibroScan-VCTE (AUC of 0.79/0.84 in training/validation sets), FIB-4 (AUC 0.77/0.75), and ELF (AUC 0.81/0.76). For LiMITT-MASH, in training/validation sets respectively, the AUC was 0.83/0.84 (Sensitivity 0.81/0.83, Specificity 0.73/0.72) and outperformed AST (AUC 0.74/0.70 in training/validation sets). Additionally, time-to-event analysis uncovered 92 proteins linked to fibrosis progression, 44 of which overlapped with the fibrosis proteomic signature.
Conclusion: Circulating protein analysis has enabled the development and validation of the LiMITT suite of accurate, non-invasive predictive models for diagnosing advanced fibrosis and at-risk MASH. Furthermore, proteins associated with future fibrosis progression have been identified, providing insights into the mechanisms driving the disease and supporting the prognostic utility of this approach.

TOP-378-YI
Dynamics in lab-based non-invasive tests predict the development of liver-related outcomes in tertiary care

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Background and aims: Non-invasive tests (NITs) are essential tools to identify individuals at risk of developing complications associated with steatotic liver disease (SLD), and to direct patient pathways. While conventional algorithms only consider one-time assessments, longitudinal trajectories of NITs might provide unexploited additional information. We aimed to assess the prognostic value of longitudinal trajectories of NITs in predicting liver-related outcomes.
Method: This retrospective cohort study included 3399 outpatients with suspected SLD characterized at the time of first referral to a tertiary hospital. All available labs from hospital records were used to model trajectories of NITs including FIB-4, APRI, CORE score (%) and LiverPRO (%), generating the best-fitting line per patient indicating the direction and degree of change over time. These dynamics were linked to liver-related endpoints including the development of compensated advanced chronic liver disease (cACLD, defined as reliable liver stiffness measurement ≥10 kPa), hepatic decompensation, and liver-related death retrieved from national death registries, using a joint modelling approach.
Results: We included 2712 (80%) patients with SLD, 136 (4%) with cryptogenic and 551 (16%) without chronic liver disease. Prevalence of cACLD was 845 (25%) at first referral.
A total of 74,907 lab timepoints were used to model lab-trajectories over a median period of 9.4 years (median time from the first lab prior to referral: 1.9 years [IQR: 8.6–0.1]). 118 (4%) patients developed hepatic decompensation, 268 (8%) died including 80 (2%) liver-related deaths during a median follow-up of 5.4 years from first referral.
Adjusting for age and sex, dynamics in LiverPRO (adjusted hazard ratio [aHR] per logit-change: 1.28 [95% CI: 1.18–1.39], FIB-4 (aHR per log-change: 2.84 [95% CI: 1.54–4.45] and CORE (aHR per logit-change: 1.29 [95% CI: 1.08–1.50]), but not APRI, were independently associated with development of cACLD, indicating a direct relationship between an averaged increase in these scores and an increased subsequent risk of cACLD. Results for hepatic decompensation were similar [aHR LiverPRO: 1.61 [1.25–1.86], FIB4: 3.04 [2.10–4.45], CORE: 1.31 [1.06–1.59]). However, only LiverPRO (aHR: 1.78 [95% CI: 1.51–1.99]) and FIB-4 (aHR: 4.17 [95% CI: 2.37–12.66]) were associated with liver-related death.
Notably, when considering dynamics within the previous 5 years to predict outcomes in the subsequent 5 years, discrimination was numerically highest for LiverPRO, with an area under the curve (AUC) of 0.716 for cACLD, 0.889 for hepatic decompensation and 0.904 for liver-related death, as compared to FIB-4 (0.691/0.869/0.882) and CORE (0.665/0.812/0.837).
Conclusion: Dynamics in LiverPRO, FIB-4 and CORE score yield early prognostic information for subsequent development of liver-related outcomes in tertiary care.

TOP-379-YI
Untargeted lipidomic profiling in pediatric metabolic dysfunction-associated steatohepatitis: insights from youth enrolled in NASH CRN studies

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Background and aims: Disruptions in lipid metabolism play a significant role in the pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH). Lipidomics offers a comprehensive approach to identifying lipid alterations contributing to disease mechanisms and potential biomarkers or therapeutic targets. However, research on the lipidomic profile of pediatric MASH remains limited. This cross-sectional study applied lipidomic profiling to identify lipid alterations associated with biopsy-confirmed pediatric MASH using data from youth in NASH CRN studies (TONIC, DB1) and healthy controls.
Method: Untargeted lipidomics was performed on fasting serum samples from 160 pediatric participants using ultra-high-performance liquid chromatography-mass spectrometry (UHPLC-MS/MS). Clinical assessments included anthropometrics, lipid and liver enzyme levels, and glucose metabolism markers. MASLD/MASH status was determined by liver biopsy for NASH CRN participants and MRI for controls. Lipidomics data were processed using MS-DIAL (v4.9) and analyzed with MetaboAnalyst 6.0. Statistical methods included partial least squares discriminant analysis (PLS-DA), differential expression, and lipid class enrichment analysis.
Results: The cohort included 102 participants with MASH (29% Zone 1 pattern, 19% Zone 3 pattern, 52% definite MASH) and 58 non-MASH participants. The age range was 7–18 years, 77% male, with a mean BMI z-score of 2.01 ± 0.77, and 58% were Hispanic. Participants with

MASH demonstrated significantly higher BMI z-scores, waist circumference, ALT, AST, insulin, HOMA-IR, triglycerides, total cholesterol, LDL, and lower HDL than non-MASH ($p < 0.05$). Lipidomics analyses revealed distinct metabolic profiles between MASH and non-MASH participants. Key metabolites driving group separation included hexosylceramides Hex2Cer 28:2;2O, HexCer 39:4;3O, and HexCer 29:1;4O, indicating disruptions in ceramide metabolism. Altered lipid species included phospholipids (PC 33:4) and triglycerides (TG 58:8), reflecting changes in lipid homeostasis. Differential expression identified Hex2Cer 28:2;2O and HexCer 39:4;3O as significantly elevated in MASH participants ($p < 0.05$). Lipid class enrichment revealed significant alterations in HexCer and TG classes, driven by these ceramide species.

Conclusion: These findings highlight significant alterations in ceramide and TG pathways, potentially contributing to pediatric MASH through mechanisms involving inflammation and apoptosis. Elevated hexosylceramides may reflect deranged sphingolipid metabolism and serve as potential biomarkers of disease severity. These results align with previous studies suggesting that targeting ceramide metabolism could offer a promising therapeutic strategy. Longitudinal studies are needed to validate these findings and assess their implications for treatment.

TOP-380-YI

Baseline liver elastography and its longitudinal changes predict liver-related outcomes in patients with metabolic dysfunction associated steatotic liver disease (MASLD)

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Background and aims: Liver fibrosis is the primary prognostic factor in MASLD. Liver biopsy is the gold standard for staging fibrosis, although it is invasive and expensive procedure. Currently, non-invasive methods are available to stratify the degree of fibrosis.
The aim of this study is to validate liver stiffness as a prognostic factor both at baseline and in its variation over time during follow-up.

Method: This is a retrospective single-center cohort study including 389 patients who underwent at least two Fibroscan liver stiffness measurements, with a minimum 6-month interval between scans, from January 2011 to December 2023. They were stratified into 3 risk groups according to Baseline liver stiffness measurements (LSM) (<10, 10–20, > 20 kPa). Primary outcome was a composite of Liver Related Events (LRE), death or liver transplantation.
Kaplan-Meier curves were generated for time to primary outcome stratified by Baseline LSM and Δ% Fibroscan categories (worsening: LSM increase > 20%, stable, improved: LSM decrease > 20%). Multivariable Cox regression analysis, adjusted for age, gender, BMI and type 2 diabetes, was used to assess the association of baseline LSM and Δ% fibroscan with primary outcome event. Cumulative incidence curves and incidence rates have been assessed and compared for each risk subgroup.

Results: During a median follow-up of 28 months (IQR 14.4–43.4), 29 (7.5%) patients experienced the composite primary endpoint. These patients were older and had a higher LSM at baseline (median 23.3 vs 6.2 kPa, $p < 0.01$) and higher Δ% fibroscan (16.9% vs −3.5%, $p < 0.01$) than patients who did not experienced a LRE. Baseline LSM show a good predictive performance for the composite endpoint events with an AUC of 0.897 (95% CI 0.845–0.948). Compared to patients with an LSM <10, patients with LSM between 10 and 20 kPa had a 9.7 fold higher risk for the primary outcome (HR 9.7 [2.05–45.79], $p \leq 0.01$) and those with LSM > 20 had a 55.6-fold higher risk (HR 55.63 [12.15–254.74], $p \leq 0.01$).
Multivariate Cox regression analysis also revealed significantly lower risk of developing LRE for high-risk patients (>20 kPa) who showed longitudinal improvements (Δ%LSM ≥20%) on fibroscan results (HR 0.16, 95%CI 0.04–0.68, $p = 0.01$), and a significantly higher risk of developing LRE in intermediate patients (10–20 kPa) who showed worsening longitudinal changes (Δ%LSM > 20%) on fibroscan results (HR 6.66, 95%CI 1.69–26.23, $p < 0.01$). Incidence rate of composite outcome per 1000 person-year was 15.5, 19.7, 81.4 for LSM improved, stable or worsened groups respectively.

Conclusion: Our study strengthens the use of LSM both at baseline and during follow up as reliable prognostic factors in MASLD able to identify the subgroups of patients with MASLD at risk of LREs. In patients with intermediate or high risk of events at baseline, elastography surveillance should be encouraged.

TOP-393-YI

Liver stiffness as a predictor of major adverse cardiac events in metabolic dysfunction-associated steatotic liver disease

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Background and aims: There is a growing burden of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) globally. Given the risk factors MASLD shares with cardiovascular disease, patients with MASLD are prone to major, adverse cardiac events (MACE). Several studies evaluate an individual's risk of MACE, however they seldom assess the impact of liver fibrosis. The aim of this study was to assess whether liver stiffness measurement (LSM), as measured by Vibration controlled Transient Elastography (VCTE), is associated with incident MACE in patients with MASLD.

Method: This was a retrospective study of patients with MASLD and VCTE conducted at four major hospital networks in Victoria, Australia. The primary outcome was the 5-point MACE, a composite of acute myocardial infarction, stroke, cardiovascular death, unstable angina and heart failure. LSM by VCTE was categorized using a rule of five (10, 15, 20 and 25 kPa) for analysis. The risk of incident MACE was assessed using a Cox regression model, with adjustment for age, sex, diabetes, obesity, dyslipidemia, hypertension, chronic kidney disease and smoking status. Discriminatory performance of the model was evaluated using C-index, and compared to a model without LSM using the likelihood ratio test.

Results: Among 6,088 patients with VCTE, 292 experienced MACE (23,408 person-years, median follow-up 3.84 years). Univariable Cox regression demonstrated significant, stepwise increases in the risk of MACE across each LSM category compared to LSM <10 (HRs 1.71, 2.23, 2.77, 5.23, all $p < 0.001$). This trend persisted with multivariable Cox regression, with a significantly higher risk of MACE for the LSM 20–25 (HR 1.64, 95% CI:[1.01, 2.70], $p = 0.048$) and LSM > 25 (HR 2.52, 95% CI: [1,83, 3.46], $p < 0.001$) categories. When LSM was treated as a continuous variable, each 5kPa increase was independently associated with a 10.4% increased risk of MACE (HR 1.104, 95% C:[1.07, 1.139], $p < 0.001$). The model demonstrated good discriminatory performance and outperformed a model without LSM as a predictor (C-index 76.7 vs 75.4%, $p < 0.001$).

Conclusion: Higher LSM, as measured by VCTE, is independently associated with increased risk of MACE in patients with MASLD, and may improve existing risk stratification tools. Further research is required to build on these findings.

TOP-394

Comprehensive analysis of biomarker performance targeting "advanced fibrosis" and "at-risk" metabolic-dysfunction associated steatotic liver disease (MASH) – primary analysis of the LITMUS study cohort

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Background and aims: The advent of regulatory approved pharmacological treatments for metabolic dysfunction associated steatotic liver disease (MASLD) calls for precise, non-invasive biomarkers that facilitate early diagnosis, support patient selection for therapy, and aid clinical trial enrolment. The European multi-center LITMUS Study evaluated >30 non-invasive biomarkers, assessing their performance in identifying patients with at-risk MASH or advanced fibrosis.
Method: In this diagnostic accuracy analysis we used data from adult patients with biopsy-confirmed MASLD prospectively recruited across 13 countries in Europe and the US (2018–2023). The reference standard was centrally scored liver histology conducted by the LITMUS Histopathology Group according to the NASH-CRN system. We focused on detecting at-risk MASH, defined by a MASLD activity score (MAS) ≥4, with at least one point in each component + significant fibrosis (F≥2); and advanced fibrosis (F≥3). We assessed 12 single markers (AST, ALT, CK18-M30, CK18-M65, GDF15, GGT, PROC3, PROC6, PROC4, thrombospondin-2 [TSP2], YKL-40, Fibroscan-VCTE) and 18 multi-marker panels (ABC3D, ADAPT, APRI, Agile 3+, Agile 4, ELF, FAST, FIB-4, FIBC3, FibroMeter-VCTE, FNI, MACK-3, NFS, NIS2+, NIS4, OWLiver [two models], and SomaSignal). Performance was evaluated by area under the receiver operating characteristic curve (AUC), with a target AUC > 0.80 to indicate potential replacement of biopsy for detecting at-risk MASH.

Results: Of the 1,557 participants analysed, single markers exhibited AUCs ranging from 0.52 to 0.76 for at-risk MASH detection and from 0.53 to 0.84 for advanced fibrosis (with the best-performing marker being TSP2 with AUCs of 0.76 and 0.84 for at-risk MASH and advanced fibrosis, respectively). Multi-markers performed better overall, with AUCs ranging from 0.65 to 0.83 for at-risk MASH and 0.58 to 0.92 for advanced fibrosis with SomaSignal outperforming single markers in detecting both target conditions; AUCs of 0.83 and 0.92, respectively. Considering biomarkers adopted in clinical practice guidelines, ELF and Fibroscan-VCTE had AUCs of 0.80 and 0.79 respectively for advanced fibrosis. Two other multi-markers, FibroMeter-VCTE and Agile 3+, however showed acceptable AUC values in detecting advanced fibrosis (0.87 and 0.84, respectively).
Conclusion: The LITMUS Study is the largest and most comprehensive biomarker validation study performed to date in liver disease. Single biomarkers alone are unlikely to replace liver biopsy; however, multi-marker panels have great potential, with panels like SomaSignal showing high diagnostic performance. Although non-invasive detection of steatohepatitis remains challenging, biomarkers for fibrosis are better performant. These results support the development of reliable, non-invasive diagnostic panels to reduce the need for invasive liver biopsies and enhance patient care.

TOP-395

A global analysis of patients with metabolic dysfunction associated steatotic liver disease with liver biopsy, non-invasive tests and mortality

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent worldwide. We evaluated the global performance of non-invasive tests (NITs) and mortality predictors in MASLD.
Method: This GNC collaboration enrolled MASLD patients with liver biopsies and NITs [FIB-4, ELF, liver stiffness measurement (LSM) by transient elastography]. FAST, Agile-3+ and Agile-4 were calculated. NITs' performance to predict ≥F2 (significant fibrosis, SF), ≥F3 (advanced fibrosis, AF) or cirrhosis (F4) was determined by assessing area under the ROC curve (AUC). In those with follow-up, predictors of mortality were assessed.
Results: 17,561 MASLD patients from 41 countries [30% North America (NA), 30% Europe (EU), 24% Southeast Asia (SEA), 7% MENA, 6% South Asia (SA), 3% Latin America (LA)] were included [age 51 ± 13 years, 48% male, BMI 33 ± 8 kg/m^2, 46% type 2 diabetes (T2D), 53% SF, 36% AF, 14% F4]. SF and AF were most prevalent in NA (68% and 49%), lowest in SA (33% and 21%) ($p < 0.001$). The NIT performance showed variability across regions [AUC of FIB-4 for AF: 0.80 (95% CI 0.79–0.81), lowest in LA (0.72 (0.67–0.77)), highest in MENA (0.84 (0.82–0.87)), $p < 0.001$]. AUC of ELF: 0.77 (95% CI 0.76–0.79), lowest in EU (0.72 (0.69–0.75)), highest in NA (0.80 (0.78–0.82)), $p < 0.001$. AUC of LSM: 0.84 (0.83–0.85), similar across regions ($p > 0.05$). AUC of FAST: 0.76 (0.74–0.77), similar (up to 0.79) in all regions except NA (0.70 (0.67–0.73)), $p < 0.01$. AUC of Agile-3+ for AF: 0.87 (0.86–0.88), similar (≥0.85) in all regions ($p > 0.05$). AUC for predicting SF were similar for all NITs: 0.76 (0.76–0.77) for FIB-4, 0.77 (0.75–0.78) for ELF, 0.81 (0.80–0.81) for LSM, 0.75 (0.74–0.76) for FAST, 0.82 (0.81–0.83) for AGILE-3+. AUC of Agile-4 for predicting cirrhosis was 0.90 (0.89–0.91), lowest in NA (0.85 (0.83–0.87)), highest in MENA (0.96 (0.94–0.98)), $p < 0.001$. Presence of T2D and age ≥65 years reduced AUC of FIB-4 and ELF by 0.05–0.08 ($p < 0.01$) but not LSM ($p > 0.05$). N = 7285 subjects had follow-up (mean (SD) 6.6 (7.2) years) with 7% deaths. In adjusted (age, sex, T2D) Cox proportional hazards models, fibrosis severity by histology or NITs (regardless of modality) was associated with higher mortality: adjusted hazard ratio (aHR) (95% CI) for ≥F2 = 1.61 (1.33–1.94), ≥F3: 2.2 (1.8–2.7), F4: 3.1 (2.4–3.9); FIB-4 ≥1.30: 1.5 (1.2–1.8), FIB-4 ≥2.67: 2.0 (1.6–2.5), FIB-4 ≥3.25: 2.1 (1.6–2.8); LSM ≥10 kPa: 2.6 (1.8–3.7), LSM ≥15 kPa: 3.2 (2.2–4.6), LSM ≥20 kPa: 3.7 (2.5–5.4); Agile-3+ ≥0.678: 3.4 (2.1–5.4); Agile-4 ≥0.251: 3.5 (2.4–5.2); Agile-4 ≥0.842: 6.3 (3.6–11.2) (all $p < 0.001$). Other predictors of mortality were older age, male sex, history of hypertension ($p < 0.05$).
Conclusion: NIT diagnostic performance in MASLD varies across the world. The most accurate NITs were Agile-3+ and Agile-4, with minimal variability. Histologic fibrosis stage and NITs were independently associated with mortality in MASLD.

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WED-365

Does measuring the components of the Fibrosis-4 index (FIB-4) separately on different days affect its diagnostic and prognostic performance in patients with metabolic dysfunction-associated steatotic liver disease (MASLD)?

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Background and aims: Current guidelines recommend FIB-4 as an initial assessment of fibrosis in patients with MASLD. However, in routine practice, the components of FIB-4 might be measured on different dates. The same issue might also affect big data research calculating FIB-4 with existing laboratory values. This study aims to determine the impact of the varying time intervals between the component laboratory tests used to calculate FIB-4 on the diagnostic and prognostic performance of FIB-4.
Method: We examined a cross-sectional liver biopsy cohort and a longitudinal territory-wide cohort from Hong Kong. In the cross-sectional liver biopsy cohort, the baseline date was the date of liver biopsy. In the territory-wide Clinical Data Analysis and Reporting System (CDARS) cohort, the baseline date was the date of MASLD diagnosis. Considering that alanine transaminase (ALT) and aspartate transaminase (AST) are commonly measured together in clinical practice, the performance of FIB-4 was examined using two approaches: i) ALT/AST measured at baseline with platelets (PLT) measured 1 or 2 years apart; or ii) PLT measured at baseline with ALT/AST measured 1 or 2 years apart. The area under the receiver operating characteristic curve (AUC) and 95% confidence intervals (95% CI) of FIB-4 to identify F3-4 fibrosis was calculated at the respective time intervals in the biopsy cohort. In the CDARS cohort, the C-index by Fine-Gray subdistribution hazard model was used to assess the discriminatory performance of FIB-4 in predicting liver-related events (LRE).

Results: 573 patients with biopsy-proven MASLD and 4524 patients in the CDARS cohort were included in the final analysis. In the biopsy cohort, the AUC of FIB-4 for F3-4 fibrosis was 0.764 (95% CI: 0.723-0.805) when all laboratory tests were taken at the time of liver biopsy, 0.760 (95% CI: 0.713–0.807) and 0.754 (95% CI: 0.703–0.804) when PLT was taken 1 and 2 years earlier, and 0.786 (95% CI: 0.689–0.883) and 0.796 (95% CI: 0.691–0.902) when ALT/AST were taken 1 and 2 years earlier, respectively. The sensitivity and specificity of FIB-4 were 56.5% and 97.3%, respectively and were similar regardless of the relative timing of PLT and ALT/AST tests. In the CDARS cohort, the reference C-index of FIB-4 in predicting LRE were 0.737 (95% CI: 0.692–0.783) when all tests were collected at baseline. The C-indices of FIB-4 were 0.763 (95% CI: 0.720–0.806) and 0.732 (95% CI: 0.689–0.783) when PLT was measured 1 or 2 years earlier, respectively. When ALT/AST were measured 1 or 2 years earlier, the C-indices of FIB-4 were 0.757 (95% CI: 0.711–0.804) and 0.725 (95% CI: 0.671–0.778), respectively.
Conclusion: The diagnostic and prognostic performance of FIB-4 remains stable when its components are measured at different time intervals. This suggests that FIB-4 can be used broadly in clinical practice, even when not all components are available simultaneously.

WED-366
Enhancing the non-invasive diagnosis of fibrosis in metabolic dysfunction-associated steatotic liver disease: the role of transient elastography and a two-stage machine learning diagnostic model

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising chronic liver disease linked to lifestyle changes and obesity. Its progression leads to liver inflammation and fibrosis, increasing the risk of severe conditions like cirrhosis and hepatocellular carcinoma. Currently, early diagnosis of liver fibrosis relies on invasive liver biopsy. This study aims to develop a two-step diagnostic model that integrates demographic data, laboratory data, and transient elastography to improve liver fibrosis assessment in MASLD patients.
Method: We selected 361 patients with pathologically confirmed MASLD admitted to our hospital from July 2018 to July 2024. Collected data included gender, age, BMI, ALT, AST, GGT, albumin, platelet count, Chitinase 3-like 1 (CHI3L1), hypertension, diabetes and hyperlipidemia. Patients were categorized based on liver fibrosis degree (F≥2 and F<2). Various machine learning algorithms (decision trees, random forests, lasso, XGBoost, SVM, single hidden layer neural networks (SHLNNs), LightGBM) were employed to create a first-stage diagnostic model. Transient elastography was incorporated into the establishment of the second-stage model. The first-stage model with high sensitivity and the second-stage model with high specificity are regarded as the recommended diagnostic strategy. Diagnostic performance was evaluated using ROC, calibration, and decision curves, comparing results with established formulas like APRI, NFS, FIB-4, Agile3+, and Agile4.
Results: A total of 278 patients with complete data were included in the analysis, with 106 having liver fibrosis (F≥2) and 172 without (F<2). Among first-stage training set models, random forests (AUC 0.945; sens 0.934; spec 0.802), LightGBM (AUC 0.837; sens 0.651; spec 0.849), XGBoost (AUC 0.775; sens 0.774; spec 0.640), SVM (AUC 0.767; sens 0.830; spec 0.599), and Lasso (AUC 0.759; sens 0.868; spec 0.558) showed AUCs exceeding 0.75. In the second-stage training set model, random forests (AUC 0.957; sens 0.915; spec 0.855), LightGBM (AUC 0.963; sens 0.925; spec 0.963), XGBoost (AUC 0.874; sens 0.717; spec 0.878), SVM (AUC 0.781; sens 0.802; spec 0.645), Lasso (AUC 0.776; sens 0.811; spec 0.599), and SHLNNs (AUC 0.764; sens 0.640; spec 0.764) also exceeded 0.75. Established formulas had AUCs below 0.75. In the two-stage modeling, CHI3L1 and elastography each ranked high in importance.
Conclusion: The machine learning models outperformed existing diagnostic formulas for liver fibrosis in MASLD. The first-stage model highlighted the significance of CHI3L1. While transient elastography enhances the overall diagnostic efficacy of the machine learning models, it may compromise sensitivity in favor of improved specificity, making it unsuitable for large-scale liver screening in the initial stage. The optimal two-step diagnostic strategy identified in this study involves using the random forest model followed by the transient elastography enhanced LightGBM model.

WED-367-YI
Frequency and risk factors of fibrosis staging discrepancies between transient elastography and liver biopsy in patients with metabolic-associated steatotic liver disease: role of obesity and type 2 diabetes

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Background and aims: Discordance between transient elastography (TE) and liver biopsy (LB) in fibrosis staging among patients with metabolic-associated steatotic liver disease (MASLD) has been linked to metabolic factors, remarkably obesity and type 2 diabetes mellitus (T2D), but their independent roles remain unclear. This study evaluates the frequency and risk factors of discordance in fibrosis staging in a large cohort of patients with biopsy-confirmed MASLD.
Method: This cross-sectional observational study included patients with MASLD who underwent TE and a subsequent LB within 6 months, between 2013 and 2024. Concordance was defined as an identical fibrosis stage reported by both methods, with discordance assessed using Cohen's kappa. The primary outcome was the rate of discordance between TE and LB in determining fibrosis stage. Factors associated with discordance were analysed using univariate methods and multivariate logistic regression. Subgroup analyses were conducted for patients with ≥grade II obesity (BMI, body mass index, ≥35 kg/m²) and those with T2D.
Results: Among 415 patients, concordance between TE and LB was low (kappa = 0.220, p < 0.001), with an overall discordance rate of 58.1%. Reliable TE results were similar in concordant (74.5%) and discordant (75.9%) groups (p = 0.776). Higher rates were observed in the misclassification of advanced fibrosis (F3-F4 52.3% vs. 49.8% F0-F2). Univariate analysis identified age, obesity, liver stiffness, and platelet count as variables significantly associated with overall discordance. No association was found between discordance and transient elastography's technical validity. In multivariate analysis, liver stiffness (OR 0.93; 95%CI 0.91–0.97; p < 0.001), platelet count (OR 1.003; 95%CI 1.000–1.007; p = 0.049) and obesity (OR, 1.81; 95%CI 1.12–2.92; p = 0.015) were independently associated with discordance, while T2D was not (OR 0.94; 95%CI 0.59–1.51; p = 0.811). Discordance was subclassified into overestimation (38.6%) and underestimation (19.5%). Only BMI (OR 1.12; 95%CI1.07–1.16; p < 0.001) and bilirubin (OR 0.33; 95%CI 0.14–0.82; p = 0.016) remained significantly associated with overestimation. In the subgroup analysis, the discordance rate was higher among obese patients (63.1%) compared to diabetic patients (56.4%). BMI was linked to overestimation in both diabetic (OR 1.08; 95%CI 1.02–1.14; p = 0.011) and non-diabetic patients (OR 1.14; 95%CI 1.07–1.22; p < 0.001). Interestingly, higher HbA1c levels were inversely associated with overestimation in diabetic (OR 0.59; 95%CI 0.42–0.82; p = 0.002) and obese patients (OR 0.50; 95%CI 0.30–0.86; p = 0.011), but not in non-obese patients.
Conclusion: BMI ≥35 kg/m² was independently associated with higher discordance, driven by an increased rate of overestimation

regardless of T2D status. HbA1c levels were inversely associated with overestimation in both obese and diabetic patients.

WED-368

Three proteins in advanced liver fibrosis: a minimalistic shallow-deep neural network approach on metabolic dysfunction–associated steatotic liver disease patients using open data

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Background and aims: Steatotic liver disease affects 20–30% of the global population, representing a growing epidemic among metabolic dysfunction–associated steatotic liver disease (MASLD) patients. Non-invasive diagnosis of advanced liver fibrosis (ALF) (F3, F4) remains challenging due to the limitations of liver biopsy. This study aims to explore the feasibility of achieving robust diagnostic performance with a small dataset and a minimalistic biomarker set, leveraging shallow-deep neural networks (sDNN), inductive learning (IL), and explainable artificial intelligence (XAI).
Method: We used open data from 191 biopsy-validated MASLD patients, processed via SomaScan v.4.0 proteomics, which measured 4,730 proteins. Employing a non-linear feature selection (FS) methodology, integrating IL and feature engineering (FE), we identified three critical proteins. A 3-layres sDNN architecture (23, 23, 7) was trained using 10-fold cross-validation (10CV) for robustness and validated on a test set (train/test~90%/10%). Performance metrics included specificity (Spec), sensitivity (Sens), ROC-AUC, and F1-score.
Results: Three proteins—ADAMTSL2, MFAP4, and GDF2—emerged as the most informative biomarkers for ALF. ADAMTSL2 interacts with ECM proteins; MFAP4 is implicated in fibrogenesis; GDF2 regulates hepatic lipid homeostasis and angiogenesis. Using these proteins, the sDNN achieved exceptional performance: 10CV (Spec: 0.76 ± 0.21, Sens: 0.88 ± 0.14, ROC-AUC: 0.82 ± 0.13, F1: 0.79 ± 0.13) and Test (Spec: 0.91, Sens: 0.75, ROC-AUC: 0.83, F1: 0.80).
Conclusion: This study demonstrates that a minimalist approach using only three proteins and an optimized sDNN architecture can achieve remarkable diagnostic accuracy for ALF in MASLD patients, even with a limited dataset. These findings highlight the transformative potential of data science, XAI and sDNNs in biomedical research and warrant validation on larger cohorts.

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A shallow-deep neural network approach combining non-invasive tests to enhance advanced fibrosis detection in metabolic dysfunction–associated steatotic liver disease patients

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Background and aims: Advanced fibrosis detection in MASLD patients often relies on non-invasive tests (NITs), such as FIB-4, NFS, APRI, and AST/ALT. Despite their clinical utility, the sensitivity and specificity of individual NITs remain limited. We developed and validated a machine learning-enhanced NIT (MLE-NIT) framework using a deep neural network (DNN) to combine these scores and their underlying features. This study evaluates the performance of MLE-NIT on advanced fibrosis detection compared to standalone NITs in both internal validation and external cohorts.
Method: The training dataset consisted of 540 MASLD patients from a Chinese cohort, and the external validation set comprised 147 patients from a Malaysian cohort. Individual NIT cutoffs were determined for advanced fibrosis: FIB-4 (1.3), NFS (−1.455), APRI (0.64), and AST/ALT (0.87). A three-layer DNN architecture (5, 19, 17 nodes) was trained with a learning rate of 0.01 and 10 iterations. Performance metrics, including specificity, sensitivity, ROC-AUC, and F1-score, were calculated using 10-fold cross-validation (10CV) on the training set and on the external test set.
Results: The MLE-NIT approach significantly outperformed standalone NITs. For 10CV, MLE-NITs achieved an average ROC-AUC of 0.75, specificity of 0.76, and sensitivity of 0.74, compared to 0.70 (FIB-4), 0.70 (NFS), 0.64 (APRI), and 0.54 (AST/ALT) on ROC-AUC. On the external test set, MLE-NIT demonstrated superior generalization, achieving a ROC-AUC of 0.79, specificity of 0.84, and sensitivity of 0.74, whereas standalone NITs exhibited suboptimal results: (FIB-4, NFS, APRI, AST/ALT) = (0.75, 0.77, 0.71, 0.57) on ROC-AUC. These findings highlight the robustness and clinical utility of the MLE-NIT framework across diverse cohorts.
Conclusion: Our MLE-NIT framework provides a scientifically superior approach to advanced fibrosis detection in MASLD patients, leveraging the synergy of multiple NITs and their features. It demonstrates marked improvements in performance metrics over standalone tests in both internal and external validations. This approach underscores the potential of machine learning, and in particular DNNs, to transform fibrosis diagnostics, paving the way for broader implementation in clinical practice.

WED-370-YI

Comparative performance of controlled attenuation parameter and ultrasound-derived fat fraction in detecting hepatic steatosis in MASLD patients

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Background and aims: The amount of hepatic fat is the main determinant of Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) progression to cirrhosis and hepatocellular carcinoma. For this reason, non-invasive tools capable of accurately determining hepatic fat content are essential. While Controlled

Attenuation Parameter (CAP) obtained using FibroScan® is widely used, Ultrasound-Derived Fat Fraction (UDFF) is emerging as a promising alternative. Here we aimed to evaluate correlation and degree of agreement in the diagnosis of steatosis at least 5% between CAP and UDFF in a large cohort of dysmetabolic subjects. We also assessed their performance against histological findings in a smaller subgroup undergoing liver biopsy.

Method: The All-Liver Interventional Global Network (ALIGN) screening study enrolled at the Fondazione Policlinico Universitario Campus Bio-Medico of Rome (ALIGN-CBM) 837 participants with a history of MASLD and/or diabetes and/or obesity. MASLD was diagnosed by CAP when >248 dB/m, and by UDFF when >5%. Correlation, and agreement between CAP and UDFF for the diagnosis of MASLD were evaluated, along with factors linked to discordance. In a subgroup undergoing liver biopsy (46 patients), CAP and UDFF accuracies for diagnosing MASLD and significant steatosis were compared to the histological gold standard (steatosis of at least 5% and 33%, respectively).

Results: After excluding individuals with other causes of chronic liver disease, missing CAP and UDFF data, or unreliable measurements, 707 cases were analyzed. There was a strong correlation between CAP and UDFF ($r = 0.71$, $p < 0.0001$). For the diagnosis of MASLD, CAP and UDFF were concordant in 583 cases (82%), and discordant in 124 cases (18%). Indeed, MASLD was diagnosed only by UDFF in 73 cases (11%), and only by CAP in 51 cases (7%). HOMA index, glycated hemoglobin, hypertension, ultrasound-measured visceral adipose tissue, and waist circumference were negatively associated with discordance in each of the 2 direction (all $p < 0.05$). In the biopsy subgroup, all cases displayed at least 5% steatosis. At the prespecified cut-offs, UDFF showed 100% sensitivity vs. 93.5% for CAP ($p = 0.3$). The AUC for significant steatosis were 0.815 for CAP and 0.825 for UDFF (Z score = −0.11, $p = 0.91$).

Conclusion: UDFF and CAP are effective non-invasive tools for detecting hepatic steatosis, with comparable diagnostic performance. Metabolic factors are negatively associated with discordance between the two methods, suggesting that, when one of the two tests is negative, the boundary between false positives and false negatives is more borderline. In this context, at the proposed cut-offs, UDFF appears slightly but non-significantly more sensitive, while extending the series with negative cases will allow comparison in terms of specificity. The performance of the two tools for detecting significant steatosis is comparable.

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ALT is an effective screening tool for advanced MASLD in children with obesity and overweight

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has a high prevalence among children with obesity. However, screening remains controversial as neither the optimal method nor risks and benefits of screening have not been established. This study aims to evaluate the effectiveness of an Alanine Aminotransferase (ALT)-based screening algorithm for advanced MASLD in children with obesity or overweight.

Method: Children aged 8–18 years with (i) obesity or (ii) overweight and ≥1 additional risk factor seen at obesity outpatient clinics for co-morbidity screening were included. Participants were screened for MASLD using ALT and analysed in four groups based on ALT levels. Vibration-controlled transient elastography (VCTE) was performed to determine probable significant fibrosis (VCTE ≥7.4 kPa). Patients features associated with VCTE ≥7.4 kPa were assessed using logistic regression analysis. The diagnostic accuracy of ALT was compared to other non-invasive tests.

Results: Among 322 children (64% male, median age 13 years, mean BMI z-score 3.5), the prevalence of VCTE ≥7.4 kPa increased significantly with ALT elevation: 1.9% for normal ALT, 16.4% for mild ALT elevation (≥ULN: ♀ 22 IU/L, ♂ 26 IU/L), 21.3% for moderate ALT elevation (≥2 ULN: ♀ 44 IU/L, ♂ 52 IU/L), and 38.9% for strong ALT elevation (≥80 IU/L) ($p < 0.001$). Other non-invasive tests did not perform superiorly in this cohort. VCTE ≥7.4 kPa was positively associated with ALT ≥80 IU/L (OR 2.91, 95%CI: 1.25–6.74), age (OR 1.50, 95%CI 1.27–1.76), male gender (OR 2.37, 95%CI 1.04–5.40), BMI z-score (OR 3.01, 95%CI 1.62–5.61), and HOMA (OR 1.10, 95%CI 1.00–1.13).

Conclusion: This study shows that ALT is an effective primary screening tool for advanced MASLD in children with (i) obesity or (ii) overweight and additional risk factors.

WED-372

Epigenetic biomarkers and methylome-wide association study (MWAS) for non-invasive diagnosis of at-risk MASH from plasma cell-free DNA

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Background and aims: The emergence of the first treatment for MASH underscores the pressing need for a single, non-invasive rule-in blood test (NIT) capable of identifying treatment candidates at scale. This study aims to assess the diagnostic accuracy of a proprietary AI algorithm applied to whole-methylome sequencing of cell-free DNA (cfDNA) in identifying at-risk MASH among patients with biopsy-proven MASLD.

Method: Cell-free DNA extraction was methylation library preparation was performed on plasma samples obtained from the Duke University Biobank. Deep methylome sequencing was performed using Illumina instruments. This approach allows for interrogation of methylation patterns across hundreds of millions of cfDNA molecules per sample. The dataset was randomly split into training and validation sets with a 2-to-1 ratio. A novel transformer-based neural network, designed to understand the contextual and interactive relationships between cfDNA fragments, was trained to detect at-risk MASH (NAS ≥4 and F2+). Diagnostic performance was calculated and compared to FIB4 and other NITs in literature. Additionally, a methylome-wide association study (MWAS) was conducted to identify relevant genes and pathways.

Results: The study cohort consisted of 217 patients with biopsy-confirmed MASLD and 59 control subjects without histologic MASLD. Among the MASLD participants, fibrosis staging was as follows: F0: 59, F1: 53, F2: 31, F3: 47, F4: 27, with 123 having NAS ≥4. In the validation set, the whole-genome methylation signature panel achieved an AUC of 0.86 [0.77–0.94] and a positive likelihood ratio (PLR) of 10.09 [8.74–13.4], both clinically and statistically significant. This performance significantly exceeded that of FIB4, which demonstrated an AUC of 0.69 [0.58–0.79] and a PLR of 3.25 [2.71–4.06]. Compared to state-of-the-art NITs reported in the literature, the methylation panel demonstrated superior diagnostic performance. Further analysis revealed methylome-wide differences in genes regulating pathways known to drive MASH progression. These findings not only bolster the biological plausibility of the model but

could also offer insights into the underlying mechanisms of the disease.
Conclusion: Whole methylome sequencing coupled with state-of-the-art AI represents a highly accurate and biologically grounded method for the non-invasive diagnosis of at-risk MASH. By delivering a superior PLR, this approach holds significant promise as a reliable single-test solution for identifying individuals with at-risk MASH and guiding treatment decisions.

WED-373
Agreement between hepatic histology and non-invasive methods and their ability to detect MASLD/MASH among morbidly obese patients undergoing bariatric surgery: an egyptian cross-sectional study
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Background and aims: Obesity is a major risk factor for metabolic-associated steatotic liver disease (MASLD) and steatohepatitis (MASH), influencing their progression. This study evaluates the prevalence of MASLD/MASH in morbidly obese patients undergoing bariatric surgery and assesses the predictive accuracy of non-invasive diagnostic methods compared to liver biopsy.
Method: This cross-sectional study was conducted at Cairo University Hospital, Egypt, from March 2023 to September 2024. Morbidly obese patients (BMI ≥40) attending the bariatric clinic were recruited consecutively. Preoperative assessments included clinical and laboratory investigations, as well as non-invasive methods: Controlled Attenuation Parameter (CAP) and transient elastography (TE), alongside fibrosis scores (AST to Platelet Ratio Index [APRI], Fibrosis-4 [FIB-4], NAFLD Fibrosis Score [NFS], and FibroScan-AST [FAST]). Intraoperative liver biopsies were assessed using the NAFLD Activity Score (NAS), with cut-off values of ≥5 and ≤3 to rule in and rule out the diagnosis of MASH, respectively. The degree of macrovascular hepatic steatosis (HS) and hepatic fibrosis by Metavir score were also reported. Statistical analyses included the kappa statistic for agreement, area under the receiver operating curve (AUROC) for diagnostic accuracy, and sensitivity and specificity calculations for proposed cut-off points.
Results: Among 58 patients (89.6% females; mean age 37.98 ± 7.80 years; mean BMI 44.77 ± 4.14 kg/m²), diabetes mellitus and hypertension were reported in 13.79% and 22.41%, respectively. Definite MASH was diagnosed in 34.48%, and HS >33% was observed in 37.9%. Significant fibrosis (SF) ≥F2 was present in 27.59%. CAP demonstrated modest agreement with biopsy for HS ($\kappa = 0.262$, $p < 0.001$), with high concordance for S3 (88.9%) but more overlap for S1 and S2. CAP ≥285 provided better performance in detecting HS > S2 steatosis (AUROC = 0.92; sensitivity 86%; specificity 84%). TE, FIB-4, NFS, and APRI showed poor discrimination for SF ≥F2 (AUROC = 0.52 to 0.58). Fib-4, TE, and APRI exhibit high specificity (95.2–97.6%) but very low sensitivity (0–12.5%). NFS shows better sensitivity (71.4%) but lower specificity (40.5%). The agreement between non-invasive markers and biopsy classifications, measured by Kappa, was minimal (0–0.1). FAST score showed moderate rule-out ability for MASH with SF (AUROC = 0.60, sensitivity 31%, specificity 89%).
Conclusion: Although CAP measurements showed modest agreement with liver biopsy for diagnosing HS in a cohort of morbidly obese Egyptian patients, higher CAP cutoffs are suggested to improve its diagnostic accuracy. TE, FIB-4, NFS, APRI, and FAST scores had limited diagnostic accuracy for differentiating fibrosis stages, indicating further validation and the potential need for integrating hepatic histology assessment in bariatric surgery.

WED-374
Utilizing AI digital pathology for quantitative measurement, grading and differentiation of lobular and portal inflammation in MASH: preliminary analysis in liver histology
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Background and aims: Accurate histopathological assessment is pivotal for measuring treatment response in metabolic dysfunction-associated steatohepatitis (MASH). Accurately quantifying lobular and portal inflammation, important in disease progression, is challenging using light microscopy. AI-digital pathology automates and quantifies histological features, enabling standardized, reproducible evaluations. While qFibrosis, qSteatosis, and qBallooning algorithms are validated, qInflammation algorithm (qI) was developed last due to its greater complexity in development and validation.
Method: 269 MASH liver biopsy samples (from Peking University People's Hospital) were scanned by Leica Aperio system and randomly divided into training (n = 180) and validation (n = 89) cohorts. Inflammatory foci (as defined in Brunt et al. Am J Gastroenterol. 1999;94(9):2467–74) were identified by H&E-stained image analysis by qI. Images acquired by separate Hematoxylin & eosin imaging channels were processed to segment nuclei, detect inflammatory cells, and identify foci. Portal tracts were localized by convolutional neural networks, distinguishing portal from lobular inflammation by overlaying inflammation foci. Morphometric features like density, perimeter, and eccentricity informed qI-lobular and qI-portal indices, were built via multiple linear regressions on training cohort and validated on validation cohort. Statistical analysis by Spearman correlation (r-value), inter-rater concordance (weighted Kappa values). Concordance between pathologist and qI was by sensitivity (percentage of pathologist-identified inflammation also identified by qI), Positive predictive value (PPV; percentage of qI-identified inflammation also identified by pathologist).
Results: Histological portal inflammation grades were I0 (14%), I1 (48%), I2 (36%), I3 (2%), while lobular inflammation grades were I0 (2%), I1 (44%), I2 (47%), I3 (7%). qI-based identification had 58% PPV, 83% sensitivity for lobular foci, and 72% PPV, 89% sensitivity for portal inflammation detection. qI-lobular index had $r = 0.556$ ($p < 0.001$), whereas qI-portal index had $r = 0.606$ ($p < 0.001$). Inter-rater Kappa values of qI algorithm with pathologist grading for lobular and portal inflammation were 0.32 and 0.38 respectively, comparable to pathologist based inter-rater Kappa values in literature of 0.33–0.6 for lobular and 0.45 for portal inflammation respectively.
Conclusion: qI provides a promising tool for identifying and quantifying inflammation types in MASH, though further validation is needed on additional cohorts. Improved evaluation of portal and lobular inflammation can enhance screening and stratification in MASH trials and for optimized therapeutic strategies. The development of qI algorithm completes development of the panel of qFIBS algorithm to comprehensively assess and quantify MASH histology.

WED-375

Relevant incidental histologic diagnoses in MASLD patients enrolled in the NASH CRN

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Background and aims: Selection of patients with metabolic dysfunction associated steatotic liver disease (MASLD) for clinical trials and for FDA approved therapies requires strict inclusion criteria. The impact of coexistent chronic liver diseases is underrecognized. The aim of the study is to describe incidental histologic diagnoses observed in the NASH CRN cohort and their clinical correlations.
Methods: A total of 3,149 adult biopsies collected from 1988 to 2024 and reviewed in a consensus fashion by expert liver pathologists from the NASH CRN were included. Inclusion criteria for all studies required clinically suspected MASLD and exclusion of other liver diseases. Incidentally found histologic patterns of injury were assessed if present and classified into 5 patterns: cholestatic (bile duct proliferation/injury, cholestasis), hepatitic (chronic and/or acute), vascular, granulomatous and miscellaneous (cytoplasmic changes, inclusions, iron, suspicion of alcohol related injury, hepatocellular necrosis, hepatocellular atypia). A control population of patients with MASLD and no incidental histologic diagnosis was included for comparison (n = 2,727).
Results: There were 422 biopsies with incidental histologic findings: 124 cholestatic, 23 hepatitic, 25 vascular, 55 granulomatous, and 195 miscellaneous. There were no clinically meaningful differences in age, gender, race, BMI, or autoantibody detection (ANA, ASMA, AMA) when comparing study groups to controls. AST was higher in the hepatitic group than controls (67 U/L vs 50 U/L, $p = 0.02$). Alkaline phosphatase (ALK) and bilirubin (BIL) were higher in the cholestatic and vascular groups compared to controls (ALK 103 U/L and 113 U/L, respectively, versus 85 U/L in controls, $p < 0.001$; BIL 0.81 U/L and 0.87 U/L respectively versus 0.68 U/L in controls, $p \leq 0.02$). Most study groups, except granulomatous pattern, had lower NAS associated with lesser degree of steatosis in comparison to controls ($p < 0.001$). All study groups, except vascular injury, demonstrated higher percentages of cases with stage 3 and 4 fibrosis in comparison to controls ($p < 0.001$).
Conclusion: Incidentally found histologic diagnoses in patients with MASLD enrolled in our study was not uncommon despite strict inclusion criteria, representing 13% of cases. The most common patterns of injury are cholestatic and granulomatous injury; hepatitic and vascular injury are less frequent. Importantly, more advanced fibrosis (stage 3–4) was associated with the identification of these patterns in comparison to our control MASLD cases. The study highlights the importance of biopsy assessment in identifying other causes of liver disease, unsuspected by clinical screening, in a population at risk for MASLD.

WED-376

Fibroblast activity assessed by PRO-C3 is prognostic for fibrosis progression in MASH patients treated with insulin sensitizer MSDC-0602 K during a phase IIb clinical trial

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Background and aims: Liver fibrosis is a dynamic process driven by hepatic stellate and other mesenchymal cells forming ECM and disrupting normal organ architecture, while releasing ECM fragments into the bloodstream. These fragments are surrogates of ECM formation that can be leveraged as fibrosis biomarkers. Here, we measured the N-terminal of procollagen type 3 (PRO-C3) during EMMINENCE (ClinicalTrials.gov NCT02784444), a phase IIb clinical trial testing MSDC-0602 K, an insulin sensitizer, in MASH patients. While liver biopsies reveal the cumulative result of fibrosis, ECM biomarkers evaluate disease activity and can be used to prognosticate and monitor drug effectiveness. Here, we show that PRO-C3 discriminated between patients with regressing or progressing fibrosis and detected patients who would respond to treatment. MSDC-0602 K decreased collagen type III synthesis significantly.
Method: 392 MASH patients were randomized to placebo (PL), 62.5 mg, 125 mg or a 250 mg daily dose of MSDC-0602 K for 12 months. 334 completed the study. The primary efficacy endpoint was defined as an improvement of ≥2 points in NAS score, with ≥1 decrease in either ballooning or inflammation and no increase in fibrosis stage. Blood samples were collected at baseline, 6 months, and 12 months to assess PRO-C3.
Results: Treated patients who reached primary endpoint had lower baseline PRO-C3 ($p = 0.026$). PRO-C3 levels discriminated between patients showing regressing, stable or progressing fibrosis according to biopsy scoring ($p = 0.0076$). Patients with baseline F0/F1 fibrosis scores, but high PRO-C3, were likely to progress ($p = <0.0001$), while patients with F3/F4 and low PRO-C3 likely regressed ($p = <0.001$). The 125 mg and 250 mg doses of MSDC-0602 K reduced PRO-C3 at 6 months ($p = 0.0103$ and $p = 0.026$ respectively) and 12 months ($p = 0.0274$ and $p = 0.0311$) compared to placebo.
Conclusion: Lower fibroblast activity (PRO-C3) at baseline was associated with achieving primary endpoint as well as fibrosis regression, while higher baseline PRO-C3 was associated with fibrosis progression. MSDC-0602 K significantly reduced PRO-C3, suggesting an anti-fibrotic effect. PRO-C3 can identify MASH patients who are likely to respond to treatment and prognosticate their evolution.

WED-381

Identifying risk factors for "major liver-related outcomes" in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic Dysfunction-Associated Liver Disease (MASLD) affects approximately 30% of the general population. It is characterized by fat accumulation in the liver and cardiometabolic risk factors. Understanding which subgroups of MASLD patients are at risk of major adverse liver outcomes (MALO) is crucial for developing personalized preventive strategies and treatments.
Method: 9,692 participants of the UK biobank cohort with available abdominal MRI and a proton density fat fraction (PDFF) of at least 5% were analyzed regarding their biochemical, genetic and lifestyle risk factors for MALO (n = 26). Proteomics analyses were available for 1237 participants in the cohort. To reduce the imbalance, propensity score matching was implemented in a 1:10 ratio, corrected for sex, age and BMI.

Results: The strongest predictors for MALO were elevated alkaline phosphatase (OR = 5.54 [2.35, 12.2]), elevated aspartate aminotransferase (OR = 2.05 [0.87, 4.49]) and gamma-glutamyl transferase (OR = 4.11 [1.89, 9.39], all p < 0.05). Insulin-like growth factor 1 was significantly lower in the participants with MALO (15.7 nmol/L [12.0, 20.7] vs. 20.6 nmol/L [16.3, 23.9], p = 0.008,). Arterial hypertension and type 2 diabetes were more common in the MALO group (OR = 4.88 [2.19, 11.9], p = 0.003, OR = 4.29 [1.81, 9.55], p = 0.047). History of risky alcohol consumption increased chances of MALO (OR = 13.1 [3.8, 34.9], p < 0.001). Transmembrane 6 superfamily member 2 (TM6SF2) polymorphism rs58542926 was associated with MALO (OR = 6.9 [1.07, 44.38], p = 0.042), while patatin-like phospholipase domain containing 3 (PNPLA3) I148M was not. Our proteomics analysis demonstrates a link between inflammation and cardiovascular disease and MALO risk.
Conclusion: We show that biomarkers might be a valuable contribution to the clinically challenging process of identifying patients at risk of MALO. Furthermore, lifestyle interventions are likely useful even in late disease stages, as common metabolic comorbidities heavily impact the disease course. Previous alcohol consumption affects MALO occurrence, even after years of abstinence. Genetic testing for common polymorphisms connected to liver disease could be evaluated in MASLD patients. These risk factors might identify a group of MASLD patients that could benefit from more detailed and frequent surveillance

WED-382-YI
Thrombospondin-2, a direct serum marker of fibrogenesis, to assess treatment response in MASLD in a 6-month lifestyle intervention program

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Background and aims: Lifestyle intervention aiming at weight loss (WL) is the cornerstone of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) management. However, the non-invasive assessment of treatment response is not yet established. A novel fibrogenesis marker Thrombospondin-2 (TSP2) showed high accuracy to detect advanced fibrosis in cross-sectional multicentric cohorts of biopsied MASLD. Here, TSP2 was tested to assess antifibrotic treatment response in an intensive lifestyle intervention program.
Method: A 6-month lifestyle intervention program in 94 patients including guideline-based recommendations for a healthy diet and physical activity aiming at WL. Inclusion criteria: MASLD according to guidelines, Body Mass Index (BMI) between 25 and 35 kg/m^2, age<65 years. Exclusion criteria: HbA1c > 9.5%, insulin-dependent type 2 diabetes (T2D) or use of glucagon-like peptide 1 receptor agonists. Endpoints were 7% WL and improvement in HOMA index. Clinical and biochemical parameters were assessed at baseline and end of treatment. Serum T2 was measured through in-house optimized and standardized ELISA assay (Mainz), and compared to FIB-4 and liver stiffness measurement by vibration-controlled transient elastography (VCTE).
Results: Median age was 50.5 [IQR 43.0–61.0] years (71.3% male). Median BMI was 30.8 [28.8–34.2] kg/m^2 (17% with T2D). Overall, 17.0% of patients achieved 7–10% WL, and 11.7% achieved >10% WL. Median baseline TSP2 values were 58.3 [IQR 44.2–73.9] ng/ml and were similarly distributed between those who achieved <7% WL, 7–10% WL and >10% WL (p = 0.177). Median FIB-4 and VCTE values were 0.91 [0.71–1.29] and 5.2 [4.5–6.1] kPa, similarly distributed in the 3 groups. TSP2 levels significantly decreased after 6 months in patients achieving >10% WL: from median 53.8 ng/ml to 44.6 ng/ml (p = 0.009), which was higher than changes observed in <7% WL and 7–10% WL (inter-arm p = 0.034). Delta TSP2 values showed a stepwise increase across the 3 groups: from median 0.0 [−10.3 to 7.5] ng/ml in <7% WL to median −5.2 [−13.1–0.74]ng/ml in 7–10% WL to median −9.7 [−24.0 to −3.3] ng/ml in >10% WL (p = 0.029). In patients with baseline HOMA>2.7 (n = 29), delta TSP2 values were higher in those achieving HOMA normalization (−10.3 ng/ml, p = 0.023). FIB-4 and VCTE did not show clinically significant trends with regard to both endpoints. Delta TSP2 values were independently associated with at least 7% WL (aOR 0.96 [95%CI 0.92–0.99], p = 0.02) adjusted by age, sex, T2D and BMI. In patients achieving at least 7% WL, delta TSP2 were similarly distributed across ages (< or ≥50 years) (p = 0.757), sex (p = 0.683), BMI (< or ≥30 kg/m^2) (0.558) and across PNPLA3 genotypes (CC, CG, GG) (p = 0.973 l).
Conclusion: TSP2 levels fell significantly in MASLD patients in correlation to WL achieved through lifestyle intervention, and may be a useful tool to assess attenuation of hepatic fibrogenesis.

WED-383
Change in cT1 following interventions in metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis

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Background and aims: Liver corrected T1 (cT1), measured with multiparametric magnetic resonance imaging (MRI), offers an alternative to liver biopsy to monitor treatment response and liver disease activity. However, a systematic evaluation of change in cT1 following a treatment intervention in adults with metabolic dysfunction-associated steatotic liver disease (MASLD) has not yet been performed.
Method: We searched the Cochrane Library, PubMed Central, and MEDLINE from 2014 to September 2024 for studies that examined cT1 responses following intervention in adults with MASLD. Two authors independently screened records, assessed risk of bias and extracted data. Meta-analyses were performed to explore the mean change in cT1 between baseline and end of study and the cT1 response rate (≥80 ms reduction).
Results: A total of 16 studies comprising 1134 individuals with MASLD were analysed (13 randomized controlled trials (n = 1077 individuals) and three prospective diet, lifestyle and bariatric surgery studies (n = 57)). Across all interventions, mean change in cT1 was −57 ms [95% CI: −62, −52] over a median 17 weeks (IQR: 12–24) treatment course. By treatment type, fibroblast growth factor (FGF) analogues (aldafermin; pegozafermin), glucagon-like peptide (GLP)-

1 receptor agonists (pemvidutide; tirzepatide) and farnesoid X receptor (FXR) agonists (vonafexor; ocaliva; TERN-101), cT1 had a mean change of −79 ms [95% CI: −90, −68], −8 ms [95% CI: −77, −58] and −62 ms [95% CI: −74, −49], respectively. In contrast, the placebo arms showed a mean change in cT1 of 0 ms [95% CI: −8, 8]. The proportion of responders on cT1 was 29% (95% CI: 25, 34) and 8% (95% CI: 3, 14) in the treatment and placebo group, respectively.
Conclusion: Evidence to-date supports a significant treatment-induced reduction in cT1 as compared to minimal changes in the placebo group. Our findings could inform current and future study designs for investigational therapies for liver disease and support monitoring of treatment response in individuals with MASLD in clinical trials and clinical practice.

WED-384
Non-invasive identification of MASLD patients eligible for resmetirom treatment – data from a multicenter biopsy-proven MASLD cohort
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Background and aims: The liver-directed thyroid hormone receptor (THR)-β agonist resmetirom has shown promising results in resolving metabolic dysfunction-associated steatohepatitis (MASH) and reversing fibrosis. Based on phase-3 trial data, the Food and Drug Administration (FDA) granted the conditional approval of resmetirom for treatment of MASH with moderate to advanced (F2/F3) fibrosis. An expert panel recently recommended vibration-controlled transient elastography (VCTE) with values between 10 and 19.9 kPa to identify patients with F2/F3 fibrosis who can benefit from resmetirom treatment, provided the absence of cirrhosis features (Noureddin M et al., Clin Gastroenterol Hepatol 2024).
Method: In a real-world multicenter study, we followed the recently provided guidance and evaluated the utility of VCTE as a recommended non-invasive tool for identifying patients with resmetirom indication. VCTE was performed in 291 primary biopsy-proven MASLD patients, who were not pre-selected for pharmacotherapy trials.
Results: We show that VCTE values <10 kPa were mainly associated with no or low fibrosis, while VCTE values ≥20 kPa primarily indicated advanced fibrosis or cirrhosis. Among MASLD patients with VCTE values of 10–19.9 kPa, a substantial subset did not meet the label criteria for resmetirom treatment, despite lacking features of cirrhosis such as thrombocytopenia/portal hypertension. Narrowing the range to 10–15 kPa reduced the off-label classification of the MASLD patients for resmetirom treatment but remained suboptimal.
Conclusion: The recommended VCTE cut-offs effectively excluded most MASLD patients with F0/F1 fibrosis from resmetirom treatment. However, in patients with VCTE values of 10–19.9 kPa and no features of cirrhosis, additional diagnostic tools, including liver biopsy or other non-invasive assessments, may be needed to minimize misclassification and optimize the identification of eligible patients.

WED-385
Prevalence and risk factors of steatotic liver disease in primary care in Slovakia
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Background and aims: In recent years, steatotic liver disease has attained epidemic proportions. Screening, prevention and education of individuals with potential diseases in their initial forms, early detection and treatment is an important task of primary care.
The goal of the work was to investigate the prevalence and risk factors of steatotic liver disease in Slovakia. We aimed to raise awareness of liver health in primary care practitioners and patients and to emphasize the importance of performing non-invasive tests to assess the degree of liver steatosis and fibrosis.
Method: We retrospectively analysed the occurrence of steatotic liver disease in patients whose data were entered to free accessible online questionnaire www.hepkalkulacka.sk during their visit at primary care practitioner. We evaluated gender, age, BMI, occurrence of hyperglycemia or diabetes, hypertension, alcohol consumption, and lipid profile in 774 patients. We also retrospectively analysed the occurrence of steatotic liver disease in Slovakia regions based on BMI, FLI, APRI, NSF and FIB-4 indices.
Results: The participation of primary care practitioners in the project was 17%. We found differences in BMI and indices of steatosis and liver fibrosis among Slovakia regions, with alarming results exceeding the world average. Fasting hyperglycemia and/or diabetes were associated with the risk of developing hepatic steatosis, higher BMI and FLI values, but not with liver fibrosis predictors NFS, APRI and FIB-4. The risk of steatosis and liver fibrosis were higher in people consuming more alcohol.
Conclusion: We conclude that effective primary care screening of steatotic liver disease based on predictive indices is essential strategy to reduce advanced forms of steatotic liver disease and complications. We expect that this work will promote proper education, management and treatment of the affected patients.

WED-386
Alpha-1 antitrypsin Pi*MZ variant and risk of disease progression in MASLD and MASH
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Background and aims: Most investigational treatments for metabolic dysfunction-associated steatohepatitis (MASH) have shown modest anti-fibrotic effects. This is likely due to multifactorial etiology including genetics that impede a one-size-fits-all strategy. Among the genetic factors, the Pi*Z mutation in *SERPINA1* leads to proteotoxic liver injury, with homozygosity conferring a strong susceptibility to cirrhosis. The aim of this study was to investigate whether carriage of a *SERPINA1* Z mutation is associated with disease progression in MASH.
Method: A population of metabolic dysfunction-associated steatotic liver disease (MASLD) patients of European ancestry were identified

in UK BioBank using ICD-10 codes (N = 7339). To avoid misclassification bias, participants with alternative aetiologies of chronic liver disease diagnosed before or concurrently with MASLD were excluded (n = 1020), leaving 6319 participants for analysis. We used logistic and Cox models to estimate risk ratios for advanced liver disease as the primary outcome (composite of incident cirrhosis, hepatic decompensation and liver-related death or transplant) associated with the MZ genotype. The strength of association was compared with metabolic risk factors (obesity, dyslipidemia, hypertension and type 2 diabetes) and established genetic risk factors (PNPLA3, HSD17B13).
Results: During 38,422 person-years of follow-up, 499 of 6319 individuals experienced a primary outcome of advanced liver disease. The prevalence of the MZ genotype was 3.9% among individuals who did not experience the primary outcome and 7.6% among those who did. Event rates for the primary outcome among MM and MZ individuals with MASLD/ MASH were 12.8 and 22.1 per 1000 person-years, respectively. After adjustment for established metabolic and genetic risk factors, a significant association was observed for the primary outcome with the MZ genotype (adjusted OR 1.98, 95% CI 1.36–2.87). Genetic variants in PNPLA3 (I148M), type 2 diabetes, and presence of ≥2 metabolic risk factors all increased risk, whereas a common variant in HSD17B13 (rs9992651) was protective. The MZ genotype (unadjusted OR 1.90, 1.33–2.73) was a risk equivalent to ≥2 metabolic risk factors (uOR 1.75, 1.45–2.10) and PNPLA3 (uOR 1.32, 1.15–1.51).
Conclusion: Carriage of the Pi*Z mutation significantly affects the risk of future clinical outcomes among individuals with MASLD/ MASH. The MZ genotype confers a risk equivalent to established risk factors in MASLD/ MASH, underscoring the importance of screening and further work to understand the mechanisms behind this association.

WED-387
Improved reader alignment in metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis with the use of a study reading plan

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Background and aims: Clinical trials use multiple expert pathologist readers in two formats; 1) to produce consensus scorings or 2) in a 2 +1 adjudicated format, where one pathologist acts as a tie-breaker in case of disagreement. While liver pathology is the gold-standard in Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)/ Metabolic Dysfunction-associated Steatohepatitis (MASH) diagnosis, the levels of agreement between pathologists can be low, particularly with inflammation and ballooning scores. Our aim was to measure whether a study reading plan, which was curated over multiple alignment meetings with expert pathologists, increased agreement. The reading plan used the RAND/UCLA scoring criteria for MASLD/ MASH which included: NASH CRN fibrosis staging, NAS Steatosis grading, NAS expanded ballooned hepatocyte grading, Goodman portal inflammation, Goodman Mallory-Denk bodies grade and an alternate lobular inflammation grade. To determine fibrosis quality in advanced cases, the Beijing Classification of Regressive, Indeterminate and Progressive (P-I-R) fibrosis was scored.
Method: A prior scoring round which consisted of three pathologists scoring 35 slides using the NASH CRN scoring system was included as a baseline (R0). The initial round of scores (R1) involved four expert pathologists scoring 60 MASLD/MASH liver biopsies from 2 clinical cohorts using the RAND/UCLA and P-I-R scoring systems. This was performed 'blind' with no reading plan or alignment meetings between the pathologists. The second round (R2) was performed on the same slides and with the same pathologists after 4 alignment meetings and a finalized reading plan. In between each round there was a wash-out period of >4 weeks. Cohen's Kappa between each pathologist was calculated for all rounds.
Results: There was a moderate agreement with the RAND/UCLA scoring baseline and improved scores with the reading plan. The final Kappa scores for the metrics scored from each round (R0-R1-R2) showed a general increase in consensus, notable with lobular inflammation (0.17 kappa increase) and P-I-R scores (0.27 kappa increase): NAS Steatosis; 0.56-0.65-0.58, Expanded hepatocyte ballooning; 0.47–0.55–0.65, alternate lobular inflammatory score; 0.30–0.35–0.52, Goodman portal inflammation; 0.48–0.58–0.50, NASH CRN Fibrosis stage; 0.33–0.50–0.57. Not scored with original NAS criteria were Goodman Mallory Denk bodies grade; which showed a 0.05 kappa increase from 0.43–0.48 between R1–R2 and P-I-R fibrosis quality which increased by a substantial 0.27 kappa from 0.53–0.80 between R1–R2.
Conclusion: Our findings show that a reading plan improved inter-rater reliability across most metrics, particularly those with low baseline agreement. The introduction of a more detailed and granular scoring system early in a clinical trial setting will not only align pathologists with study-specific scoring criteria but assist in reducing inter-rater disagreement, which can heavily impact the outcome of phase 2b/3 trials.

WED-388
Artificial intelligence measurement of portal tracts enables quantification of portal, lobular and interface inflammation in metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatohepatitis and autoimmune hepatitis

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Background and aims: A fundamental aspect of any pathological assessment of liver biopsies is the identification of Portal Tracts (PTs) as it allows assessment of biopsy adequacy (>6 PTs are required) and as differentiation of liver diseases often depending on recognising the differing anatomical distribution of abnormalities (e.g. portal, interface and lobular inflammation). We have developed a PT detection model showing good correlation with expert pathologists, which allows for the segmentation of individual PTs and accurate quantification and differentiation between lobular inflammation, portal inflammation, and interface hepatitis.
Method: Our AI model segmented core features of liver tissue (foreground, bile duct, hepatic artery, portal vein, and connective tissue) and performs geospatial processing to identify PTs and lobular regions based on the portal triad elements present in a region of connective tissue. PT segmentations were then paired with segmentations of inflammatory cells to measure portal and lobular inflammation. Concentric radial zones of ~100 microns thickness around PTs were identified to generate metrics across interface and periportal regions. The model was applied to Haematoxylin and Eosin stained Whole Slide Images (WSIs) from 3 Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)/Metabolic Dysfunction-associated Steatohepatitis (MASH) datasets [N = 606] and 1 pediatric Autoimmune Hepatitis (AIH) study [N = 70]. Inflammation was measured as the percentage of inflammatory cells in proportion to total tissue area (Inflammatory Burden - IB) and the inflammatory

cell number (ICN). Comparisons were evaluated using Mann-Whitney and Kruskal-Wallis tests and correlations with inflammatory scores using Spearman's rho.
Results: Our system was able to accurately delineate and identify interface, portal and lobular regions across WSIs. Overall, when comparing across lobular and portal inflammation scores, the IB and ICN were significantly higher in AIH patients than MASLD/MASH patients, especially in zone 1 regions (closest to the PT) consistent with interface hepatitis (Median: 343 in AIH vs 109 in MASLD; $p < 0.001$). AIH also displayed significant ($p < 0.001$) ICN increases in portal (Median: 4332 vs 1579) and lobular regions (Median: 1707 vs 460) compared to MASLD/MASH. In addition, IB correlated with expert pathologist scorings for lobular ($r = 0.42$) and portal inflammation ($r = 0.64$). Patients matched for portal inflammation and fibrosis histology scores indicated significantly higher IB ($p < 0.001$) in AIH (5.29%) vs MASLD/MASH (1.53%).
Conclusion: PT characterisation is fundamental for establishing histological scoring and sample adequacy of liver biopsies. Our AI model for PT identification generates detailed segmented overlays to assist in pathological review and clinical trial pathology, as well as revealing a higher degree of granularity in the level of inflammation across WSIs.

WED-389
Cost-effectiveness of hepatic fibrosis screening in suspected MASLD cases in primary care settings
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Background and aims: In clinical practice, only a limited number of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) undergo ultrasonographic examinations. Therefore, practice guidelines recommend screening for hepatic fibrosis even in suspected MASLD cases. This study aimed to analyze the cost-effectiveness of screening for hepatic fibrosis in suspected MASLD cases using serological noninvasive tests (NITs).
Method: Individuals with suspected MASLD were defined as those meeting criteria based on serological NITs, such as a fatty liver index (FLI) or a hepatic steatosis index (HSI). A combined decision tree and Markov model approach was employed from a healthcare perspective to estimate life-years, quality-adjusted life-years (QALYs), costs, and the incremental cost-effectiveness ratio (ICER) between the screening and no-screening groups in the United States.
Results: Advanced hepatic fibrosis prevalence in individuals with suspected MASLD using the FLI was significantly higher at 10.6% than at 1.3% in those without MASLD ($P < 0.001$). Regarding HSI, the prevalence was 8.6% versus 2.2% in non-MASLD cases ($P < 0.001$). Screening (base case) for suspected MASLD defined by FLI had an ICER of $69,192 per QALY and by HSI, $74,729 per QALY, both of which were considered cost-effective based on the implicit ICER threshold of $100,000/QALY in the United States. However, screening for other subgroups without evidence of MASLD was not deemed cost-effective. When applying medical costs and fibrosis distribution data from Korea, similar results were also observed.
Conclusion: Implementing a two-step screening algorithm for advanced hepatic fibrosis in patients with suspected MASLD based on HSI or FLI calculation is cost-effective in primary care settings.

WED-391
LiverPRO to diagnose and monitor liver fibrosis in patients with MASLD and obesity
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Background and aims: Obesity is linked to liver fibrosis and progression in metabolic dysfunction-associated steatotic liver disease (MASLD). While weight loss improves metabolic health and reduces inflammation, monitoring fibrosis progression in individuals with obesity remains difficult due to the limited availability of reliable non-invasive biomarkers. This study aimed to validate LiverPRO in patients with obesity, evaluating its diagnostic performance for liver fibrosis and its ability to track changes in fibrosis and weight over time.
Method: This analysis used data from a case-control study of matched patients with obesity, either undergoing bariatric surgery or receiving standard of care, based on clinical decision-making and patient preferences. Patients were followed for 2.5 years, with liver biopsies performed prior to the bariatric surgery, and at the end of study. This analysis evaluated LiverPRO's diagnostic accuracy in detecting liver fibrosis and its ability to monitor changes in fibrosis and weight over time. We used Spearman's correlation coefficient due to the ordinal and non-parametric nature of Kleiner fibrosis score.
Results: The study included 266 participants with a mean age of 45 years (IQR 36–54), of whom 71% (n = 189) were female. The mean BMI was 43 kg/m² at baseline, and 38 kg/m² at the study's conclusion (follow-up in 103 patients). At inclusion, 29% of participants had fibrosis stage F2, 7% had F3 fibrosis, and 1% had cirrhosis. LiverPRO's diagnostic accuracy (ROC AUC) for advanced fibrosis (≥F3) was 0.78 (95% CI: 0.67–0.87), with a sensitivity of 0.74 (95% CI: 0.52–0.92) using a rule out cut off of 5%, and a specificity of 0.88 (95% CI: 0.84–0.92) using a rule in cut off of 15%. During follow up a total of 15 patients improved in fibrosis, 62 were stable, and 26 showed progression in fibrosis stage. No patients changed more than one fibrosis stage. LiverPRO scores correlated significantly with fibrosis progression (Spearman's $\rho > 0.33$, $p < 0.01$) and varied across fibrosis trajectory categories (improving, stable, or progression; Kruskal-Wallis $H = 11.38$, $p < 0.01$). Dunn's post-hoc test further demonstrated LiverPRO's ability to detect fibrosis progression, with significant differences between progression and both improvement ($p < 0.01$) and stable categories ($p < 0.03$). Participants were further categorized by weight change: improvement (≤−10 kg), stable and progression (≥+10 kg). While LiverPRO scores correlated modestly with weight changes (Spearman's $\rho = 0.245$, $p = 0.01$) and differed across weight-change groups (Kruskal-Wallis $H = 6.84$, $p = 0.03$), pairwise comparisons between groups (e.g., decreasers vs. increasers, $p = 0.112$) were not statistically significant.
Conclusion: LiverPRO shows robust diagnostic accuracy for advanced fibrosis in individuals with obesity and potential for monitoring fibrosis progression and weight-related changes over time.

WED-392

Diagnostic and clinical implications of high spleen-to-liver stiffness ratio in MASLD – a prospective, comparative study

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Background and aims: Spleen stiffness (SSM) and liver stiffness measurements (LSM) are widely recognized as non-invasive markers of portal hypertension (PH), both showing a strong correlation with the hepatic venous pressure gradient (HVPG). In contrast to HVPG and LSM, SSM may offer an advantage in identifying presinusoidal contributions to PH. This study explored the SSM-to-LSM ratio and its relationship with HVPG, as well as other PH surrogates — including spleen size, platelet count (PLT), and von Willebrand factor (VWF)— across diverse liver disease etiologies.
Method: A total of 314 patients with compensated liver disease were prospectively enrolled for the study. All participants underwent HVPG measurement concurrent with LSM and SSM using SuperSonic-Imagine technology. Demographic, clinical, and laboratory data were recorded.
Results: Patients with alcohol-related liver disease (ALD; n = 162) exhibited higher median LSM (45.9 kPa) and HVPG (16.0 mmHg) compared to those with metabolic dysfunction-associated steatotic liver disease (MASLD; n = 28; LSM: 19.4 kPa; HVPG: 10.0 mmHg). However, SSM values were comparable between the two groups (median: 58.6 kPa vs. 52.0 kPa; p = 0.213). This resulted in a higher SSM/LSM ratio in MASLD (2.42) than in ALD (1.30), with the highest ratio observed in patients with porto-sinusoidal vascular liver disorder (3.45). VWF levels and spleen size were significantly higher in MASLD compared to ALD patients, even after adjusting for HVPG. Notably, stratification of patients across all etiologies by SSM/LSM ratio tertiles revealed no significant correlations with these PH surrogates.
Conclusion: Our study highlights distinct SSM/LSM ratio patterns across different liver disease etiologies. After controlling for liver disease severity, MASLD patients exhibited higher SSM/LSM ratios and more pronounced PH surrogates compared to ALD patients. These findings support the hypothesis of a presinusoidal component contributing to PH in MASLD.

WED-397

Nuclear magnetic resonance metabolomics for non-invasive MASLD phenotyping

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a significant health challenge and is both likely underdiagnosed yet rising in incidence globally. Early diagnosis and treatment are paramount to prevent illness progression and late-stage conditions, such as cirrhosis. However, current diagnostic approaches often lack adequate accuracy required for effective disease staging, and biopsies are invasive and costly. Given the central role of the liver in metabolic processes, we hypothesized that circulating metabolites could serve as biomarkers to differentiate clinically relevant MASLD disease stages. Specifically, we aimed to identify metabolomic constellations capable of identifying NAFLD Activity Score ≥4 (NAS 0–3 vs. NAS 4–8) and excluding advanced fibrosis (Fibrosis Stage F0-2 vs. F3-4) on a nuclear magnetic-resonance (NMR) platform.
Method: Using NMR spectroscopy in a retrospective multicenter European study, we analyzed blood samples from 281 biopsy-confirmed MASLD patients spanning various disease stages. NMR biomarker discovery was performed in all serum samples passing quality control. Biostatistical modelling was then performed in conjunction with clinical data and protein biomarkers in samples where available. Regularized logistic regression, as well partial least squares regression, was applied in nested cross-validation to build and evaluate prediction models. The prediction performances of these models were numerically compared to established tools, including FIB-4 and VCTE (Fibroscan LSM).
Results: Of 281 patients, 152 (54%) had a NAS ≥4, 98 (35%) had at-risk NASH and 54 (16%) had advanced fibrosis. In samples with available clinical data, the NMR metabolomics-based model for NAS stratification (NAS 0–3 vs. NAS 4–8) reached an AUC of 0.75, exceeding both FIB-4 (AUC 0.46) and Fibroscan (AUC 0.46). For fibrosis staging (F0-2 vs. F3-4), the NMR model achieved an AUC of 0.78, outperforming FIB-4 (AUC 0.66) and matching Fibroscan (AUC 0.76).
Conclusion: This study provides evidence that metabolomic constellation profiling measured on the NMR platform can offer a precise, non-invasive approach to staging MASLD. Beyond its diagnostic utility, metabolomics may shed light on patient-specific disease mechanisms, paving the way for personalized interventions and care. Ongoing efforts include expanding the dataset to enhance the robustness of the data and utility of this approach.

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Bone fragility and fracture risk assessment in metabolic disfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and Type 2 diabetes (T2D) share several risk

factors for bone fragility despite the precise mechanism implied in fracture development is not defined. This study aims to evaluate fracture bone risk in patients with MASLD and T2D using the trabecular bone score (TBS), an index of bone microarchitecture quality.

Method: One-hundred-eight patients with MASLD and T2D (median age 62 years, 54% male, 26 cirrhotic, 47% with BMI > 30 kg/m^2) who consecutively attended the Hepatology Unit of the University Hospital of Messina from February 1st,2024, to October 31st,2024, were enrolled. Exclusion criteria were the presence of decompensated cirrhosis, thyroid/parathyroid diseases, chronic kidney disease, heart failure, active malignant neoplasia, and bone metabolism therapies used for >3 months. All patients underwent liver stiffness measurements (LSM)/Controlled Attenuation Parameter (CAP) evaluation by fibroscan and dual-energy X-ray absorptiometry (DEXA) with TBS assessment.

Results: Overall, study population presented median LSM and CAP values of 7.5 kPa (5.8–13.9) and 298 dB/m (255–324) respectively. Sixty-three patients (58.9%) had a pathological TBS (cut-off <1.350), and 55 (52%) presented sub-clinical vertebral fractures at DEXA. Patients with pathological TBS showed higher BMI values ($p < 0.0001$), LSM > 8 kPa ($p = 0.038$), higher CAP levels ($p = 0.007$), and LDL-c ($p = 0.035$) compared to patients without. TBS values were inversely correlated with CAP and visceral adiposity index ($p = 0.006$; $p = 0.003$, respectively) and directly with L1-L4 and femur BMD ($p < 0.0001$, $p = 0.002$). Patients with vertebral fractures showed higher BMI levels ($p = 0.001$), LSM ($p = 0.027$) and CAP ($p = 0.010$) values, and pathological TBS ($p < 0.001$). At logistic univariate and multivariate regression analysis, independent variables associated with the presence of a pathological TBS score were BMI > 30 kg/m^2 ($p < 0.001$), CAP > 298 dB/m ($p = 0.020$), and higher values of total FRAX score ($p = 0.027$).

Conclusion: Evaluation of TBS in MASLD and T2D patients could be useful for assessing bone fragility and enabling an early fracture diagnosis.

WED-399

Metabolic associated steatotic liver disease- related significant and advanced fibrosis' prevalence in Brazil and the associated accuracy of FIB-4 and vibration-controlled elastography - a national register

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Background and aims: Latin America (LATAM) has the highest prevalence of metabolically associated steatotic live disease (MASLD) globally. Recent data regarding the prevalence of significant and advanced MASLD-related fibrosis in Brazil, the largest country in LATAM, is unknown. We aimed to evaluate the prevalence of both significant (SF, F ≥2) and advanced (AF, F≥F3) fibrosis according to liver biopsy (LB) according to its different geographic regions, as well as the accuracy of FIB-4 and liver elastography by VCTE (Fibroscan, Echosens, Fr) for the diagnosis of SF and AF respectively.

Method: This was a sectional study in nine Brazilian hepatology university centers (Southeast, n = 5; Northeast, n = 1; South, n = 3). Demographics, clinic, liver stiffness measurement by VCTE (Fibroscan®, Echosens, Fr), and liver histology were registered, and PNPLA3 genotypes were registered if available.

Results: 2905 patients were included (53% women, 64% white, 51 ± 14 yrs). Regarding metabolic profile, 44% had T2DM for 8 (3–14) years, 60% had systemic arterial hypertension, and 58% had dyslipidemia. ALT and AST were abnormal in 36.2% and 18.1% respectively. According to LB (n = 2122), 75% were F0-F1, 12% F2, 9% F3 and 4% F4. Most patients with LB were in the South region (n = 1520, 72%) ($p < 0.001$). However, most data from VCTE are related to Southeast Brazil (n = 1084, 85%). The median liver stiffness measure (LSM) was 8.8 (6.1–15.8) kPa. LSM<8 kPa, between 8 and 12 kPa and ≥12 kPa was observed in 44%, 25% and 31% of patients. Most from the Southeast presented a LSM ≥ 12 kPa ($p = 0.01$). Overall, FIB-4 was under 1.3 in 81% of patients. The PNPLA genotype distribution (n = 707) was 41%,45% and 14% for CC, CG and GG respectively. For F3, the AUROC for FIB-4 and LSM were 0.75 (95% CI: 0.70–0.80; $p < 0.01$) and 0.72 (95% CI: 0.68–0.77; $p < 0.01$) respectively and for F2, 0.67 (95% CI: 0.62–0.72; $p < 0.01$) for FIB-4 and 0.64 (95% CI: 0.60–0.69; $p < 0.01$) for VCTE.

Conclusion: Although there is an underrepresentation of the North, West-Central and Northeast Brazilian regions, most MASLD patients with advanced fibrosis determined by LB or VCTE are from the Southeast. VCTE is available mostly in the Southeast region, which impacts the fibrosis stratification of MASLD in other regions due to the lack of equipment, justifying the higher proportion of LB in the South. The accuracy of FIB-4 and liver elastography by Fibroscan® is good for diagnosing stage 3 fibrosis, but neither NIT is a good tool for diagnosing F2 fibrosis. PNPLA distribution is similar to other countries, with a higher CC and CG genotype prevalence.

WED-400

Good diagnostic performance of Hepatoscope™ in diabetology clinics for the screening of MASLD patients with high risk of advanced liver fibrosis

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Background and aims: The screening for metabolic dysfunction-associated steatotic liver disease (MASLD) related advanced fibrosis (AF) is recommended in patients with type 2 diabetes (T2D) and obesity with metabolic comorbidities. We aimed at evaluating the diagnostic performance of a new ultrasound imaging point-of-care device: Hepatoscope™ for the detection of patients with high-risk of AF in diabetology.
Method: This is an ancillary study from of a prospective multicenter study (NCT04435054) including participants with T2D and/or obesity and MASLD age 40–80 years, BMI <40 kg/m^2 enrolled in 4 diabetes clinics in France between Dec 2022 and Sep 2024. Any other etiology of liver disease was systematically excluded. All participants underwent the same day: liver stiffness measurement using vibration-controlled transient elastography (VCTE) by FibroScan®, 2D-transient elastography (2DTE) using a prototype version (2DTE-V1) of Hepatoscope™. Post-acquisition reprocessing of the 2DTE data using the CE-certified version (2DTE-V2) of Hepatoscope™ was performed in a subgroup of n = 206 participants. High risk of AF was determined using a hierarchical composite criterion using either a liver biopsy ≥F3 if available, or magnetic resonance elastography (MRE) ≥3.62 kPa, or VCTE ≥12 kPa. The Spearman's correlation coefficients between VCTE and 2DTE-V1 or 2DTE-V2 were assessed in participants with valid VCTE (interquartile range/median ratio ≤0.30). The area under the ROC curve (AUROC) and 95% confidence interval (CI) were assessed for the detection of AF. An exploratory subgroup analysis was performed in n = 48 participants with magnetic resonance imaging proton density fat fraction (MRI-PDFF) and backscattering coefficient (BSC) by Hepatoscope™ for the quantification of hepatic fat content.
Results: 308 participants were included in the study: 57.5% male, 83.4% with T2D, 70.5% with obesity and with mean age: 60.1 ± 9.6 years, BMI: 32.6 ± 4.7 kg/m^2 and median [Q1–Q3] 2DTE-V1 of 5.7 [4.5–7.5] kPa, VCTE of 6.1 [4.9–7.9] kPa. The proportion of patients with AF was 10.7% (n = 33). VCTE and 2DTE-V1 were significantly correlated r^2: 0.38 [0.28–0.47], p < 0.001. The AUROC (95% CI) for the detection of high risk of advanced fibrosis was 0.81 (0.72–0.90). The correlation between VCTE and 2DTE-V2 was improved r^2: 0.61 [0.48–0.71] and 2DTE-V2 had an AUROC of 0.84 (0.73–0.95) for the detection of AF. Finally, exploratory analyses showed excellent correlation between BSC and MRI-PDFF: r^2: 0.80 [0.67–0.88], p < 0.001.
Conclusion: This proof-of-concept study indicates that Hepatoscope™ 2DTE has a good diagnostic performance for the identification of patients with high-risk of AF among patients with T2D and/or obesity screened in diabetology. Further studies in larger cohort using the 2DTE-V2 by Hepatoscope™ are needed to determine the optimal cut-offs.

WED-401-YI

Correlation between transient elastography, clinical scores and liver histology in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a rising cause of chronic liver disease. Liver stiffness measurement (LSM) is widely used as non-invasive tool to assess and quantify liver fibrosis in MASLD, but the diagnostic accuracy is uncertain. The aim of this study was to assess the correlation between LSM and liver histology in MASLD.
Method: We conducted a single center retrospective cohort study in patients with biopsy confirmed MASLD who underwent LSM within 6 months before biopsy, between 2015 and 2022. The primary endpoint was the correlation between LSM and histological grade of fibrosis. Secondary endpoints were correlation between Controlled Attenuation Parameter (CAP) values and histological grade of steatosis, diagnostic accuracy of steatosis by CAP compared to ultrasound, correlation of non-invasive scores and histological grades of fibrosis, and lastly to validate LSM cut-off values.
Results: We included 139 patients [53% male, median age 51] with a median BMI of 31 kg/m^2. Forty-six patients had diabetes mellitus (33%). Histological distribution of fibrosis stages was as follows: F0: 5%, F1: 15%, F2: 56%, F3: 14%, and F4: 9%. The median LSM (IQR) per histological fibrosis stage was 8.9 (20.4), 7.8 (4.5), 8.8 (5.4), 12.8 (4.8), and 37.4 (43.1) kPa, respectively. Our findings indicate a moderate positive correlation between LSM and histological fibrosis grade (r = 0.42, p < 0.001). When comparing individual groups of fibrosis, no significant difference in LSM was found between low degrees of fibrosis (F0–F2). However, a difference was found in comparison with F3 and upwards (p < 0.001). Moreover, when clustering fibrosis grades into low levels of fibrosis (F0–F2) and severe fibrosis (F3–F4), a difference was found between these two groups (p < 0.001). LSM ≥12 kPa demonstrated an excellent sensitivity (0.75) and specificity (0.80) in detecting severe fibrosis (≥F3), with an area under the receiver operating characteristics (AUROC) curve of 0.80. Clinical scores performed sub optimally in detecting and staging fibrosis, with exception of the APRI and NAFLD score. We found a weak positive correlation between CAP values and histological steatosis grades (r = 0.21, p = 0.21), with no significant differences between each grade of steatosis. Ultrasound and Fibroscan performed similarly in detecting the presence of steatosis.
Conclusion: LSM cannot discriminate between low levels of fibrosis but can accurately identify severe fibrosis/cirrhosis in MASLD patients using a threshold of LSM ≥12 kPa. LSM in combination with non-invasive scores may be suitable to confirm severe fibrosis or aid in the decision making for the need of liver biopsy. Fibroscan does not

accurately assess different grades of steatosis but can detect the presence of steatosis with the same accuracy as ultrasound.

WED-402

Clinical validation of MRI-PDFF super-response in identifying MASH resolution: data from a prospective cohort and validation in an RCT

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Background and aims: MRI-proton-density-fat fraction (MRI-PDFF) response (defined as ≥30% relative decline in MRI-PDFF) can help to detect metabolic dysfunction-associated steatohepatitis (MASH) resolution. The association of MRI-PDFF super-response (defined as ≥50% decline or greater in MRI-PDFF) on the likelihood of MASH resolution has not been systematically assessed and quantified. We examined the association between an MRI-PDFF super-response and MASH resolution in 2 prospective cohorts.
Method: This study included a cohort of 95 well-characterized adult participants (67% female) with biopsy-confirmed MASH who underwent contemporaneous laboratory testing, MRI-PDFF, and liver biopsy at two time points. The *primary outcome* was MASH resolution with no worsening of fibrosis. The findings were validated in a distinct cohort of 163 participants (64% female) with MASH from a clinical trial.
Results: The median (IQR) age and body mass index (BMI) were 55 (45–62) years and 32.0 (30–37) kg/m^2, respectively, in the primary cohort. The histologic response rate was significantly higher in combined MRI-PDFF super-responders versus non-super-responders (57% versus 12%, $p < 0.001$). After multivariable adjustment for age, sex, BMI, race/ethnicity, and type 2 diabetes, MEI-PDFF response (adjusted OR 4.94, 95% CI 1.53–15.94, $p = 0.007$) and MRI-PDFF super-response (adjusted OR 9.08, 95% CI 2.39–35.53, $p = 0.002$) remained statistically significant predictors of histologic response. We determined similar findings in a distinct cohort, with MRI-PDFF response (OR 5.47, 95% CI 1,81–16.60, $p = 0.003$) and MRI-PDFF super-response (OR 7.42, 95% CI 2.82–19.50, $p < 0.001$) associated with MASH resolution.
Conclusion: MRI-PDFF super-response predicts a greater likelihood of histologic response than MRI-PDFF response. These data have important implications for clinical trial design in MASH and assessing dose response and selection for Phase 3.

WED-403

Evaluation of liver fibrosis by FIB4, liver stiffness (Fibroscan, ShearWave), LiverRisk score and EASL 2-step approach in a cohort of 1169 patients (STEATOLIB) followed for MASLD

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Background and aims: The STEATOLIB cohort was established to prospectively monitor patients with steatosis in hepatology private practice over a decade. This study focuses on liver fibrosis evaluation in this patient population.
Method: From February 2021 to June 2023, 18 centers enrolled 1,169 adult patients with morphological and/or histological steatosis and abnormal liver tests (ASAT, ALAT, GGT, and/or PAL) into the STEATOLIB cohort.
Results: Among the 1,169 patients included, 56% were men, with a mean age of 56 years (SD: 13). Comorbidities included diabetes (37%), hypertension (45%), and dyslipidemia (36%). Weekly alcohol consumption was: no consumption (56%), 1–10 units (33%), and >10 units per week (11%). The mean BMI was 31 ± 5.8 kg/m². Fibrosis was assessed using the FIB-4 score in 936 patients: 69% had a low fibrosis risk (FIB-4 <1.3/<2, age-dependent), 23% had an intermediate risk (FIB-4: 1.3/2–2.67), and 8% had a high risk (FIB-4 >2.67). Liver stiffness measurement (LSM) was available in 87% of patients: Fibroscan (n = 407) showed a mean stiffness of 8.3 kPa (SD 6.1), with 66% <8 kPa, 19% between 8 and 12 kPa, and 15% > 12 kPa. Shear Wave Elastography (n = 429) yielded similar results (mean: 8.0 kPa (SD 5.2)). The LiverRisk Score (LRS) was calculated in 654 patients: 41% had minimal risk (LRS <6), 51% had low risk (LRS <10), 7% had medium risk (LRS 10–15), and 1% had high risk (LRS >15). Confirmed fibrosis (LSM ≥8 kPa) was significantly associated with diabetes, FIB-4 > 1.3/>2, and LRS > 6. Liver biopsy, performed in 90 patients (8%), revealed advanced fibrosis (F2–F4) in 55 patients, significantly correlated with age, diabetes, and LSM. Using the EASL-recommended 2-step approach: Low fibrosis risk by FIB-4 was confirmed by LSM (<8 kPa) in 79% and by LRS (<10) in 96% of cases. Intermediate FIB-4 risk was confirmed by LSM (≥8 kPa) in 55% of cases and by high-risk LRS (≥10) in 16%. High FIB-4 risk was confirmed by LSM (≥8 kPa) in 77% of cases and by medium or high-risk LRS (≥10) in 30%. LRS <6 was observed in: 52%, 20%, and 4% of patients with low, intermediate, and high FIB-4 risks, respectively ($p < 0.001$), in 47% of patients with LSM <10 kPa vs. 4% with LSM ≥10 kPa ($p < 0.001$).
Conclusion: Hepatic fibrosis was confirmed in one-third of patients consulting for MASLD in hepatology private practice. The EASL 2-step approach is effective in identifying liver fibrosis. In resource-limited settings, second-line fibrosis testing can be restricted to patients with intermediate FIB-4 scores. While FIB-4 and LRS show strong concordance in low-risk zones, their agreement is more limited in the intermediate or high-risk zones of the FIB-4.

WED-404

Fibroblast activity (PRO-C3) and liver stiffness correlate with spatial distribution of collagens in MASLD and ALD: insights from digital pathology

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Background and aims: In patients with metabolic dysfunction associated steatotic liver disease (MASLD) and alcohol-related liver disease (ALD) Kleiner fibrosis stage provides limited information on

the spatial distribution of collagen in the liver. Digital pathology provides a more advanced assessment of collagen localization; however, there is limited knowledge linking non-invasive tests to the spatial distribution of collagen.
Method: Liver biopsies and serum samples from 121 patients with MASLD and 33 patients with ALD were evaluated. Second harmonic imaging (SHG) was used to quantitate hepatic fibrosis by qFibrosis (qFib). qFib is a composite index combining collagen strings (#StrNumber), length of collagen strings (StrLength) in the central vein (CV), portal tract (PT) and zone 2. NordicPRO-C3, a blood-based type III collagen formation marker of fibroblast activity was measured and correlated to the SHG.
Results: The median age (Q1-Q3) of the MASLD or ALD cohort were 54[43–60]/64[59.5–68.5) years, 53%/84% male and a mean BMI of 32/30, respectively. Pathology assessed fibrosis distribution was as follows: F0-4 = 3/0%, 28/0%, 35/3%, 24/36% and 11/61% for MASLD/ALD. The median (Q1, Q3) at baseline for qFibrosis value for MASLD/ALD was 1.70 (1.4–2.4)/3.4 (2.4–5.0); PRO-C3 (11.5 (9.4–16.2)/22.6 (19.2–28.3) ng/mL; Transient Elastography (TE) for MASLD/ALD was 8.2 (5.6–12.7/21.1 (14.4–32.0). The Spearman correlation between PRO-C3 and qFib was similar in MASLD: ($r = 0.56$, $p > 0.0001$) and in ALD ($r = 0.55$, $p = 0.001$). The ADAPT score (PRO-C3, diabetes, platelets, age) was highly correlated to qFib in MASLD ($r = 0.72$, $p > 0.0001$) and less in ALD ($r = 0.43$, $p = 0.018$). TE was correlated to qFib in MASLD ($r = 0.58$, $p > 0.0001$) and in ALD (0.46, $p = 0.010$). The absolute amount of collagen across all regions (%SHG) correlated to PRO-C3 in MASLD ($r = 0.33$, $p = 0.0002$), and in ALD ($r = 0.54$, $p = 0.002$); ADAPT in MASLD ($r = 0.39$, $p = p > 0.0001$) and ALD ($r = 0.39$, 0.032) as well as TE in MASLD ($r = 0.38$, $p < 0.001$) and ALD ($r = 0.51$, $p < 0.004$). No correlation between qFib or %SHG were seen for AST or ALT in MASLD and ALT in ALD, except for AST versus qFib ($r = 0.41$, $p = 0.028$) and AST versus %SHG ($r = 0.42$, $p = 0.024$) in ALD only. Finally, the spatial distribution of collagen correlated with PRO-C3, ADAPT, TE for portal tract (StrAreaPT, StrArea; StrLengthPT) however not to AST or ALT.
Conclusion: We observed correlations between spatial distribution of collagens and systemically assessed active fibrogenesis and liver stiffness in both MASLD and ALD. While similarities and differences were observed, potentially influenced by etiology and sample size, these findings underscore the connection between biopsy-based digital pathology assessments and non-invasive tests for liver fibrosis.

WED-405
PRO-C4, a biomarker of perisinusoidal fibrosis, is related to cardiometabolic risk factors, steatosis, and liver stiffness

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Background and aims: Early intervention in patients with steatotic liver disease (SLD) is crucial to mitigating the risk of adverse outcomes. A histological characteristic of early liver damage is the formation of perisinusoidal fibrosis with thickening of the hepatocyte basement membrane. Type IV collagen is a key component of the basement membrane of the extracellular matrix and can be assessed serologically by the biomarker PRO-C4. Thus, PRO-C4 could potentially reflect early features of liver damage in patients with early-stage SLD.
Method: NordicPRO-C4 was measured in serum samples from a large Danish screening cohort of healthy individuals with known risk factors of SLD (n = 4736). NordicPRO-C4 was quantified using a chemiluminescence immunoassay on a high sensitivity IDS-i10 automated platform and compared between risk groups and to liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by vibration-controlled transient elastography (VCTE) within well-defined risk groups.
Results: PRO-C4 was elevated in patients with metabolic-associated risk factors for liver disease, compared to patients with alcohol-related risk factors only or no known risk factors ($p < 0.0001$). PRO-C4 increased with presence of metabolic syndrome (MetS) and was elevated for all subcomponents of metabolic dysfunction ($p < 0.0001$). Furthermore, PRO-C4 increased with increasing steatosis estimated by CAP in all subgroups ($\rho = 0.315$, $p < 0.0001$) and was higher in patients with LSM by VCTE ≥8 kPa in all risk groups, however not in patients with no known risk factors.
Conclusion: Elevated PRO-C4 is associated with presence of cardiometabolic risk factors and LSM≥8 kPa. PRO-C4 potentially reflects perisinusoidal fibrosis from early liver damage and repair due to its relation to increasing degree of steatosis. Interestingly, PRO-C4 was also related to elevated liver stiffness in a population at risk of SLD.

WED-406
FICE-4C nomogram can help anticipating liver related complications in non-cirrhotic MASLD patients

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Background and aims: The arrival of novel therapies for MASLD requires strategies to improve priorization. FICE-4C diagnostic algorithm has shown utility for fibrosis screening (*manuscript in preparation*), but its prognostic value remains unknown. Aims of this project are to: 1) Integrate FICE4C in a nomogram to facilitate its implementation at screening sites 2) Assess in a non-cirrhotic population its diagnostic accuracy for fibrosis together with its prognostic capacity to identify patients at higher risk of progressing to cirrhosis and its complications (ascites, hepatic encephalopathy, oesophageal varices bleeding and HCC).
Method: FICE-4C nomogram was created from data of two independent cohorts [N = 345 (4 Spanish hospitals)]. Variables were dichotomized and combined in two scores: Nomogram Intermediate risk (FICE4C-NIR), which requires FICE4 and any of the risk factors that compose the score, and Nomogram High Risk (FICE4-NHR) which requires at least two. Risk scores were estimated exclusively in non-cirrhotic patients and compared against VCTE, using EASL (≥8 kPa & 12 KPa) or Baveno cutoffs [10 & 15 kPa w/wo platelets $\leq 150 \times 10^9$/L)]. Diagnostic accuracy was assessed in each cohort separately (N = 179 & N = 127) and in the overall cohort. Prognostic analyses were restricted to patients in which follow-up data was available [(N = 125) (mean FU = 37 mo) (event rate = 9.3%] using Cox regression with and without adjusting for co-variates. All measurements come from baseline visit, which was performed within 3 months of the histological diagnosis.
Results: FICE4C-NIR showed a diagnostic accuracy comparable to the FICE4C original algorithm (FICE4C) and equal or even slightly better than VCTE for the detection of significant fibrosis [F2+ FICE4-NIR (AUC 0.70[0.65–0.75]) *vs* FICE4C (AUC 0.73[0.68–0.78]) *vs* VCTE at 8 kPa (AUC 0.62[0.58–0.67]), 10 kPa (AUC 0.67[0.62–0.73]), 12 kPa (AUC 0.67[0.62–0.73]) and advanced fibrosis [F3+ FICE4-NIR (AUC 0.71[0.66–0.76]) vs FICE4C (AUC 0.78[0.73–0.83]) vs VCTE at 8 kPa (AUC 0.66[0.62–0.69]), 10 kPa (AUC 0.73[0.69–0.78]), 12 kPa (AUC 0.73[0.67–0.79]) and 15 kPa (AUC 0.69[0.63–0.75])]. Both of them showed a strong prognostic association to liver outcomes [FICE4-NIR (HR 30.29 [7.03–129.9] p-value 4.12 E-06 & FICE4-NHR (HR 52.26 [10.64–256.8] p-value1.11 E-06)], paralleling the predictive capacity of VCTE [8 Kpa (HR 7.25 [0.93–56.16] p-value 0.058) 10 Kpa (HR 14.41 [1.86–111.6] p-value 0.011 12 Kpa (HR 26.88 [3.46–208.5] p-value 1.64 E-04) 15 Kpa (HR 12.39 [3.33–46.09] p-value 1.74 E-05) and 15 Kpa with low platelets (HR 22.49 [4.89–103.5] p-value 6.37E-05)] and histological fibrosis [F2-F3 (HR 7.96 [2.12–29.91] p-value 0.00214) F3 (HR 16.28 [4.77–55.54] p-value 8.37 E-06).
Conclusion: The FICE-4C nomogram, which is assessed via ELISA and uses routine care data, shows promise for identifying non-cirrhotic MASLD patients at high risk for severe outcomes.

WED-407
Are doppler alterations of the liver prognostic markers for MASLD Severity? How do doppler results correlate with transient elastography and anthropometric data?

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Background and aims: MASLD (Metabolic Associated Steatotic Liver Disease) has emerged as a significant global health concern, requiring the validation of reliable prognostic markers. There is a lack of conclusive evidence regarding the correlation between clinical algorithms, ultrasound (US), and transient elastography (TE), with the latter being limited in accuracy, especially in patients with higher body mass index (BMI), waist circumference (WC), or increased parietal wall thickness, leading to significant failure rates in assessing liver stiffness. This study aimed to explore correlations between anthropometric data, Doppler US parameters of hepatic artery (HA), portal vein (PV), right hepatic vein (RHV) waveform patterns, and the degree of steatosis estimated by US elastography (US-E) and TE (Fibroscan®).
Method: A cohort of 142 patients, with a mean age of 52.3 ± 9.5 years, was classified based on the degree of steatosis using controlled attenuation parameter (CAP) values as a reference. We analyzed variations in the HA resistive index (HARI), PV pulsatility index (VPI), and RHV flow patterns, and examined their relationship to steatosis and anthropometric data (BMI, WC and preperitoneal fat (G).
Results: Significant differences were observed when comparing HARI and VPI between patients with significant steatosis (S2 and S3) and those with non-significant steatosis (S0 and S1): for HARI 0.683 versus 0.542, p = 0.04), for VPI 0.16 versus 0.28 (p = 0.03). Notably, anthropometric data, triphasic RHV flow pattern, and Doppler flow characteristics differed significantly between the two groups. HARI showed a stronger negative correlation, followed by VPI, with the severity of steatosis. Furthermore, a negative correlation between G and all US Doppler parameters was noted, suggesting the need to analyze US and TE data separately for lean versus overweight patients with MASLD.
Conclusion: The severity of steatosis in MASLD correlates significantly with HARI and VPI, demonstrating potential for diagnosing significant steatosis. The alterations in vascular compliance observed in Doppler US provide valuable insights into disease severity and hepatic parenchymal changes.

WED-408
Can we use coronary-CT scan for screening of metabolic-associated steatotic liver disease?

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Background and aims: Metabolic-associated steatotic liver disease (MASLD) comprises a spectrum of pathologies frequently encountered in the general population, with rising incidence. There are common risk factors for MASLD and coronary artery disease (CAD) suggesting that these 2 pathologies require common management. Coronary-CT scan has become a routine evaluation for CAD in at risk populations. The aim of this study is to determine whether we can use information derived from coronary CT to diagnose liver steatosis, thus involving radiologists and cardiologists in MASLD screening and early diagnosis and management.
Method: We evaluated 138 patients with metabolic syndrome referred for coronary CT scan. On the native CT acquisitions, we measured liver and spleen density (LD, SD), as well as the thickness of epicardial adipose tissue (EAT). Patients were then referred for liver disease evaluation by Fibroscan (controlled attenuation parameter CAP). On CT, liver steatosis was defined as LD <40 HU or difference between SD and LD > 10 HU. We also determined liver function tests and body mass index (BMI). Patients with other causes of liver disease were excluded from the study.
Results: Mean age in the study group was 57.32 ± 22.72 years with 51.1% male and 48.5% female. Coronary CT scan revealed 107 patients with liver steatosis (77%). CAP analysis revealed 6 S0 patients (5.9%),

18 S1 patients (16.8%), 54 S2 patients (50.4%) and 29 S3 patients (27%) in the group with CT suspicion of steatosis and 23 S0 patients (74.1%), 5 S1 patients (15.1%) and 3 S2 patients (9.6%). We found a significant correlation between CAP and LD values (p = 0.01) as well as difference between SD and LD (p = 0.02). Increased EAT correlated to the presence of steatosis (S1 to S3) in patients with BMI > 30 kg/m^2 (p < 0.01) but not in patients with BMI <30 kg/m^2 (P = 0.08).
Conclusion: Coronary CT scan for CAD detection can be a useful tool for screening of liver steatosis, given the common pathological background between the two pathologies. Including data regarding LD and SD in the scan report may indicate a need for a hepatology consult in patients with suspicion of CAD and may lead to an early diagnosis of MASLD.

WED-413

Does hyperferritinemia predict ferroptosis in metabolic dysfunction associated steatotic liver disease? A real-world experience

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Background and aims: Ferroptosis (iron-dependent oxidative damage resulting in programmed cell death) has been linked to metabolic diseases including hepatic steatosis. Ferroptosis leads to increased intracellular iron and serum ferritin has been investigated as a marker of liver fibrosis in metabolic dysfunction associated steatotic liver disease (MASLD). However, there is limited evidence to support use of serum ferritin as a surrogate marker of disease progression in MASLD. Herein, we aim to evaluate the role serum ferritin in predicting major clinical outcomes in patients with MASLD.
Method: We performed a retrospective cohort study utilizing a large research network (TriNetX) comprising data of over 110 million patients. Study period was January 2016 to December 2020. Patients 18 years with steatotic liver disease and at least one of the cardiometabolic factors were identified. Patients with other etiologies of chronic liver disease were excluded. Patients were followed for up to five years. Hyperferritinemia was defined as serum ferritin ³300 ng/ml. Control group was MASLD patients with serum ferritin <200 ng/ml. Primary outcomes were development of decompensated cirrhosis, hepatocellular carcinoma (HCC) and all-cause mortality in patients with MASLD with hyperferritinemia compared with the control group. Propensity score (1:1) matching was performed to control confounding variables. Kaplan-Meier survival analysis was performed to calculate the hazard ratio.
Results: We identified 3,185 patients with hyperferritinemia and 8,729 controls. Patients in the hyperferritinemia cohort were older (55.6 vs. 53.3), Black (8.35% vs. 6.68%) or Asian (5.79% vs. 3.37%) men (48.86% vs. 30.68%). Obesity (53.07% vs 40.34%) and diabetes mellitus (50.80% vs. 47.52%) were more common in the control group while cardiac comorbidities – ischemic heart disease (24.28% vs. 21.14%) and heart failure (15.26% vs. 11.19%) were more common in the hyperferritinemia group. In age-, gender- and comorbidity-matched cohorts, there was greater rate of decompensated cirrhosis (21.84% vs. 17.85%, hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.18–1.47) and worse overall survival (71.16% vs. 83.09%, HR 2.03, 95% CI 1.81–2.29) in patients with hyperferritinemia compared with the control group, after a median follow up was 48.67 months. There was no difference in the incidence of HCC (1.94% vs. 1.92%, HR 0.83, 95% CI 0.69–0.99) between the two groups.
Conclusion: Hyperferritinemia is common in MASLD and serum ferritin above 300 ng/ml is associated with increased risk of decompensated cirrhosis and all-cause mortality. Our findings support the use of hyperferritinemia as a marker of worse clinical outcomes in MASLD.

WED-414

Non-invasive assessment of fibrotic metabolic dysfunction-associated steatohepatitis by multisensorial electronic technologies

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Background and aims: Fibrotic MASH, the inflammatory form of MASLD with significant activity and fibrosis (necroinflammatory activity -NAS score- ≥4 and fibrosis ≥2), is the most treatment-requiring progressive form of MASH. For this reason, much research is focusing on identifying non-invasive tools capable of diagnosing this condition. In the last years, multisensory analysis techniques are emerging as diagnostic/prognostic tools potentially useful in various disorders, including liver diseases. We aim to evaluate multisensorial electronic-technologies (e-nose and e-tongue) as novel noninvasive tools for the identification of fibrotic MASH.
Method: Consecutive patients with MASLD attending the Hepatology Unit of "Fondazione Policlinico Universitario Campus Biomedico" were enrolled. MASLD was diagnosed by the presence of cardiometabolic criteria and either histological or ultrasonographic steatosis. Fibrotic MASH was defined non-invasively as Fibroscan-AST (FAST) score ≥0.67 or fibrotic NASH index (FNI) ≥0.33 and, histologically, as NAS score ≥4 and fibrosis stage ≥2. All patients underwent breath sampling, analyzed by BIONOTE e-nose, and urine and saliva sampling, analyzed by BIONOTE e-tongue. The ability of e-nose/e-tongue to identify fibrotic-MASH was evaluated using Partial Least Squares Discriminant Analysis (PLS-DA) and described by confusion matrices.
Results: A total of 75 patients were enrolled (median age 58 years, male 64%, mean BMI 32.6 kg/m^2). FAST score and FNI were available for 67 and 49 patients, respectively, and 37 patients received liver biopsy. Fibrotic MASH was diagnosed by FAST score and FNI in 12/67 and 11/49 patients, respectively, and by histological criteria in 18 of the 37 patients undergoing liver biopsy. Breath, urine, and saliva samples were suitable for analysis in 57, 71 and 68 patients, respectively. Breath, saliva and urine accuracies were 75%, 70%, and 79% for predicting fibrotic MASH by FAST score, and 70%, 72%, and 71% by FNI score. While combining different sample analyses did not improve prediction by FAST, integrating urine, saliva, and breath enhanced fibrotic MASH prediction by FNI to 79%. In the histological subgroup, e-nose showed total accuracy (100%), correctly classifying 18/18 patients, while e-tongue saliva and urine had accuracies of 82% and 69%, respectively. Combining saliva and urine improved accuracy to 88%. Overall, e-technologies outperformed FAST (accuracy 64%) and, except for urine e-tongue alone, FNI (accuracy 75%), in predicting fibrotic MASH diagnosed by histology.
Conclusion: E-technologies exhibit good accuracy in identifying fibrotic MASH, outperforming FAST and FNI, two widely used noninvasive reference scores. These results, derived from a limited sample, suggest the potential of these tools for risk stratification in patients with MASLD/MASH, but require further validation in larger cohorts.

WED-415-YI

The association between non-invasive tests of liver fibrosis and early diastolic dysfunction in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) may contribute to cardiac impairment, especially through diastolic dysfunction and heart failure with preserved ejection fraction. Non-invasive tests (NITs) for liver fibrosis are useful tools for risk stratification, though their utility in identifying patients with early or established diastolic dysfunction remains uncertain. In this study we aimed to assess the association between liver NITs (FIB-4 and liver stiffness measurement [LSM]) and echocardiographic markers of diastolic dysfunction.
Method: We prospectively enrolled 150 patients with MASLD and without cardiovascular disease history who referred to the hepatologic center of the "AOU Città della Salute e della Scienza di Torino" University Hospital. All patients underwent clinical and biochemical evaluation, vibration-controlled transient elastography for LSM, and screening echocardiography with speckle tracking analysis. Significant fibrosis was defined by FIB-4 > 1.3 or LSM ≥7 kPa. Diastolic dysfunction was defined by mitral E/E' ratio >9, while early diastolic dysfunction was defined by left atrial strain reservoir (LARS) (<22%) and left atrial stiffness index (LASi) ≥25 kPa. Pericardial fat thickness was also assessed.
Results: Increased FIB-4 was observed in 23.3% of patients (median age 62 [58.2–65.0]) with higher prevalence of type 2 diabetes (T2DM) (20%), arterial hypertension (74.3%) and dyslipidemia (62.9%). Overall prevalence of obesity was 43.9%. Compared to patients with low FIB-4, those with FIB-4 >1.3 had increased E/E' ratio, LASI and pericardial fat (respectively median 8.0 [6.0–9.2], p = 0.007; 0.34 kPa [0.20–0.42], p < 0.0001; 12.5 mm [8.5–17.2], p < 0.0001), and had reduced LARS (26.5% [19.0–33.0], p < 0.0001). In a multivariable stepwise regression analysis using 3 models (progressive adjustments for T2DM, obesity, sex, arterial hypertension, dyslipidemia and age > 50) FIB-4 >1.3 was independently associated with diastolic dysfunction (aOR 3.41 [1.08–10.74]) and with early diastolic dysfunction (aOR for reduced LARS 10.03 [2.01–49.8]; aOR for reduced LASi 4.24 [1.16–15.5]), while LSM ≥7 kPa was independently associated with LARS (aOR for reduced LASi 3.63 [1.01–13.0]). Finally, FIB-4 displayed Area Under the Curve (AUC) of 0.838 for the prediction of reduced LARS.
Conclusion: In patients with MASLD and without cardiac disease, NITS for liver fibrosis may be a useful tool to identify a high-risk group with early cardiac dysfunction. This would support tailored echocardiographic surveillance strategies to improve early detection and management. This study was funded by the Italian Ministry for Education, University and Research (MIUR) under the programme 'Dipartimenti di Eccellenza 2018–2022' Project code D15D18000410001.

WED-416

Establishing a training protocol for liver stiffness measurement by transient elastography in metabolic dysfunction-associated steatotic liver disease screening

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Background and aims: Transient elastography (TE) is the preferred non-invasive method for assessing liver fibrosis and steatosis, especially in metabolic dysfunction-associated steatotic liver disease screening. Although TE is generally considered straightforward to learn, the accuracy and reproducibility depend on operator skill, requiring a structured training protocol to minimize technical variability. As part of the GENESIS (Genomics and Environmental Non-invasive Evaluation for Saudi Intrahepatic Steatosis) project, we aimed to develop and validate a competency-based TE training protocol for new operators to ensure reliable results.
Method: A team of hepatologists and gastroenterologists developed a standardized TE training protocol using FibroScan. Seven healthcare workers with no prior TE experience were pre-assigned as research coordinators for the GENESIS project and trained under certified supervision using hands-on experience with immediate feedback for each case. Each trainee performed 100 supervised and 10 unsupervised TE measurements. Supervisors, blinded to the unsupervised results, conducted TE on the same patients in the same setting for comparison. We recorded the controlled attenuation parameter (CAP), liver stiffness measurements (LSM), and the interquartile range (IQR) for both trainee and supervisor measurements. Reliable LSM data required an IQR-to-median ratio threshold of <30%. We assessed inter-operator reliability using intraclass correlation coefficients (ICCs), with a threshold of > 0.80 to indicate a strong agreement.
Results: Trainees (57.1% female), with a median age of 35 years (range: 26 to 38), and five years of clinical experience (range: 1 to 13). Their backgrounds included nursing (57.1%), pharmacy (14.3%), genomic medicine (14.3%), and radiology (14.3%). The trainees were supervised by six certified supervisors, five of whom were female (83.3%). Their backgrounds included three pharmacists (50.0%), one hepatologist/gastroenterologist (16.7%), one ultrasound technologist (16.7%), and one biochemist (16.7%). The median training duration was 20 days (range: 14 to 20), with a median of 6 hours daily (range: 4 to 8). Each trainee was supervised by a median of 2 supervisors

(range: 1 to 3). Six of seven trainees met the ICCs competency threshold on the first attempt; however, one trainee required a second attempt. For the first attempt, the median ICC for CAP was 0.95 (IQR: 0.92–0.99), and for fibrosis scores was 0.99 (IQR: 0.95–0.99), indicating high inter-operator reliability across the cohort. Median IQR-to-median ratio across all trainees was 13.0% (range: 8.5% to 17.5%), and for supervisors, it was 14.0% (range: 8.0% to 17.5%).
Conclusion: A rigorous training across an average of 20 days with 100 supervised measurements ensures that new operators achieve expert-level proficiency in TE. This protocol enhances diagnostic reliability and establishes a benchmark for training in diverse clinical and research settings.

WED-417

Multiparametric ultrasound-based algorithm SteatoScore 2.0 versus monoparametric controlled attenuation parameter in clinical practice: a comparison study in a monocentric MASLD cohort

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Background and aims: A quantitative, accurate and non-invasive measurement of liver fat content (LFC) is an unmet need of clinical practice for Steatotic Liver Disease (SLD) evaluation. The most widespread non-invasive test in clinical practice is controlled attenuation parameter (CAP) by FibroScan ®. Multiparamatric Steatoscore 2.0 (StSc) was shown recently to provide LFC measures highly comparable to MRI-PDFF. Aim of the study was to analyze the StSc-CAP agreement in patients with metabolic dysfunction-associated SLD (MASLD) spectrum and their correlation with clinical/biochemical parameters.
Method: 450 patients consecutively evaluated from January 2019 to October 2024 for SLD at the Hepatology Unit of Pisa University Hospital were enrolled at MASLD diagnosis. Clinical, anthropometric, biochemical and instrumental data were collected. LFC was simultaneously measured with CAP and StSc and liver fibro-inflammatory one with FibroScan® liver stiffness measurement (LSM).
Results: Overall CAP and StSc were significantly correlated ($r = 0.485$, $p < 0.001$), but the agreement was poor and varied by LSM categories (<8 kPa: $r = 0.485$, $p < 0.001$; 8–12 kPa: $r = 0.462$, $p = 0.001$; 12–20 kPa: $r = 0.494$ $p = 0.005$, >20 kPa $r = -0.326$ $p = 0.330$) and BMI classes (normal weight: $r = 0.501$ $p < 0.001$, overweight: $r = 0.546$ $p < 0.001$, obese: $r = 0.385$ $p = 0.001$). StSc correlated inversely with age ($r = -0.111$ $p = 0.025$) and directly with overweight ($r = 0.133$ $p = 0.047$), while CAP did not. In non-advanced MASLD cohort (LSM < 12 kPa) we found a difference in correlation of StSc and CAP with AST (StSc $r = 0.290$ $p < 0.001$ vs CAP $r = 0.167$ $p < 0.001$, p for comparison = 0.010) and ALT (StSc $r = 0.358$ $p < 0.001$ vs CAP $r = 0.191$ $p = 0.001$, p for comparison = 0.0005).
Conclusion: In a MASLD cohort LFC measures by StSc and CAP were correlated but their agreement varied consistently along the spectrum of liver disease stage stratified non-invasively by LSM. Multiparametric StSc outperformed mono-parametric CAP and it significantly correlates with body weight. In earlier forms of MASLD StSc correlated better than CAP with liver enzymes in patients with progressive steato-hepatitis.

WED-418-YI

One-year changes in ALT and LSM, not in CAP, predict long-term liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: The availability of new drugs for the treatment of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) underlines the need of early predictors of response to such therapies. This study evaluated the impact of 1-year changes in liver stiffness measurement by Vibration-Controlled Transient Elastography (LSM by VCTE), controlled attenuation parameters (CAP), and serum alanine aminotransferase (ALT) on liver outcomes in patients with MASLD-related liver disease.
Method: A large multicentre cohort of MASLD patients with LSM≥8 kPa and prospective follow-up was enrolled. Liver-related events (LRE), including hepatocellular carcinoma (HCC) and liver decompensation (LD), were evaluated during follow-up. LSM, CAP, and ALT were assessed at baseline and at 1-year follow-up. Cumulative incidence functions and cause-specific Cox regression analyses were performed to correlate 1-year reduction in LSM, CAP, and ALT with the risk of developing LRE, LD and HCC.
Results: In 2443 patients with MASLD and LSM≥8 kPa, a 1-year reduction in ALT of 17 IU/L (HR 0.62; 95% CI 0.41–0.95; p = 0.02) and a 20% reduction in LSM (HR 0.44; 95% CI 0.29–0.67; p < 0.001) were both independently associated with a lower risk of LRE. Similarly, in 1412 patients with MASLD and LSM≥10 kPa, a 1-year reduction in ALT of 17 IU/L (HR 0.62; 95% CI 0.39–0.98; p = 0.04) and a 20% reduction in LSM (HR 0.42; 95% CI 0.27–0.66; p < 0.001) were independently associated with a decreased risk of LRE. Comparable results were observed when considering LD separately, but not for HCC. One-year changes in CAP did not predict liver outcomes. When combining 1-year reduction in ALT of 17 IU/L and a 1-year 20% reduction in LSM, the 5-year probabilities of LRE ranged from 2.1% in the best profile to 5% in the worst profile in patients with LSM≥8 kPa, and from 3.3% to 8.1% in those with LSM≥10 kPa.
Conclusion: One-year reductions in ALT of 17 IU/L and in LSM by 20%, not changes in CAP, reduce long-term liver outcomes in patients with MASLD, providing a new perspective on monitoring therapy effectiveness.

WED-419

The urine steroid metabolome combined with machine learning performs similarly to established non-invasive markers to risk stratify for the presence of advanced MASLD fibrosis

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects around 30% of people worldwide (Younossi, Z.M., et al. 2023). The strongest predictor of clinical outcome in patients with MASLD is liver fibrosis stage (Dulai, P.S., et al. 2017, Ekstedt, M., et al. 2015, Sanyal, A.J., et al. 2021). Due to limitations with the liver biopsy, there is a need to develop reliable non-invasive tests to identify patients with advanced fibrosis. There are currently no validated non-invasive urine tests to stage MASLD; The TrUSt-NAFLD study aimed to prospectively validate the use of urine steroid metabolite analysis coupled with machine learning to diagnose and stage MASLD (Miller, H., et al. 2024)
Method: Between May 2021 and November 2023, 461 patients were recruited to the TrUSt-NAFLD study with ethical approval. 151 healthy control patients were recruited from the Oxford Biobank and 310 patients with biopsy-proven MASLD were recruited from 8 centres across the United Kingdom. Urine samples were analysed using liquid chromatography tandem mass spectrometry (LC-MS/MS) for 19 steroid metabolites. A machine learning based classifier, Generalised Matrix Learning Vector Quantisation (GMLVQ), was used to classify patients into early (F0-2) or advanced (F3-4) fibrosis.
Results: The TrUSt-NAFLD cohort is a representative cohort of patients with MASLD who underwent a clinically indicated liver biopsy to determine MASLD stage and a matched healthy control cohort. The advanced fibrosis (F3-4) cohort were significantly older

than those with early fibrosis (F0-2) (59 *vs.* 48 years, $p < 0.01$) but there were no significant differences in sex or BMI between the groups. There was a significantly higher rate of diabetes in the advanced fibrosis group when compared with participants with early fibrosis (69.1 *vs.* 38.8%, $p < 0.01$) and consistent with this, glycated haemoglobin was also higher (49.0 *vs.* 41.5 mmol/L; $p < 0.01$). The urine steroid metabolite analysis coupled with GMLVQ performed similarly to other established non-invasive biomarkers (AUROC = 0.67), including Fib-4 (0.72), NFS (0.69) and VCTE (0.69) at distinguishing early from advanced fibrosis. It was also able to distinguish healthy controls from patients with MASLD (AUROC = 0.79).

Conclusion: The urine steroid metabolome provides a non-invasive method of assessing liver phenotype based on non-classical liver markers. None of the non-invasive tests performed well at distinguishing early from advanced fibrosis, emphasizing the need to refine these tests, including this analysis, to limit the use of the liver biopsy. Further work needs to be undertaken to better understand how the urine steroid metabolome changes over time in relation to liver phenotype.

WED-420

Prescreening with a novel machine learning model (LiverPRO) may improve trial enrollment efficiency in metabolic dysfunction-associated steatohepatitis (MASH): a retrospective analysis of the SYNERGY-NASH trial

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Background and aims: MASH is a progressive liver disease linked to increased liver-related morbidity and mortality. Patient recruitment for MASH clinical trials often requires liver biopsies, leading to screen failure rates exceeding 70%. LiverPRO is a machine learning model that predicts the risk of significant (≥F2) or advanced (≥F3) liver fibrosis based on age and 3 to 9 standard laboratory test results: AST, ALP, GGT, INR, albumin, bilirubin, platelets, sodium, and cholesterol. We evaluated the use of LiverPRO to improve enrollment efficiency of patients with biopsy-proven MASH and ≥F2 or ≥F3 fibrosis.

Method: We evaluated the performance of LiverPRO on screening data from SYNERGY-NASH, a completed phase 2 trial of tirzepatide in patients with biopsy-confirmed MASH and stage 2 or 3 fibrosis, which reported an overall screen failure rate of 87%. The trial used AST and Fibroscan-based criteria to select participants for "per-protocol" biopsies; LiverPRO's diagnostic performance was assessed on participants in this group (historical biopsies were excluded). We validated a strategy for deploying LiverPRO as a prescreening tool prior to applying the Fibroscan-AST (FAST) score.

Results: Of the 1583 screened patients, 1148 had results for ≥5 LiverPro input variables, allowing prediction (94%, 99% and 99.8% had 10, ≥9 and ≥8 variables, respectively); of these 462 had "per-protocol" biopsies. Using a standardized LiverPRO rule-in cutoff of 0.20 for detecting ≥F2 fibrosis across all sites, LiverPRO demonstrated a sensitivity of 89%, a specificity of 33%, and a positive predictive value (PPV) of 57%. When applying site-specific rule-in cutoffs for ≥F2 (0.20 for gastroenterology/hepatology sites and 0.65 for other sites), LiverPRO achieved a sensitivity of 54%, a specificity of 64% and a PPV of 60%. For detecting ≥F3 fibrosis with a rule-in cutoff of 0.15, LiverPRO showed a sensitivity of 25%, a specificity of 93% and a PPV of 58%. Based on these results, LiverPRO is predicted to improve the success rate for identifying patients with ≥F2 fibrosis from 50% to 60% (a 20% relative improvement) and for ≥F3 fibrosis from 29% to 58% (a 100% relative improvement) compared to the patient selection strategies used in SYNERGY-NASH. To evaluate a potential future screening strategy combining LiverPRO and the FAST score, we analyzed data from 952 participants with results from both tests. Using LiverPRO as a prescreening tool could reduce the number of patients screened for trial eligibility by 65% for the ≥F2 and by 89% for the ≥F3 population. This approach could also decrease the number of liver biopsies by 45% and 79% and improve enrollment by 96% and 307% for targeted ≥F2 and ≥F3 populations, respectively.

Conclusion: These data suggest that LiverPRO could significantly enhance the enrollment efficiency of MASH clinical trials with fewer liver biopsies, reduced costs and lower patient burden.

WED-421

Novel metabolomics-based non-invasive test for pediatric metabolic dysfunction-associated steatohepatitis using data from youth enrolled in NASH CRN studies

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Background and aims: Noninvasive tests (NITs) for identifying pediatric metabolic dysfunction-associated steatohepatitis (MASH) remain a critical need. The NASH Clinical Research Network (CRN) provides an extensive dataset of children and adolescents with biopsy-confirmed MASLD and MASH, including detailed clinical phenotyping and metabolomics data. This study aimed to identify and validate a robust screening panel for pediatric MASH using clinical and metabolomic biomarkers from a cross-sectional sample of youth enrolled in one of three NASH CRN studies (TONIC, DB1, and DB2), along with healthy controls.

Method: Untargeted metabolomics analysis was performed on fasting serum samples using liquid chromatography-mass spectrometry (LC-MS). Clinical assessments included anthropometrics, blood lipids, liver enzymes, and measures of glucose and insulin metabolism. MASLD/MASH status was determined by liver biopsy for NASH CRN participants and MRI for controls. A machine learning pipeline was developed to train a classification model. Clinical features were selected using the Kolmogorov-Smirnov test ($p < 0.05$), and the metabolomics feature set was initially reduced to the 52 metabolites that were assigned non-zero coefficients during LASSO regression. Feature importance was ranked using CatBoost, a gradient-boosted decision tree algorithm. The top 10 annotated metabolites, based on feature importance, were included in the final CatBoost model. The

model underwent hyperparameter tuning, and data were split into training, validation, and test sets to ensure robust classification.
Results: The cohort included 587 children aged 5–18 years, 70% male, with a mean BMI z-score of 2.35 ± 0.84, and 72% identifying as Hispanic. Among the participants, 391 were diagnosed with MASH (21% Zone 3 pattern, 41% Zone 1 pattern, and 38% definite MASH), while 196 were non-MASH. The model incorporated eight clinical variables: AST, ALT, GGT, platelets, HOMA-IR, BMI z-score, TG:HDL ratio, and alkaline phosphatase. Metabolite features prioritized by the model included amino acid derivatives (cysteine-glutathione disulfide, argininosuccinic acid, glutamic acid), the microbial byproduct indole, the polyamine diacetylspermine, and lipid-associated metabolites (oleic acid, methyl decanoate, LysoPC(16:1), PC(40:5), and PE(38:9)). The final model achieved an AUROC of 0.88, with 92% sensitivity and 71% specificity.
Conclusion: The screening panel integrating clinical and metabolomics features demonstrates high potential to differentiate between pediatric MASH and non-MASH, surpassing previous diagnostic tools with an AUROC of 0.88. Capitalizing on the depth provided by metabolomics analysis, this model offers a comprehensive approach to characterizing pediatric MASH. Future directions include validating the model's predictive performance in a longitudinal cohort.

WED-422

The diagnostic ability for hepatic steatosis by attenuation imaging using MRI-PDFF as reference standard; a prospective multicenter study in Japan

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Background and aims: Attenuation imaging have been wide-spread as the non-invasive methods using ultrasound for diagnosing hepatic steatosis. We aimed to estimate the diagnostic ability of Attenuation Imaging(ATI) for diagnosing the degree of hepatic steatosis by magnetic resonance imaging(MRI)-based proton density fat fraction (PDFF) as reference standard.
Method: We performed the prospective, multicenter and large cohort study of 1059 patients with chronic liver disease who underwent ATI and MRI-PDFF from September 2021 to March 2023. Steatosis grade was defined as grade 0 (S0) with MRI-PDFF <5.2%, grade 1 (S1) with 5.2% ≤ MRI-PDFF <11.3%, grade 2 (S2) with 11.3% ≤ MRI-PDFF <17.1%, or grade 3 (S3) with MRI-PDFF ≥17.1%. ATI values were measured five times and defined as the median of five measurement values with IQR/Median≤0.3 and R^2 value ≥0.7. In patients with 10 valid CAP measurements, IQR/median >30% was defined as unreliable. Patients with SCD ≤25 mm were evaluated using the M probe and patients with SCD > 25 mm were evaluated using the XL probe.
Results: Median age was 61 years old and there were 109 (10.3%) patients with HBV, 100 (9.4%) with HCV, 5 (0.5%) with HBV and HCV, and 845 (79.8%) with nonBnonC including 573 (54.1%) with MASLD. The correlation coefficient (CC) for ATI and log MRI-PDFF was strong correlation(r = 0.78). The ATI values according to the degree of hepatic steatosis using MRI-PDFF as reference standard were significantly increased with the progression of hepatic steatosis grade (P < 0.001). Area under the receiver operating curve(AUROC) and cutoff values of ATI for detecting ≥S1, ≥S2 and S3 steatosis using MRI-PDFF as reference standard were 0.91(95%CI; 0.89–0.92) and 0.65(dB/cm/MHz), 0.93(95%CI; 0.91–0.94) and 0.69(dB/cm/MHz), 0.91(95%CI; 0.89–0.93) and 0.72(dB/cm/MHz), respectively. For the 562 out of 1059 patients, Controlled Attenuation Parameter(CAP) were also measured. The correlation coefficient (CC) for ATI and log MRI-PDFF was significantly higher than that for CAP and log MRI-PDFF (P < 0.001). CC for CAP and log MRI-PDFF in the BMI ≥30 kg/m^2 groups were significantly lower than those in the BMI<30 kg/m^2 groups, respectively, but CC for ATI and log MRI-PDFF were not. ATI and CAP according to hepatic steatosis grade increased significantly with increasing hepatic steatosis grade. The AUROCs for ATI in detecting ≥S1, ≥S2 and S3 steatosis were significantly higher than that for CAP (P = 0.004, <0.001 and <0.001).
Conclusion: ATI is a useful non-invasive method for diagnosing hepatic steatosis.

WED-423

Risk factors for hepatic steatosis- a study of deceased liver donors

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Background and aims: Higher degrees of hepatic steatosis in liver donors are associated with higher rates of primary nonfunction and poorer liver transplant recipient outcomes. Therefore, assessing steatosis is an important factor to consider when selecting a liver donor. While there are some imaging techniques and basic calculators to non-invasively evaluate steatosis, liver biopsy with histologic analysis remains the gold standard. In this study we utilized a large, national donor database to identify risk factors for biopsy proven hepatic steatosis.
Method: Using the Scientific Registry of Transplant Recipients (SRTR) database, all deceased liver donors in the United States between 1987–2024 older than 18 years with recorded macrovesicular steatosis that was determined from a liver biopsy assessed by a pathologist were included in the study. Risk factors for hepatic steatosis were evaluated using univariate and multivariate logistic regression with least squares means and Tukey-Kramer adjustment for multiple comparisons. A binary outcome of less than or greater than 30% steatosis was used in statistical analyses. P < 0.05 was considered significant.
Results: 63,885 deceased liver donors met criteria to be included in the study, of which 53,433 (83.6%) had less than 30% and 10,452 (16.4%) had greater than or equal to 30% biopsy proven macrovesicular steatosis. After adjusting for covariates, the following variables were identified as independent risk factors for having greater than 30% steatosis on liver biopsy: female sex (OR = 1.21, p < 0.05), Hispanic ethnicity (OR = 1.28, p < 0.05), higher body mass index (BMI) (OR = 1.06, p < 0.0001) higher total bilirubin (OR = 1.13, p < 0.01), higher hemoglobin A1c (OR = 1.10, p < 0.01). Donors without a history of heavy alcohol use were at a decreased odds of having > 30% steatosis compared to those that did (OR = 0.59, p < 0.001).
Conclusion: Our outcomes demonstrate that sex, ethnicity, BMI, total bilirubin, Hgb A1c, and heavy alcohol use are independent risk factors for having greater than 30% macrovesicular steatosis on liver biopsy.

These results may inform transplant surgeons of steatosis when selecting liver donors when a biopsy is not able to be done.

WED-424

Fibroscan-based screening to determine the prevalence and severity of steatotic liver disease in type 1 diabetes – an australian quantentary centre experience

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Background and aims: Type 2 Diabetes (T2D) is one of the strongest risk factors for the development of Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD), but the association with Type 1 DM (T1D) is less clear. Patients with T1D are at increased risk of hepatic steatosis due to traditional metabolic risk factors and also T1D-specific factors. There are limited epidemiological data for the prevalence of steatosis in T1DM, and no recommendations in EASL or AASLD guidelines on appropriate screening for MASLD. Here we prospectively screened patients with T1D for steatosis and fibrosis by in comparison to a population of T2D. Secondary aims were to determine clinical factors associated with MASLD and significant fibrosis, and the sensitivity of non-invasive blood markers for screening for significant fibrosis.
Method: ProspectiveFibroscan® assessment of consecutive patients attending outpatient T1D & T2D diabetes clinics was undertaken over a 9 month period in 2024. Steatosis was defined as CAP > 250 db/m^2 for M probe, CAP > 263 db/m^2 for XL probe.MASLD was defined by the AASLD 2023 consensus criteria. Significant fibrosis was defined as LSM ≥8.0 kPa. Clinical records were assessed for severity of diabetes, complications, and presentations related to major adverse cardiac events (MACE). FIB-4score ≥1.3 and NAFLD-fibrosis score ≥ - 1.455 were considered at risk for advanced fibrosis.
Results: Fifty four patients with T1D and 57 with T2D were assessed. For T1D, prevalence of steatosis and significant fibrosis were 48% and 17% respectively. Of those with steatosis, all met the definition for MASLD, independent ofHbA1c. Significant fibrosis was associated with higher BMI (37 vs 28 kg/m^2, p = 0.001), ALT (34 vs 21 U/L, p = 0.002), and recurrent unexplained hypoglycaemia (67% vs 4%, p = 0.028) but male sex (33% vs 44%), median duration of diabetes (31 yrs vs 24 yrs), HbA1c (8.0% vs 8.2%), MACE outcomes, microvascular and macovascular complications were not significantly different. Application of non-invasive tests in T1D cohort showed FIB-4 score had a sensitivity of 22% and specificity of 80% while NAFLD-fibrosis scores had a sensitivity of 67% and specificity of 38% to detect advanced fibrosis. In comparison in T2D, the prevalence of steatosis and significant fibrosis were 84% and 42%. Significant fibrosis was also associated with BMI (34 vs 28 kg/m^2, p = 0.002), ALT (42 vs 27, p = 0.033) and recurrent unexplained hypoglycaemia (50% vs 18%, p = 0.020). FIB-4 score had a sensitivity of 73% and specificity of 67%, and NAFLD-fibrosis scores had a sensitivity of 95% and specificity of 67% to detect advanced fibrosis.
Conclusion: Fibroscan-based screening in a quaternary diabetes clinic population showed a high prevalence of both steatosis and significant fibrosis for T1D but not to the same level as T2D. Significant fibrosis is associated with high BMI, ALT and also unexplained recurrent hypoglycaemia in both T1D and T2D. Non-invasive tests performed poorly to screen for advanced fibrosis in people with T1D and T2D.

WED-425

Validation of proposed non-invasive criteria for resmetirom treatment in metabolic-associated liver disease in clinical practice

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Background and aims: Resmetirom is the first FDA-approved drug for the targeted treatment of metabolic-associated liver disease (MASLD) in F2–F3 patients with steatohepatitis (MASH), initially excluding those with mild fibrosis or cirrhosis. Non-invasive criteria have been proposed for initiating treatment; however, these have not yet been validated in clinical practice. We aimed to evaluate the validity of proposed criteria for initiating resmetirom treatment in fibrotic MASH in clinical practice.
Method: Cross-sectional study of 1281 patients from the Hepamet registry with liver biopsy, comorbidity assessment, analytical profile, transient elastography (TE), and CAP. Fibrotic MASH was considered as fibrosis stage 2 and 3 with presence of MASH. A comprehensive review of international guidelines and expert consensus up to November 1, 2024, focusing on therapeutic indications for resmetirom and criteria for referral to specialists: a) Noureddin criteria for treatment: CAP > 280 dB/m, ALT > 20 UI/L in men and 17 UI/L in woman, TE > 10 kPa and TE<20 kPa, platelets > 140; b) AASLD Practice Guidance for treatment: TE 8–15 kPa; c) EASL guidelines for referring patients: FIB-4 > 2.67 or FIB-4 1.30–2.67 and TE > 8 kPa; d) AASLD guidelines for referring patients: FIB-4 > 2.67 or FIB-4 1.30–2.67 and TE > 12 kPa.
Results: MASH was identified in 44% (567/1281) of the population, while the distribution of fibrosis stages was as follows: F0 in 26% (331/1281), F1 in 26% (330/1281), F2 in 18% (227/1281), F3 in 20% (259/1281), and F4 in 10% (134/1281). Considering the primary endpoint, 22% (281/1281) of patients exhibited fibrotic MASH (F2 and F3 with MASH). However, only 31% (using AASLD therapeutic criteria) to 67% (using EASL referral criteria) of these patients met the treatment eligibility criteria under any strategy. Treatment-focused criteria included a higher proportion of patients at early fibrosis stages (approximately 45%), whereas referral-focused criteria included more patients with cirrhosis (around 25%). Consequently, false positive and false negative rates ranged from 26% to 45% and 32% to 59%, respectively. Sensitivity and specificity were: a) Noureddin criteria: 41% and 74%; b) AASLD treatment criteria: 53% and 55%; c) EASL referring criteria: 68% and 60%; d) AASLD referring criteria: 46% and 73%. All strategies demonstrated AUROCs below 0.65, with the EASL referral guidelines achieving the best performance (AUROC

0.63). Additionally, EASL-based referral criteria yielded the most favorable outcomes, identifying 32% (175/552) of patients compared to 13% (84/647) (p = 0.0001). These results were further corroborated by Cohen's kappa statistics and decision curve analysis.
Conclusion: The diagnostic performance and reliability of the proposed non-invasive criteria for initiating resmetirom treatment and for reffering patients to specialized units were suboptimal. More than half of the indicated patients (fibrotic MASH) would not receive treatment under these criteria.

WED-429

The utility of noninvasive tests - LIVERFASt, FIB4 and vibration-controlled transient elastography (VCTE, Fibroscan) - in the initiation and monitoring of the therapy with TNR-beta agonist (resmetirom) in MASH patients

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Background and aims: Resmetirom therapy (RT) was recently approved by the FDA for non-cirrhotic MASH with fibrosis. The impact of RT on noninvasive tests (NIT) has not been assessed in real-life patients (pts). LIVERFASt (LFAST) is a new blood-based NIT that assesses liver fibrosis, activity, and steatosis, potentially useful in monitoring pts under RT. The aim was to assess retrospectively the dynamic of NITs in initiating/monitoring of pts ongoing RT [fibrosis, activity and steatosis progression rate (PR) and mean change from baseline].
Method: Pts with baseline and repeated either NITs [LFAST, vibration-controlled transient elastography (VCTE) and FIB4] during RT have been included. LFAST is a blood-based test that generates scores (0.00–1.00) proportional to the severity of fibrosis, activity, and steatosis. Statistics assessed PR between baseline (t0) and repeated (t1) NITs using repeated measurements ANOVA, descriptive and sensitivity (for GLP-1 analog treated pts) analysis.
Results: 24 eligible patients have been enrolled without RT discontinuation (42% 100 mg-dose), 46% male, 54% T2D, mean (se) age 59 (2), BMI 33 (1), ALT 48 (6), AST 36 (5), platelets 237 (11), FIB4 1.46 (0.13). Using LFAST and VCTE, baseline prevalence of F2F3 were 54% and 55%. Median (range) delays (months) t0-t1 were 6.4 (4.3;7.9) for LFAST and 5.1 (2;7.4) for FIB4. 52% patients t0-FIB4 ≥1.3 and 15 patients already had t1-FIB4, without significant change for FIB4, ALT or AST (1.62 vs 1.68), despite platelets count improvement (241 vs 226*109, p = 0.04). 6 patients that had concomitant GLP-1 analogs (FIB4 1.54 vs 1.57, p = ns). Only two patients had repeated VCTE/CAP (kPa/dB/m) with changes in LSM of 0.4/87 and in CAP of 1/10. Up to date 6 patients had achieved t1-LFAST: median fibrosis (0.39 vs 0.39), steatosis (0.62 vs 0.53), activity (0.30 vs 0.34). The median (range) PR t0-to-t1 per month were: for FIB4 –0.028 (–0.28;1.00) and for LFAST fibrosis 0.006 (–0.02;0.05), steatosis –0.009 (–0.09;0.01) and activity 0.002 (–0.07;0.03). The mean (se) decreases in total cholesterol [–18 (11) mg/dl] had no significant impact in Apolipoprotein A1 [–4.2 (8.0) mg/dl] and LFAST score [0.02 (0.02)].
Conclusion: Initiation of RT based on non-invasive assessment of patients using LFAST, FIB4 (fibrosis only) and VCTE is efficient and allows further non-invasive monitoring. A rapid trend in steatosis improvement was observed.

WED-430

Best buys to diagnose and treat metabolic dysfunction-associated steatohepatitis among people living with diabetes type 2: a multi-country generalized cost-effectiveness analysis

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis is a highly prevalent condition among people with type 2 diabetes (T2D). T2D is a major risk factor for more severe stages of liver disease (e.g., cirrhosis and hepatocellular carcinoma) resulting in a high economic burden globally. We aimed to identify cost-effective management approaches to detect, prevent and treat MASH with liver fibrosis in people with T2D.
Method: A generalized cost-effectiveness analysis was conducted from a health system perspective in 12 countries representing all six WHO regions: Brazil, Chile, Germany, Italy, Japan, Saudi Arabia, South Africa, Spain, Sweden, Tanzania, Thailand and United States of America (USA). Using an 80% coverage level for each approach, 14 approaches, including the standard of care (SoC) defined as the absence of any systematic intervention, were considered: (1) Fibrosis-4 (FIB-4) screening; (2A) FIB-4 + vibration-controlled transient elastography (VCTE); (2B) FIB-4 + enhanced liver fibrosis test (ELF);

(3A) FIB-4, VCTE, hepatologist, intensive lifestyle intervention (ILI); (3B) FIB-4, ELF, hepatologist, ILI; (4A) FIB-4, VCTE, hepatologist, resmetirom; (4B) FIB-4, ELF, hepatologist, resmetirom; (5A) FIB-4, VCTE, hepatologist, resmetirom, ILI; (5B) FIB-4, ELF, hepatologist, resmetirom, ILI; (6A) FIB-4, VCTE, hepatologist, semaglutide; (6B) FIB-4, ELF, hepatologist, semaglutide; (7A) FIB-4, VCTE, hepatologist, semaglutide, ILI; (7B) FIB-4, ELF, hepatologist, semaglutide, ILI. A cohort state-transition model simulated liver fibrosis progression/regression and the 14 approaches' impact over the cohort's lifetime among 10 health states (from no fibrosis to death). Outcomes of interest were the average cost-effectiveness ratios (ACERs) and incremental cost-effective ratios. The comparator was the null scenario. The lower the ACER, the more cost-effective the approach, for a given threshold.

Results: The SoC, had the lowest ACERs in 8 of the 12 countries (not in Chile, Germany, Saudi Arabia, and USA). Treatment with ILI, after screening through ELF or VCTE, was found to be cost-effective in all countries. ILI and treatment with semaglutide were cost-effective in 11 out of 12 countries (not Tanzania) and ILI with resmetirom was found to be cost-effective in 7 out of 12 countries (not Brazil, Chile, South Africa, Tanzania, and Thailand). One GDP per capita was used as threshold for each country.

Conclusion: Screening approaches that are followed by both lifestyle and pharmacological treatments aimed at tackling liver fibrosis in patients with T2D and liver fibrosis with MASH were found to be cost-effective based on the reported and estimated costs in the majority of the countries studied. These "best buys," evaluated in relation to the willingness to pay threshold of each country, can inform health policy decision-making.

WED-432

Noninvasive risk-based surveillance of hepatocellular carcinoma in patients with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over 30% of the general population and is the most rapidly rising cause of hepatocellular carcinoma (HCC). Current guidelines recommend HCC surveillance in patients with cirrhosis when the annual HCC incidence exceeds 1% without specifying the role of noninvasive tests in patient selection. Thus, we aimed to define noninvasive test thresholds to select patients with MASLD for HCC surveillance.

Method: This cohort study included patients with MASLD who had received vibration-controlled transient elastography (VCTE) examination at 16 centres across the US, Europe, and Asia, of which data were collected prospectively at 14 centres. Adult patients aged 18 years or older with hepatic steatosis diagnosed by histologic methods (steatosis in ≥5% of hepatocytes) or imaging studies (ultrasonography, computed tomography or magnetic resonance imaging, or controlled attenuation parameter ≥248 dB/m by VCTE) and available fibrosis-4 index (FIB-4) and VCTE results were included. The primary outcome was incident HCC, with non-liver-related death treated as a competing event.

Results: A total of 12,950 patients had FIB-4 and liver stiffness measurement (LSM) (mean [SD] age 51.7 [13.9] years; 5,316 [41.1%] male). At a median follow-up of 47.7 (IQR, 23.3–72.3) months, 109 (0.8%) patients developed HCC. FIB-4 was below the low cutoff (<1.3 for patients aged <65 years, and <2.0 for patients aged ≥65 years), between the low cutoff and <2.67, 2.67–<3.25, and ≥3.25 in 66.3%, 23.9%, 3.4%, and 6.4% of patients, and the corresponding annual HCC incidence was 0.07%, 0.17%, 0.77%, and 1.18%, respectively. As a standalone test, the annual HCC incidence exceeded 0.2% when LSM was ≥10 kPa and 1% when LSM was ≥20 kPa. If LSM was performed as a second step only among patients with FIB-4 above the low cutoff, the annual HCC incidence exceeded 0.2% when LSM was ≥10 kPa and 1% when LSM was ≥15 kPa. The performance of the noninvasive tests was consistent across subgroups based on age and the presence of diabetes.

Conclusion: HCC surveillance should be offered to MASLD patients with FIB-4 ≥3.25 or LSM ≥20 kPa. When a two-step approach is adopted, LSM ≥15 kPa in patients with increased FIB-4 predicts a high risk of HCC.

WED-433-YI

Translating genetic information into clinical practice: Improved decision-making in advanced fibrosis assessment

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Background and aims: Genetic information is not yet used for the clinical diagnosis of advanced fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Here we investigated whether incorporating genetic information regarding *PNPLA3* and *TM6SF2* into existing non-invasive fibrosis scoring systems could enhance the predictive accuracy, particularly in terms of reducing indeterminate diagnostic zones.
Method: Data were collected from a cohort of 573 patients with biopsy-proven MASLD. All participants underwent liver stiffness measurement (LSM), serum marker analysis, and genotyping for *PNPLA3* (rs738409), *TM6SF2* (rs58542926), and other relevant SNPs. We evaluated the benefit of adding genetic information to existing non-invasive tests (NIT)—including the Agile 3+, Fibrosis-4 (FIB-4) index, and NAFLD fibrosis score (NFS). Decision curve analysis (DCA) was performed to determine the net benefit of adding genetic information, and we analyzed the impact on reducing indeterminate zones.
Results: Integration of *PNPLA3* and *TM6SF2* genotypes improved the predictive accuracy of existing models, particularly by reducing the indeterminate diagnostic zones Additionally, integrating genotype data into existing NIT significantly improved their performance, as demonstrated by higher net benefits compared to models without genetic information. The net benefit at a 30% threshold increased from 18.7 to 19.0 per 100 patients with genotypes for Agile 3+, increased from 12.7 to 13.7 for the NFS, and increased from 9.2 to 12.1 for FIB-4.
Conclusion: Incorporating genetic data into NIT for MASLD enhanced their predictive accuracy. Addition of genetic data particularly reduced indeterminate zones, thereby offering a more reliable tool for identifying patients at risk for advanced fibrosis. This approach may improve clinical decision-making and outcomes.

WED-434

Use of noninvasive tests (NITs) to diagnose and follow non-alcoholic steatohepatitis (NASH) with liver fibrosis patients treated with resmetirom

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Background and aims: MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy-confirmed NASH and fibrosis. 966 patients with biopsy-confirmed NASH were randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo once daily. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis (NR) or ≥1-stage improvement in fibrosis with no worsening of NAS (FI). Both Week 52 liver biopsy endpoints, NR and FI, were achieved. Resmetirom was recently approved for the treatment of adult patients with noncirrhotic NASH and liver fibrosis consistent with F2 to F3 stages. Expert guidances recommend treatment with resmetirom based on staging fibrosis using FibroScan VCTE. EASL recommends stratifying patients using FIB-4. Most guidelines recommend using VCTE cutoffs lower than 10≤15 kPa for treatment.
Method: We assessed results from baseline noninvasive tests (FIB-4, VCTE) against biopsy results in MAESTRO-NASH to measure how well they diagnosed noncirrhotic patients with NASH (consistent with F2–F3 stages at baseline). We assessed the utility of a lower VCTE cutoff (8.5 to <10 kPa) in capture of F2 and F3 patients who otherwise would be missed. Also evaluated was the addition of MRE/MRI-PDFF or ELF to FibroScan VCTE to assess diagnostic utility.
Results: FIB-4 poorly predicted patients in the non-cirrhotic fibrosis stages: F2 (60% patients fell into low-risk) and F3 (40% fell into low-risk). Including a lower cutoff of VCTE (8.5 to <10 kPa) captured F1B (34% 8.5≤10 kPa) and many F2 (25% 8.5≤10 kPa) and F3 patients (19% 8.5≤10 kPa). The addition of MRE/MRI-PDFF to FibroScan VCTE increased diagnostic accuracy for F2/F3 to 68% and F4 to 81%. The addition of the ELF to the FibroScan VCTE suggested that a low ELF result paired with high VCTE may warrant a VCTE repeat.
Conclusion: Identification of patients with NASH F2 to F3 was achieved with FibroScan and VCTE. F1B are F2 equivalent (F1B is moderate fibrosis on biopsy). Patients with fibrosis stage F4 were effectively ruled out. In addition to FibroScan VCTE, practitioners may consider expanded noninvasive criteria (ELF, MRE) to help refine fibrosis staging.

WED-435

Development of a novel model using machine learning algorithms to predict absence of metabolic associated steatotic liver disease in healthy and patient trial volunteers. A population screening tool

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Background and aims: Metabolic associated steatotic liver disease (MASLD) affects approximately one in four of the global adult population, and ranges in severity from benign fatty liver infiltration, to hepatitis, cirrhosis, hepatocellular carcinoma, and death. MASLD has important implications for clinical trial volunteers as an occult co-morbid condition – there is evidence that MASLD modulates drug metabolism, with studies suggesting that Grade 3–4 liver reactions are four times more common in healthy volunteers with probable MASLD than without. Halting promising potential new drug therapies in clinical development due to false positive liver safety signals. Additionally, the tool could be used to screen the population for those not exhibiting symptoms.
Method: An observational cross-sectional study of 1507 clinical trial volunteers was completed, collecting bioimpedance vector analysis (visceral fat%, total body fat% and skeletal muscle %), anthropometric measurement and laboratory bloods. A FibroScan is performed as a pragmatic gold standard 'outcome' for MASLD using >248 dB/m or >7.6 kPa as a positive. The data was divided into a training set of (75%) used to build the model, (25%) used to validate its predictive accuracy. Lasso Logistic Regression, Elastic Net Logistic Regression, Random Forest and XGBoost were then compared for model with highest performance. SHAP analysis was used to identify feature importance and remodelling with reduced features to simplify clinical data needed for the model was performed.

Results: All models achieved an AUROC 0.91 or better. Random Forest produced the highest performing model using all 18 features achieving AUROC 0.92, Accuracy 0.866, F1 score 0.705 and NPV 0.932. A reduced feature model developed with 7 features (Waist circumference, WHR, BMI, ALT, ALP, weight, age) achieving AUROC 0.91, Accuracy 0.879, F1 Score 0.714 and NPV 0.923.
Conclusion: The model developed produces a highly accuracy tool which using waist circumference, height, weight, ALT, ALP and Age – readily available in clinical settings. Allowing research teams to identify prospectively confirm enrolled volunteers with pre-clinical MASLD. This is a group where the effective detection of concomitant, occult fatty liver disease is possible and has significant implications for adverse drug reactions in first-in-human studies. Feasibility in the health screening setting is now starting for earlier identification and intervention.

WED-436
Identifying risk factors linked to metabolic-associated steatotic hepatitis in people living with HIV in Newark, New Jersey
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Background and aims: People living with HIV (PLWH) have a high incidence of comorbid conditions increasing their risk for metabolic-associated steatotic hepatitis (MASH). Limited data exists on risk factors that contribute to the highest risk for MASH, particularly among PLWH. In this study, we analyze several possible demographic and metabolic risk factors to better understand their contribution to MASH risk in this population.
Method: A cross-sectional study was conducted at two HIV clinics in Newark, NJ, USA between July 2024 and October 2024. Liver elastography was used to measure the controlled attenuation parameter (CAP) in PLWH attending these clinics. Eligible participants were over 18 years old, fasting for at least two hours prior to testing, and had an HIV viral load <200 c/ml. Individuals with chronic hepatitis B or C or excessive alcohol consumption (AUDIT score >5) were excluded. Participants were categorized into two groups based on CAP values: Group 1 (CAP consistent with S0-S1) and Group 2 (CAP consistent with S2-S3). Epidemiologic data, anthropometric measurements, comorbid conditions, and current medications were collected, and visceral adiposity index (VAI) was calculated. Risk factors for MASH were analysed using bivariate and multivariate methods.
Results: A total of 222 patients underwent liver elastography, with 143 patients categorized into Group 1 and 79 into Group 2. Descriptive results indicate a higher proportion of males in both groups, with Group 1 having 69.2% and Group 2 at 59.5%. Blacks are the majority race (60.1% in Group 1, 53.2% in Group 2). Hispanic and non-Hispanic representation is consistent across groups (32.2%–32.9% and 67.1%–67.8%, respectively). Older participants (>50 years) are more prevalent in Group 2 (82.3%) compared to Group 1 (63.4%). No statistically significant differences were found between the groups in gender, race, ethnicity, use of tenofovir alafenamide, second-generation integrase inhibitors, diabetes mellitus, or concurrent statin use ($p \geq 0.05$). Significant differences were identified in age ($p = 0.0086$), BMI ($p = 0.0001$), waist-hip ratio ($p = 0.0012$), and visceral adiposity index (VAI) ($p = 0.0004$). High cholesterol (total cholesterol >200 mg/dL) showed a weak association with MASH ($p = 0.04$). Additionally, results indicated Black PLWH had a 36% prevalence of excessive fat accumulation in the liver.
Conclusion: The strongest predictors of MASH were VAI, waist-hip ratio, BMI, and age. Refining MASH screening recommendations for PLWH involves prioritizing high-risk individuals based on specific metabolic indicators, integrating non-invasive tools into routine HIV care, and addressing health disparities through resource allocation and tailored guidelines. These efforts can improve early detection, intervention, and overall outcomes for this vulnerable population.

WED-437
suPAR levels independently discriminate patients with at-risk MASLD
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading global cause of liver fibrosis. Early identification of patients at risk for significant fibrosis, which can progress to cirrhosis and other liver-related complications, relies heavily on non-invasive tests. The soluble urokinase plasminogen activator receptor (suPAR), an inflammatory biomarker linked to adverse outcome in various chronic conditions, has shown promise in liver disease and may offer added value in identifying MASLD at risk. This study aimed to assess the predictive value of suPAR for significant fibrosis in patients with MASLD and to compare its performance with other well-established non-invasive fibrosis scores, including FIB-4, APRI, NFS, and FAST. Finally, we explored whether suPAR adds predictive value or enhances current at-risk prediction models.
Method: From 2020 to 2021, we prospectively enrolled 259 patients with MASLD at the Department of Gastroenterology and Hepatology, Charité, Berlin, Germany. Each patient's epidemiological, medical, and laboratory data were systematically collected. At enrollment, all patients underwent a vibration-controlled transient elastography (by FibroScan®), routine laboratory work-up, as well as measurement of suPAR levels. Using non-invasive fibrosis assessments (FibroScan®, ultrasound, and various scoring models), we stratified patients into two groups based on their risk for at least significant fibrosis (≥8.0 kPa or sonographic signs of significant fibrosis). We then compared suPAR levels between the low- and high-risk groups and analyzed each scoring system's AUROC for fibrosis detection.
Results: In total, 66.41% (n = 172) patients were grouped in the low-risk group and 33.59% (n = 87) in the high-risk group. suPAR showed a good predictive value for significant fibrosis, still, its AUROC (0.813) was significantly inferior to the FAST and FIB-4 scores (0.865; $p = 0.012$ and 0.874; $p = 0.036$, respectively). suPAR performed non-inferior to the APRI and NFS scores. In both univariate and multivariate regression analyses, suPAR demonstrated the highest discriminatory power (OR: 1.787; $p < 0.001$ and OR: 1.263; $p = 0.013$) among all single laboratory and epidemiological parameters assessed for identifying higher stages of fibrosis (at-risk MASLD).
Conclusion: suPAR shows a good predictive power in the detection of significant stages of fibrosis compared to other, well-established scores, only FIB-4 and FAST performed better in our cohort. Still, its high discriminatory power on at-risk MASLD warrants the ability for suPAR in enhancing prognostic scores on fibrosis detection in the future.

WED-438

Systematic review of care pathways for metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background and aims: The rising prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) demands diagnostic approaches to identify advanced liver fibrosis while simultaneously reducing unnecessary referrals of mild cases. Guidelines advocate clinical care pathways using a combination of non-invasive tests (NITs). However, the optimal sequence for efficient detection of advanced fibrosis across healthcare levels has not been unequivocally established. The aim of this paper is to provide a systematic review of studies on clinical care pathways for detecting and risk stratifying advanced fibrotic MASLD.

Method: A systematic literature search identified studies describing care pathways screening for advanced fibrotic MASLD. Articles were included if they described a care pathway at least consisting of: a well-defined group of patients, a well-defined structured plan of care, and a pathway applicable to several aspects of care (and not merely diagnosis). The search strategy was applied in the databases MEDLINE, Embase, Cochrane Library, and Scopus and finalized on October 4th, 2024. Study selection was conducted by two independent reviewers.

Results: Nine studies met the criteria: 4 one-tier, 4 two-tier, and 1 three-tier pathway. Study size ranged from 162 to 3,669, encompassing a total of 11,566 participants. Pathway populations included patients with type 2 diabetes mellitus (T2DM) (4 studies), a broader range of cardiometabolic risk factors (1 study), confirmed MASLD (3 studies), or the general population (1 study). FIB-4 and VCTE were the most commonly used NITs, followed by NFS and APRI. Seven pathways ultimately stratified their patients into low- and high-risk groups for advanced fibrosis, two added an intermediate-risk category. The number needed to screen (NNS) for hepatology referral varied significantly: 2–19 in T2DM, 5–12 in confirmed MASLD, and 49 in the general population. NNS for advanced fibrosis detection ranged from 11 to 89 in T2DM and 12 to 33 in confirmed MASLD. All studies concluded that patient risk identification improved. However, the studies differed in their definition of advanced fibrosis. Attendance rate progressively declined at each subsequent pathway step.

Conclusion: Clinical care pathways with NITs can align patient flows and organize transmural care for MASLD. Implementation of care pathways for MASLD showed a considerable amount of heterogeneity in the current evidence. The NNS is acceptably low when T2DM is present, but the high NNS in the general population argues against screening in this context. Evidence for screening with NITs in large cohorts with cardiometabolic risk factors for fibrotic MASLD is lacking and is very much awaited.

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WED-439

Comparison of FibroScan© and iLivTouch© for liver stiffness and steatosis assessment in patients with MASLD

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Background and aims: Noninvasive assessment of liver stiffness and steatosis is critical for managing MASLD, given its rising prevalence and risk of progression to fibrosis and cirrhosis. Vibration-controlled transient elastography (VCTE) with FibroScan remains the clinical benchmark in clinical practice. Recently, the iLivTouch device emerged as an alternative. This study evaluates the concordance of FibroScan and iLivTouch in assessing liver stiffness and steatosis in Caucasian patients with MASLD.

Method: This study included 56 adult patients with MASLD, recruited consecutively. Clinical, biochemical and anthropometric data were recorded. Liver stiffness and hepatic steatosis were assessed using FibroScan (Echosens, France) and iLivTouch (Wuxi Hisky Medical Technologies Co., Ltd., China) on the same day. FibroScan measurements included liver stiffness in kPa (F0 – F1: ≤7 kPa, F1 – F2: 7.1–8.6 kPa, F2 – F3: 8.7–9.5 kPa, F3: 9.6–10.2 kPa, F4: >10.3 kPa) and steatosis using CAP (dB/m). iLivTouch measurements included liver stiffness (kPa) categorized into fibrosis stages based on the device-specific cut-offs for MASLD (F0 – F1: ≤8 kPa, F1 – F2: 9–11 kPa, F2 – F3: 12–14 kPa, F3: 15–17 kPa, F4: >17 kPa) and ultrasound attenuation parameter (UAP) for steatosis severity (absent: <244 dB/m, mild: 244–269 dB/m, moderate: 269–296 dB/m, severe: >296 dB/m). The diagnostic agreement between the two devices was analyzed by Spearman correlation and inter-rater agreement (k).

Results: A total of 56 adult patients with MASLD were included in the study. Patients' median age was 60 (21–77) years; 32 (57.1%) patients were males. The median BMI was 29.7 (22.5–45.5) kg/m². Laboratory evaluations showed a median ALT level of 24.5 (9–140) U/L. The agreement between FibroScan and iLivTouch, evaluated using continuous variables, showed a moderate-to-good correlation (r_s = 0.726, 95% CI 0.574–0.830, $P < 0.001$) for liver stiffness values. Similarly, CAP (FibroScan) and UAP (iLivTouch) values for steatosis demonstrated acceptable correlation (r_s = 0.742, 95% CI 0.597–0.840, $p < 0.001$).

When evaluating agreement across fibrosis stages (F0–F1, F2, F3, F4) and steatosis grades (mild, moderate, severe), FibroScan and iLivTouch showed good agreement for both liver stiffness (k = 0.79, CI 0.64–0.95, $p < 0.001$) and CAP stages (k = 0.68, CI 0.50–0.85, $p < 0.001$). Patients were further grouped into two categories: F0 – 1 - 2 (mild to moderate fibrosis) and F3 - 4 (advanced fibrosis and cirrhosis), with agreement between devices for identifying these groups showing moderate-to-good concordance (k = 0.65, CI 0.37–0.93, $p < 0.001$).

Conclusion: iLivTouch showed a good agreement with FibroScan for liver stiffness and steatosis assessment in patients with MASLD. These preliminary results suggest that iLivTouch may be a viable alternative for non-invasive evaluation, with further studies needed to confirm its broader applicability.

WED-440-YI

Effect of liver damage on telomere length in people with diabetic kidney disease

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Background and aims: Renal and hepatic changes in the pathogenesis and progression of diabetes mellitus are closely related and comorbid. Chronic kidney disease (CKD) more often manifests in type 2 diabetes (T2D) due to the influence of metabolic disorders, early microvascular damage, the activation of systemic inflammation, atherosclerotic changes, and genetics. The presence of concomitant metabolic dysfunction–associated steatotic liver disease (MASLD) worsens the course of CKD in individuals with T2D. The relative telomere length of leukocytes (RTL) is considered a prognostic marker associated with life expectancy and the frequency of complications of diabetes, including liver and renal changes. This study aimed to compare RTL in people with hepatorenal syndrome and CKD without liver damage on a background of T2D.
Method: A total of 47 people with T2D participated in the cross-sectional study. The inclusion criteria were as follows: age over 18 years, presence of T2D, and CKD. Persons were divided into 2 groups depending on the presence of MASLD: group I, with hepatorenal lesions (n = 25), and group II, with only renal lesions (n = 22). The diagnosis of MASLD was established according to the criteria of the EASL–EASD–EASO guidelines 2024 and CKD–KDIGO 2022. A standardized method of real-time quantitative monochrome multiplex polymerase chain reaction was used to determine the relative LTL. In addition, laboratory indicators of the GFR according to the EPI-CKD formula, ALT, AST, metabolic profile, and results of ultrasound examinations of the kidneys and liver were used to establish the diagnosis.
Results: The RTL in leukocytes from the group of people with combined liver and kidney pathology was significantly shorter than that in the group with only renal lesions in T2D patients (1.06 (0.97; 1.18) vs. 1.19 (1.14; 1, 36), p = 0.002), which confirms the negative effects of comorbidities on patient outcome and prognosis. An inverse correlation was found between RTL and ALT in group I (r = −0.535; p = 0.005). The RTL, with a cutoff value of 1.02, can be considered a prognostic biomarker of hepatorenal development (sensitivity of 56%, specificity of 90%). The AUROC for the model was 0.76, 95% CI 0.621–0.899 (p = 0.025).
Conclusion: The results demonstrated that hepatorenal syndrome in T2D is associated with the accelerated aging and shortening of leukocytes RTL, which could impact the course of T2D and the development of complications.

WED-445

A comparison of the prognostic value of 12 body composition markers for MASLD, at-risk MASH and Increased liver stiffness in a general population setting

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Background and aims: Excess visceral fat is the cornerstone of metabolic dysfunction steatotic liver disease (MASLD), development of metabolic dysfunction associated steatohepatitis (MASH) and fibrosis. Although body mass index (BMI) is used primarily, it might not be the body composition marker that has most prognostic value for impaired liver health. Here we compare 12 different body composition parameters and how they relate to MASLD, MASH and fibrosis.
Method: We used data from the NHANES 2017–2020 cycle, a United States population-based cohort with data on controlled attenuation parameter (CAP) and liver stiffness measurements (LSM). We selected patients with complete data on weight, height, waist circumference (WC) and hip circumference (HC). MASLD was defined as CAP ≥275 dB/m with metabolic dysfunction, MASH as FibroScan AST (FAST) score ≥0.35 and fibrosis as LSM ≥8 kPa. The prognostic value by area under curve (AUC)-analysis of a body shape index (ABSI), body adiposity index (BAI), BMI, body roundness index (BRI), fat mass (FM), HC, WC, waist to hip ratio (WHR), waist to height ratio (WHtR), waist adjusted BMI (wBMI), Weight adjusted waist index (WWI) and weight was determined for MASLD, MASH and fibrosis. Statistically significant differences were assessed by DeLong test. Non-linearity was assessed via restricted cubic splines adjusted for age, sex, ethnicity, smoking and alcohol consumption.
Results: The cohort comprised 6867 participants (age 48[32–62], 49% male) among them 41.3% had MASLD, 5.8% MASH and 8.7% fibrosis. WC obtained the highest AUC levels in the overall population for steatosis, MASH and fibrosis (AUC 0.81, 0.74 and 0.76, respectively); WHtR and BRI in male (AUC 0.83, 0.76 and 0.73, respectively) and female (AUC 0.79, 0.73 and 0.81, respectively). WC was not significantly inferior compared to WHtR or BRI in the sex-stratified analysis for all investigated outcomes. The best AUC for fibrosis was higher in females compared to males (0.81 vs 0.73). Restricted cubic spline analysis indicated non-linear associations for MASLD and fibrosis, but not for MASH. MASLD risk increased across the entire spectrum, but the increase attenuated slightly after WC >110 cm, whereas the risk of fibrosis remained stable until WC 100 cm, and started to rapidly increase thereafter.
Conclusion: Waist circumference was the body composition parameter with the highest prognostic value for MASLD, at-risk MASH, and increased LSM in a general population setting. Waist-circumference based body composition markers such as BRI or WHtR did not have significantly additional predictive value compared to waist circumference. Waist circumference should be considered as the preferred body composition parameter in individuals at risk of MASLD, MASH or fibrosis. Importantly, the risk of MASLD and MASH increases across the entire spectrum, whereas fibrosis risk only increases after waist circumference >100 cm.

WED-446-YI

Reliable quantitative multiparametric hepatic steatosis assessment by Steatoscore2.0 using routine liver ultrasound images

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Background and aims: Liver steatosis can be easily qualitative/semi-quantitative diagnosed by routine abdominal ultrasound (US) examination by mean of indirect US parameters associated with liver fat accumulation or the automated monoparametric measurement of US beams attenuation rate index. The unmet need remains a reliable quantitative US measure of liver fat content. We proposed a multiparametric method, Steatoscore2.0 (StSc) that was shown to estimate LFC from B-mode images with high correlation and agreement with the gold standard magnetic resonance LFC-based measurement (DOI: 10.1111/liv.16078). The aim of this study was to evaluate the feasibility and reproducibility of StSc using retrospectively registered abdominal US images routinely obtained for screening/diagnostic aims in a general population.
Method: We included 471 consecutive subjects (sbj) from a general population cohort (ProgeNIA including inhabitants from 4 towns in east-central Sardinia whose genetics and epidemiology of aging-related traits and diseases were prospectively studied) with available routine US abdominal images acquired during 2013–2015. In a feasibility study we investigated the percentage of sbj whose retrospectively acquired US abdominal images allowed the StSc assessment. We analyzed inter-operator reproducibility evaluating StSc assessed by two different operators [Pearson's correlation (R), Intraclass Correlation Coefficient (ICC) and Bland-Altman Analysis (BAA) with 95% limits of agreement]. Then we performed a correlation analysis between StSc and sbj characteristics: age, sex, BMI, waist circumference (WC), AST, ALT, GGT, triglycerides and Fatty liver index (FLI).
Results: The feasibility study reported a success of StSc computation equal to 92.1% (N = 434 of 471; F:M 235:199; median [IQR]: BMI 25.2 [23.0, 28.4] kg/m^2, WC 88 [81, 96] cm, StSc 2.8 [2.3 7.3] %, FLI 13.1 [5.6 32.0]). The inter-operator reproducibility analysis (N = 75 sbj) showed an R = 0.88 and ICC of 0.94; BAA revealed a non-significant bias of 0.38 and [-4.4 5.5] of 95% limits of agreements. Correlation analysis showed moderate correlations between StSc and both BMI and FLI (R of 0.42 and 0.44 for BMI, FLI, respectively, both with $p < 0.001$).
Conclusion: This pilot study demonstrated that StSc is a robust and reliable LFC quantification tool showing a very satisfactory feasibility even on retrospectively registered liver US images with very high inter-operator agreement. These results qualify StSc as a valuable first level investigation method for LFC quantification, identifying subjects from general populations that would benefit from LFC monitoring.

WED-447
The ultrasound multiparametric method Steatoscore2.0 measures liver steatosis with high inter- and intra- operator reproducibility

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Background and aims: Abdominal Ultrasound (US) is currently used to diagnose and monitor steatotic liver disease (SLD). However, there is an unmet need for quantitative US-based methods with high sensitivity and reproducibility. We recently proposed a multiparametric method, Steatoscore 2.0 (StSc), for estimating liver fat content (LFC) from B-mode images and validated against the gold standard LFC quantification by magnetic resonance. The aim of this study was to evaluate the reproducibility of StSc, through an inter- and intra-operator variability analysis.
Method: We studied 94 patients (pts) consecutively enrolled from September 2023 to October 2024 at the Hepatology Unit of the University Hospital of Pisa, Italy. US liver B-mode images were acquired according to a standardized acquisition protocol by using Esaote MyLab X8 and GE Healthcare LogiQ E9, both equipped with a convex probe (1.8–5 MHz). Three operators were involved in the study, OP1 (expert with >10 years' experience in abdominal echography), OP2 (5 years' experience), OP3 (on training). Thirty-seven pts underwent repeated B-mode acquisitions from OP1 and OP2, 44 were acquired by OP1 and OP3 and 34 by OP2 and OP3. In addition, a subset of 54 pts underwent double B-mode scans by OP3 (a/b). Finally, 14 pts were analyzed by all three operators with double acquisitions by OP3a/b. All B-mode images were processed by one specialist (>5 years' experience) and used to study the intra-/inter-operator reproducibility of the StSc measures assessed by Pearson' correlation coefficient (R), Intraclass Correlation Coefficient (ICC) and Bland-Altman analysis (BAA) with 95% limits of agreements (LoA).
Results: On the whole cohort (F:M 45:49; qualitative FLC classification S0:S1:S2:S3 26:10:33:25; mean ± standard deviation: BMI 30.4 ± 6.2 kg/m^2, age 57.2 ± 12.5 years old), inter-/intra- operator variability showed the following results:
OP1 vs OP2 on 37 pts: R = 0.94, ICC = 0.97, BAA: bias of 0.79 (p = n.s.) and LoA [−4.3 5.9];
OP1 vs OP3 on 44 pts: R = 0.93, ICC = 0.92, BAA: bias of – 0.38 (p = n.s.) and LoA [−11 9.9];
OP3a vs OP3b on 54 pts: R = 0.95, ICC = 0.97, BAA: bias of +0.70 (p = n.s.) and LoA [−5.2 6.6];
OP2 vs OP3 on 34 pts: R = 0.89, ICC = 0.94, BAA: bias of +0.70 (p = n.s.) and LoA [−6.9 7.3];
OP1 vs OP2 vs OP3 on 14 pts: ICC = 0.97, BA (OP1 vs mean(OP2, OP3)) with bias of 0.89 (p = n.s.) and LoA [−4.2 6.0].

Conclusion: StSc showed a very good performance with very high inter-/intra operator agreement (>0.89/0.95 for inter-/intra-, respectively) and high reproducibility independent from the experience of the operators in liver US. These results qualify StSc as an appropriate, reliable and cheap tool to monitor non- invasively the outcome of LFC in SLD patients in clinical practice.

WED-448
Steatotic liver disease in patients with irritable bowel syndrome- a new category? Evidence based on response to therapy

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Background and aims: Gut microbiome and permeability, as well as bile acid metabolism are altered in the setting of irritable bowel syndrome (IBS). Recent advances have found a possible link between liver steatosis and gut microbiome, thus opening the possibility of common therapeutic strategies in steatotic liver disease (SLD) and IBS. The aim of this study is to determine the prevalence of SLD in IBS patients and whether SLD can be improved by a standard treatment for IBS.
Method: From January 2023 to January 2024 241 patients with a recent diagnosis of IBS according to the ROMA IV criteria were screened for SLD by non- invasive methods: Fibroscan® determination of fibrosis and steatosis (liver stiffness and controlled attenuation parameter CAP) and Fibromax® determination of fibrosis (FibroTest) and steatosis (SteatoTest). We also determined serum levels of liver function tests. Patients were classified according to IBS category (with constipation, with diarrhea, with mixed bowel habits or unclassified). Patients received treatment with trimebutine maleate 300 mg daily and a probiotic containing Saccharomyces cerevisiae for three months and were re-evaluated.
Results: Mean age in the study group was 31.24 ± 10.92 years old, 65.1% female. IBS classification revealed 138 patients with

constipation (57.2%), 78 patients with diarrhea (32.3%) and 28 patients with mixt or indeterminate IBS (11.6%). Initial distribution according to degree of fibrosis, estimated by Fibroscan and Fibrotest revealed: 84 vs 83 F0 patients, 157 vs 144 F1 patients. No F2 values were obtained regarding liver stiffness, but Fibrotest categorized 14 patients as F2. CAP versus Steatotest revealed: 64 vs 82 S0 patients, 106 vs 132 S1 patients and 71 vs 52 S2 patients. At three months follow-up we found significantly lower values of AST and GGT in all categories, without significant changes in ALT values. Also, mean levels of liver stiffness and CAP significantly decreased in all categories: in F0: 3.4 KPa vs 2.9 KPa, in F1: 5.5 KPa vs 4.3 KPa, in S0: 198 dB/m vs 173 dB/m, in S1: 252 dB/m vs 237 dB/m, in S2: 272 dB/m vs 257 dB/m, with more patients classified as lower degrees of fibrosis and steatosis. Fibrotest reveled fewer F1 patients (54 vs 144) and fewer S2 patients (13 vs 54).

Conclusion: Rapid changes in degrees of steatosis and fibrosis under IBS treatment suggest common pathological pathways between IBS and SLD and potential reversal in the early stages.

WED-449

Exploring the evolution of circulating protein biomarkers in liver transplantation setting for MASH, ALD, and MetALD

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Background and aims: There is a significant lack of data on the utility of peripheral biomarkers (e.g. cytokines, chemokines, adipokines, and inflammatory or tissue remodeling mediators) in the non-invasive assessment of metabolic dysfunction-associated steatotic liver disease (MASLD) in the post-liver transplantation (LT) setting. This study aimed to explore whether circulating levels of selected plasma proteins could associate with graft fibrosis after liver transplantation (LT) for metabolic dysfunction-associated steatohepatitis (MASH), alcohol-associated liver disease (ALD), and metabolic dysfunction- and alcohol-associated steatotic liver disease (MetALD).

Method: This prospective cohort study included 61 adults transplanted for cirrhosis due to MASH (n = 20), ALD (n = 20), or MetALD (n = 21) between January 2019 and February 2023 in two LT centers in Spain. Plasma levels of IL-1alpha, IL-1beta, IL-6, IL-8, IL-10, IL-12p70, IL-18, MCP-1, TNFalpha, adiponectin, resistin, tPAI-1, sIL-1RI, sIL-2Ralpha, CHI3L1, CK-18 M30, CK-18 M65, IGF-1, leptin, M2BPGi and TIMP-1 were measured before LT and at 6, 12, 24 and 36 months after LT by Luminex multiplex assay or enzyme-linked immunosorbent assay (ELISA), as appropriate. The 6-month post-LT measurement was assumed as the baseline timepoint after LT without significant/advanced fibrosis. FibroScan was carried out at least 1 year after LT, and liver stiffness measurement (LSM) values <8 kPa were used to rule out significant/advanced graft fibrosis.

Results: In the pre-LT setting, all patients, regardless of the etiology, had similar levels of the biomarkers tested ($p > 0.05$), except for resistin (lower levels in ALD group vs. MASH or MetALD groups, $p < 0.001$) and tPAI-1 (higher levels in MASH group vs. ALD or MetALD groups, $p < 0.022$). When comparing pre-LT vs. 6-month post-LT timepoints, all biomarkers "normalized" after LT ($p < 0.05$), except for IL-1alpha, IL-1beta, resistin, sIL-1RI, and TNFalpha. When categorizing by etiology, only IL-6, IL-8, tPAI-1, CHI3L1, CK-18 M30, M2BPGi and TIMP-1 "normalized" in the 3 groups ($p < 0.05$). Regarding the FibroScan outcomes (median time from LT = 26.6 months/IQR: 15.5–36.5), 14 patients (23%) had LSM values >8 kPa (30% were MASH patients, n = 6; 20% were ALD patients, n = 4; and 19% were MetALD patients, n = 4; $p = 0.657$). Patients with significant/advanced fibrosis (LSM values >8 kPa*) had significantly higher levels of CK-18 M30 ($p = 0.047$) and CK-18 M65 (0.049) at the last elastographic evaluation. In addition, this former group also presented increased levels of CK-18 M30 ($p = 0.011$) and CK-18 M65 ($p = 0.013$) at 6, 12, 24 and 36 months after LT.

Conclusion: The evolution of the circulating biomarker profile among transplanted MASH, ALD or MetALD patients may serve as a potential non-invasive tool to assess/predict graft fibrosis. Nevertheless, the causal associations between specific protein biomarkers and MASLD remain elusive.

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WED-450-YI

The use of controlled attenuation parameter for the assessment of treatment response in patients with metabolic dysfunction-associated steatotic liver disease undergoing a lifestyle intervention program

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Background and aims: The identification of non-invasive biomarkers to monitor treatment response is crucial for the effective management of metabolic dysfunction-associated steatotic liver disease (MASLD). This study investigated the utility of the controlled attenuation parameter (CAP), measured by vibration-controlled transient elastography (VCTE), and the role of PNPLA3 gene variants in assessing weight loss outcomes in MASLD patients undergoing a 6-month dietary intervention.

Method: A total of 94 patients with MASLD were enrolled and randomized into three dietary intervention groups: mediterranean diet (MD), low-carb diet (LCD), and control diet (CD). Inclusion criteria were a BMI of 26–35 kg/m², CAP ≥248 dB/m, and liver stiffness measurement (LSM) <12.5 kPa. Exclusion criteria were decompensated type 2 diabetes (HbA1c >9.5%), insulin-dependent diabetes, therapy with GLP-1 receptor agonists, alcohol consumption >30 g/day for men or >20 g/day for women, liver diseases of other etiologies, or the use of steatogenic medications. The primary endpoint was achieving ≥7% weight loss at the end of the 6-month intervention. Clinical, biochemical, and VCTE assessments were performed at baseline and after 6 months.

Results: The median age of participants was 50.5 years [IQR 43.0–61.0], and 71.3% were male. Type 2 diabetes was present in 17% of the cohort, while the PNPLA3 GG genotype was observed in 19.1% of patients. After 6 months, 28.7% of participants achieved ≥7% weight loss, with the LCD group showing the highest success rate (36.2%). In patients achieving weight loss, CAP decreased significantly (from a median of 294 to 246 dB/m, $p < 0.0001$), compared to changes observed in those who did not achieve weight loss (inter-group $p = 0.001$). Delta CAP values were significantly higher in the LCD group compared to other groups ($p = 0.040$). A progressive increase in the delta CAP was observed across incremental weight loss categories (<5%, 5–10%, >10%) ($p = 0.026$). Among patients achieving ≥7% weight loss, higher delta CAP values were noted in patients with the CC/CG genotype of PNPLA3 ($p = 0.0004$), as compared to GG carriers ($p = 0.79$). Additionally, the reduction in CAP (delta CAP) associated with weight loss was more pronounced in females than in males, even though the present inter-group statement seems not to be

statistically relevant (p = 0.15). These findings highlight potential sex-related differences in treatment response.
Conclusion: The present study demonstrates that in MASLD patients, achieving ≥7% weight loss through dietary intervention is associated with significant reductions in CAP, indicating decreased hepatic steatosis. PNPLA3 genotyping may offer additional insights for stratifying patients and personalizing therapeutic approaches. Further research is needed to explore the role of genetic and sex-related factors in optimizing treatment outcomes.

WED-451
Comparison of the pathophysiology of "metabolic" and "genetic" MASLD: a multiOmics cohort study
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Background and aims: MASLD pathogenesis can be explained by a metabolic component and a genetic component. In fact, several single nucleotide polymorphisms(SNPs) have been correlated with high risk of fibrosis/inflammation in MASLD and even a "genetic risk score"(GRS) has been validated. Recently, it has been hypothesized that "metabolic MASLD"(MM-without any genetic mutation) may have a different pathophysiology in respect to "genetic MASLD"(GM). Aims: To investigate, in a large cohort of MASLD, if and how the metabolomic profiles of GM are different from MM and in respect to healthy controls.
Method: 270 MASLD patients from a tertiary center of Southern Italy and 102 controls were evaluated by clinical, laboratory, genetic and untargeted metabolomics analysis. Inclusion criteria: US evidence of steatosis in absence of any other liver disease. Patients were classified by fibrosis risk in three groups:(A)low-risk,(B)high risk of fibrosis and (C)cirrhosis, by clinical/laboratory parameters, liver stiffness and/or liver biopsy as by European guidelines. All the subjects were genotyped for PNPLA3, MBOAT7, GCKR, and TM6SF2 SNPs by TaqMan 5′-nuclease assays. Patients were defined as GM if they had any of the analyzed SNPs at-risk mutations, and MM if they did not, also categorizing them into high and low genetic risk groups on the basis of a weighted GRS. Untargeted metabolomics analysis was performed through Gas Chromatography-Mass Spectrometry.
Results: Patients with GM were the majority(216/270:80%). However, GM and MM patients did not differ for clinical parameters other than BMI(higher in MM, p:0.029) GGT(higher in GM, p:0.019) and Ferritin (higher in GM, p:0.033). The prevalence of at-risk SNP mutations was not different in patients vs controls, except for PNPLA3(higher in patients p:0.033). On the contrary, untargeted metabolomics demonstrated progressive separation between fibrosis risk classes, with key metabolites including lactic acid, urea, pyroglutamic acid, hydroxydecanoic acid, 2-hydroxyisocaproic acid, and acetoacetic acid. Pathway analysis highlighted alterations in starch, sucrose, galactose, and amino sugar metabolism. In a separate model focused on genetic risk, significant separation was observed between High- and Low-Risk groups. Metabolites in this analysis included palmitic, mandelic, pyroglutamic, lactic, and ribonic acids. Altered pathways involved phenylalanine, tyrosine, and tryptophan biosynthesis, as well as valine, leucine, and isoleucine metabolism.
Conclusion: Clinical/laboratory evaluation was not able to discriminate between "genetic" and "metabolic" MASLD. On the contrary, a marked separation emerged between high- and low- fibrosis and genetic-risk groups, indicating potential for early diagnostics and stratified patient management. This approach may offer promising avenues for personalized therapeutic strategies, ultimately supporting more effective and individualized care at the dawn of pharmacological treatment of MASLD.

WED-452
Development of novel supervised machine learning models to predict the population at risk of metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis in a spanish mediterranean population
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is among the most prevalent primary liver disease worldwide, but since it is a generally asymptomatic disease its prevalence is not well described. In this real-world, longitudinal retrospective study on a Spanish Mediterranean Electronic Health Records (EHR) database we aimed to predict the probability of potential risk of MASLD and Metabolic dysfunction-associated steatohepatitis (MASH) in the general population and in people with type 2 diabetes mellitus (T2DM) or obesity by using a novel Machine Learning (ML) approach.
Method: Supervised ML Models (SMLM) were developed from an EHR of 2267 subjects in which MASLD and MASH were identified by Vibration-Controlled Transient Elastography Controlled Attenuation Parameter (VCTE-CAP), Liver Stifness Measurement (LSM) and FibroScan-AST (FAST) score as well as available data on comorbidities and laboratory tests. SMLM (*Random forest and XGBoost*) developed to predict the potential risk of MASLD or MASH were trained with a k-fold cross-validation method and tested using classification metrics (*sensitivity, specificity, AUROC, Kappa*). Algorithms were calibrated for high sensitivity and applied in a general population of 3,6 million adult subjects and in individuals with T2DM or obesity from 2012 to 2019. The selected variables for prediction included comorbidities and analytical variables.
Results: The best-performing models for MASLD and MASH consisted of 12 and 7 variables respectively and exhibited high performance as measured by area under the curve (0.76 for MASLD, 0.84 for MASH). The proportion of individuals who could be at risk predicted by SMLM was up to 46% for MASLD and 11% for MASH in the general population. Furthermore, according to the SMLM, up to 99% of people with T2DM or obesity (2 times higher vs general EHR) could be at risk of developing MASLD if left untreated. In contrast, the prevalence of MASLD and MASH by ICD codes in the overall EHR were 2.2% and <1% with MASH being ~4 and 3 times higher in people with T2DM and obesity respectively vs general population. Moreover, from 2012 to 2019 the ICD-based prevalence and SMLM-based risk of MASLD increased from 0.8% (ICD)/31.9% (SMLM) to 2.2% (ICD)/46.1% (SMLM).
Conclusion: According to our SMLM, individuals potentially at risk of MASLD and MASH in the population could be up to 46% and 11% with 2 times higher prevalence in the T2DM or obese population. These results indicate a potentially large risk of developing MASLD/MASH within the population despite currently low diagnosis rate of the disease. Use of predictive clinical risk factors could be useful as a complementary approach to identify patients at risk of MASLD/MASH in clinical setting. This could aid in early and more comprehensive

disease management and avoid long-term outcomes associated with MASLD/MASH. Study sponsored and funded by MSD Spain

WED-453

Referral algorithm from primary care based on the risk calculation for significant fibrosis

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Background and aims: Non-invasive methods (NIMs) for diagnosing liver fibrosis in Primary Care (PC) aim to stratify risk and facilitate decision-making. However, these NIMs have a high number of false positives (FP), which increases costs and resource consumption. Our objective was to develop a referral algorithm to reduce FPs and optimize the indication of transient elastography (Fibroscan®; TE) in patients with suspected significant fibrosis (F2-4).
Method: This was a cross-sectional cohort study in which the FIB4 score was calculated for all patients aged 18–64 years from Area 6 of Madrid who underwent routine blood tests with glycated hemoglobin in PC. Patients with FIB-4 >1.3 were referred to the hospital for TE. For patients with indeterminate FIB4 results (1.3–2.67), second-line NIMs—Enhanced Liver Fibrosis (ELF) and Fatty Liver Index (FLI)—were performed.
Results: A total of 1,927 patients were evaluated. Of these, 412 patients (21.4%) had FIB4 >1.3. The baseline characteristics are: 71.2% were male, 28.2% had type 2 diabetes (T2D), and mean BMI was 29 kg/m² (41% overweight and 37.4% obese). 90.8% of referred patients had indeterminate FIB4. Within this subgroup, 45.2% had pathological ELF (≥9.8), and 54.1% had pathological FLI (≥60). We calculated the AUROC for ELF and FLI: ELF: 0.75 (sensitivity: 85.3%, specificity: 64.9%) and FLI: 0.74 (sensitivity: 93.4%, specificity: 56.4%). Based on these data, we developed a formula using ELF and FLI to establish the probability of F2-4 in TE for those with indeterminate FIB4. This formula was incorporated into an online risk calculator: https://investigacionpuertadehierro.com/calculadora-riesgo-de-fibrosis-significativa/. An arbitrary cutoff point was set, considering acceptable sensitivity and specificity. Patients with a probability >10% were referred for TE, while those with a probability <10% were not. By applying this approach, the number of transient elastographies performed was reduced by 51.2%, with the model achieving a sensitivity of 84.9%, a specificity of 57.7%, and a negative predictive value (NPV) of 95.5%.
Conclusion: The proposed referral algorithm, based on serological NIMs, allows for the selection of patients with a higher likelihood of F2-4 and reduces unnecessary referrals for TE. However, further studies are needed to optimize the cutoff point to maximize the efficiency of patient selection.

WED-454-YI

Decoding fibrosis: transcriptomic and clinical insights via AI-derived collagen clusters in MASLD

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) may remain benign or progress to cirrhosis. Fibrosis, the primary prognostic marker, is graded on an ordinal scale but has significant interobserver variability. We hypothesized that continuous, deep-learning-derived histological measures could improve predictions of MASLD progression. Additionally, we integrated molecular and morphological features by combining histological metrics with RNA-seq data.
Method: This prospective cohort study included patients with suspected MASLD with fibrosis who underwent liver biopsy. Baseline and annual evaluations were performed. Bulk RNA-sequencing of FFPE tissue was conducted using the RNeasy FFPE Kit and Illumina NovaSeq platform. Digitized slides were analysed using a bespoke deep-learning U-net model for collagen segmentation. The output of the segmentation model was used for quantification of collagen proportionate area (CPA), and secondly for the development of a novel deep-learning algorithm for subtyping collagen deposition patterns. The results of the quantitative image analysis were used alongside pathologist fibrosis staging to perform differential gene expression experiments. We performed liver stiffness measurements (LSM) at baseline and during annual follow-up visits. We defined a clinically relevant increase in LSM as ≥5 kPa and ≥20% increase from the baseline value. Liver-related events (LRE) included varices on endoscopy, variceal bleeding, ascites, jaundice, hepatic encephalopathy, hepatorenal syndrome, HCC, or cirrhosis-related death.
Results: We analysed 187 MASLD patients (F0: 35, F1: 53, F2: 50, F3: 24, F4: 25) followed for a median of 4.85 years. LSM progression occurred in 14.0% by year 2 (19/136) and 14.3% by year 3 (16/112). LREs developed in 8.0% (15 patients), including 7 cirrhosis-related deaths. Higher CPA and collagen clusters C4 and C5 were associated with increased odds of LSM progression (C5: year 2 OR 1.71, p = 0.008, AUC 0.76; year 3 OR 1.75, p = 0.01, AUC 0.80) and LREs (OR 2.28, p = 0.0008, AUC 0.86). DGE analyses identified the most enriched KEGG pathways (150) for C5, outperforming all other metrics.
Conclusion: CPA and collagen clusters C4 and C5 are significant predictors of MASLD progression. These deep-learning-derived histological parameters demonstrate considerable potential for improving risk stratification in MASLD patients. DGE revealed CPA and clustering as superior metrics for identifying fibrosis-related metabolic pathways. Validation studies are needed to confirm these findings.

WED-455

Sampling variability of liver fibrosis assessed by digital pathology in pre-cirrhotic patients with MASH

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Background and aims: Liver biopsy remains the gold standard for assessing fibrosis in patients with MASH. As highly sensitive, reproducible, and continuous digital pathology biomarkers are increasingly utilized for evaluating liver biopsies, the impact of heterogeneity in the distribution of histological features and the associated sampling variability of biopsies emerges as a critical analytical consideration.
Method: Large (10mm × 10 mm) liver wedge biopsies from 12 patients histologically diagnosed with MASH (and fibrosis stages of F0, n = 0, F2, n = 3, F3, n = 5, F4, n = 3) undergoing bariatric surgery were stained with Picro-Sirius Red (PSR) and imaged at 40X. Virtual biopsies[1] were created by selecting 4–5 Regions of Interest (ROIs) of 1.5 × 10 mm from each wedge biopsy image, simulating a half-length 16G needle adequate[2] biopsy ("adequate biopsy"). These were further divided into short (5 mm long) and thin (800micron wide, sub-adequate biopsies). FibroNest™ analysis of the virtual biopsies, extracted 335 quantitative fibrosis traits. Key traits were used to generate a Phenotypic Fibrosis Composite Score (Ph-FCS) of severity

as described[2]. The coefficient of variation CoV (standard deviation/mean, %) of the Ph-FCS was calculated and averaged for both adequate and sub-adequate biopsies.
Results: The average CoV of the Ph-FCS (<CoV>) was 6.51% ± 0.71 (n = 58, CI = 68%, range 2.29% – 11.46%) for adequate virtual biopsies. Values were slightly higher for thin (resp. short) sub adequate biopsies with <CoV> = 7.25% ± 0.63 (n = 116, CI = 68%, range 5.22% – 12.68%) and <CoV> = 8.82% ± 0.96 (n = 116, CI = 68%, range 5.25% – 15.03%). The combination of both effects of size can be interpolated to <CoV>~9.56% ± 1.88 (n = 116, CI = 68%). There is not statistically significant relationship between severity stages and COV% (F0 <CoV> = 8.6%, F2 7.0%, F3 6.3%, F4 5.6%, for adequate virtual biopsies). Extreme values of the CoV are attributed to fragments of non-contributory peri-vascular fibrosis being partially interpreted by the AI algorithms as phenotypes of severity.
Conclusion: The sampling variability of the Ph-FCS Digital Pathology biomarker in pre-cirrhotic MASH patients is 6–10% regardless of severity, outperforming other histological and computational methods. This superior performance stems from its phenotypic analytical approach and the exceptional signal-to-noise ratio (~110:1) of the FibroNest method. These findings underscore the robustness of the FibroNest™ biomarker in accurately quantifying fibrosis severity, even with minor biopsy dimension variations, reinforcing its reliability for clinical study use and interpretation.

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WED-456

Intra-abdominal fat thickness measured by ultrasound correlates with CAP (Controlled Attenuation Parameter) measured by FibroScan® in a cohort of patients followed for MASLD/MASH at an urban liver centre: Impact of utilization in clinical practice

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are very common liver diseases in clinical practice with significant global health implications and estimated prevalence over 30% worldwide. Despite its widespread use, abdominal ultrasound, the primary screening tool for diagnosis of liver steatosis, has suboptimal sensitivity and specificity for reliable diagnosis of steatotic liver disease.
Abdominal ultrasound is the initial screening test for diagnosis of steatotic liver disease in clinical practice - non-invasive and accessible. Having said that, its diagnostic accuracy is limited, particularly in cases of mild steatosis and obesity. We sought to explore weather enhancing the diagnostic accuracy of ultrasound through additional measurement of intra abdominal fat could improve liver steatosis detection without or very minimal additional costs.
Method: The measurement of intra-abdominal fat thickness was performed using a 3.5 to 3.75 MHz probe, either linear or curved array, positioned midline, 1–5 cm superior to the umbilicus or midway between the xiphoid process and the umbilicus in the transverse plane. The image was captured with the rectus abdominis muscle and aorta in view, and the measurement was taken from the anterior wall of the aorta to the posterior surface of the rectus abdominis muscle.
Results: This retrospective analysis involved 456 patients diagnosed with MASH or MASLD, including 237 females and 219 males. BMI of the patients ranged from 17.3 to 49.5 kg/m², with ages between 20 and 90 years (an average 59.5 years). Intra-abdominal fat thickness measurements varied from 1.1 to 13.4 cm and CAP scores from 142 to 400 dB/m.
Utilizing a regression statistical analysis model revealed a significant correlation between Controlled Attenuation Parameter (CAP) scores and intra-abdominal fat thickness. Both CAP and BMI were significant predictors of intra-abdominal fat thickness. We defined high risk as intra-abdominal fat thickness >9 cm for males and >8 cm for females. Although the predictive model showed some limitations due to the smaller dataset, utilizing the binary high vs. low-risk models consistently indicated CAP and BMI as significant predictors.
Conclusion: Incorporating intra-abdominal fat thickness measurement into routine abdominal ultrasound procedures can enhance the accuracy of liver steatosis assessment. Future prospective studies are planned to further explore the utility of intra-abdominal fat thickness measurement and its correlation with CAP and various components of metabolic syndrome.

WED-461

Potential issues with practical implementation of EASL-EASD-EASO clinical practice guidelines on management of metabolic-associated steatotic liver disease in a Swedish healthcare setting

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Background and aims: Metabolic-associated steatotic liver disease (MASLD) is particularly common among patients with Type 2 Diabetes (T2D), with an estimated prevalence of 65%. Its silent progression often leads to under-detection of patients at risk of fibrosis, delaying referrals to hepatology specialists. The 2024 clinical practice guidelines by EASL-EASD-EASO recommend screening individuals at a high risk for having MASLD for advanced fibrosis but their feasibility in primary care is uncertain. We aimed to estimate numbers within each proposed screening pathway and evaluate the applicability of these guidelines in a Swedish healthcare setting.
Method: We estimated the numbers for each pathway using data on FIB-4 risk categories and vibration-controlled transient elastography (VCTE) measurements (≥8.0 kPa) in individuals with T2D. Data were used from the Health Outcomes and Risk Assessment in Chronic Liver Disease (HERALD) dataset, which includes most individuals with T2D in Stockholm County between 2010 and 2020 who have FIB-4 scores available from primary and secondary care. Among the 23,070 individuals identified, 69% had a FIB-4 score of <1.3, 21% had scores between 1.3 and 2.67, and 10% had scores >2.67. Additionally, a recent cross-sectional study of 1,005 T2D patients undergoing VCTE reported a 16% prevalence of VCTE ≥8 kPa. Descriptive statistics were used to assess the healthcare landscape in Stockholm County.
Results: Applying these cutoffs to 140,000 individuals with T2D (estimated prevalence of 5.8% in Stockholm County) resulted in the following estimated distribution: around 96,600 individuals classified as low risk (FIB-4 : <1.3), 29,400 individuals at intermediate risk needing VCTE or another second test (FIB- 4: 1.3–2.67), and 14,000 individuals who would be directly referred to hepatologists (FIB-4 : >2.67). Assuming that at least 16% of patients at intermediate risk have a VCTE ≥8.0 kPa, an additional 4,704 individuals would be referred to hepatology. Thus, approximately 31% (43,400) of individuals with T2D are expected to need at least one VCTE for liver assessment, and around 13% (18,200) would require a referral to hepatology.
Conclusion: Our findings highlight the challenges of applying current EASL-EASD-EASO guidelines for liver assessment, especially with limited elastography resources and specialist care. The reduced sensitivity of FIB-4 and VCTE in T2D patients further emphasizes the

need for better tools and targeted algorithms to identify those at risk of advanced fibrosis.

WED-462

Determinants of liver stiffness improvements and worsening in metabolic dysfunction associated steatotic liver disease: insights from two cohorts

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Background and aims: Liver stiffness measurement (LSM) is key for monitoring disease progression in patients with Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD). Identifying predictors of LSM change could enhance prognosis and guide management. This study assessed metabolic and clinical factors that impact LSM changes over time in two large cohorts of MASLD patients.

Method: We included MASLD patients with ≥2 outpatient visits from 2014 to 2022. Follow-up LSM was >6 months from baseline. LSM worsening was defined as >30% increase if baseline LSM was ≥5 kPa, or as follow-up LSM >6 kPa if baseline was <5 kPa. LSM improvement was defined as >30% LSM decrease (if baseline >6 kPa). Alternate analyses used a >40% change cut-off. Significant weight and HbA1c changes were defined as >5% and >10%, respectively. We calculated the difference between actual and "expected" FIB-4 at follow-up (based on the patient's age at the follow-up visit, but using the blood tests performed at the first visit), and we defined "expected" Fibroscan improvement or worsening based on changes in weight, HbA1c, ALT, and FIB-4, where at least one variable showed a corresponding improvement or worsening while the others remained stable.

Results: Among 400 enrolled (mean age 54, 70% male), median follow-up was 20 months. LSM improved by >30% in 13.5% of patients and worsened >30% in 11.3%; using a >40% cut-off, 6.5% showed improvement and 6.0% showed worsening. Only about one-third of patients with LSM > 30% or >40% changes showed corresponding shifts in FIB-4. In multivariate logistic regression analysis, LSM worsening >30% was independently associated with increased HbA1c (OR 1.03), longer follow-up (OR 1.07) and total cholesterol change (OR 0.97, indicating a lower likelihood of LSM worsening), while LSM improvement > 30% correlated with weight reduction (OR 0.89). Similarly, in multivariate logistic regression analysis, LSM worsening >40% was independently associated with an increase in HbA1c (OR 1.04), while LSM improvement >40% was independently associated with weight reduction (OR 0.89). "Expected" Fibroscan improvement was linked with actual Fibroscan reduction (p = 0.002), showing high negative predictive values (NPV: 92–96%), but expected worsening did not predict actual LSM increase (NPV: 72–89%).

Conclusion: About 20% of MASLD patients experienced significant LSM changes over 20 months. Weight reduction improved LSM, while increased HbA1c predicted worsening LSM, supporting a focus on metabolic management. The variables contributing to "expected" Fibroscan changes may aid in guiding diagnostic pathways but require a comprehensive, multidisciplinary model of care.

WED-463

Three-tier testing pathways are required in metabolic dysfunction-associated steatotic liver disease for improved detection of advanced fibrosis

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of secondary care referrals for chronic liver disease in Western countries. Two-step hierarchical algorithms with FIB-4 followed by transient elastography (TE) or the Enhanced Liver Fibrosis (ELF) test are recommended in various guidelines to rationalize referrals from primary to secondary care. We aimed to evaluate the utility of an algorithm with TE as the thirds step after a FIB-4 and an ELF. We assessed the concordance between ELF scores and FibroScan measurements, and their diagnostic accuracy compared to liver biopsy in a consecutive cohort of patients referred with increased ELF scores.

Method: We included consecutive patients referred between June 2014 and September 2024 due to MASLD and an ELF score ≥9.5, following local referral pathways. All included patients underwent TE using FibroScan to assess liver stiffness measurement (LSM) upon referral, and met MASLD diagnostic criteria. Patients with other liver diseases were excluded. Demographic, clinical, and laboratory data were collected. Concordance between ELF scores, FibroScan results, and liver biopsy findings was assessed.

Results: A total of 777 patients were included: 47% male, mean age 62 ± 10 years, mean BMI 32 ± 7 kg/m². 38% had diabetes, 65% dyslipidaemia, and 60% hypertension. Median LSM was 6.1 (4.6–8.7) kPa. LSM was ≥8 kPa in 231 (30%) patients and ≥10 kPa in 143 (18%). Therefore, the concordance of LSM and ELF for advanced fibrosis (cut-off 10 kPa) was 18%, while there was a significant discordance (LSM <6 kPa) in 368 (47%) of the cases. Liver biopsy data were available for 109 patients (14% of the total population studied) and 54 (50%) had advanced fibrosis (≥F3). 41 (37.6%) patients with a high ELF score had no or minimal fibrosis (F0-F1) on liver biopsy. 22 and 14 of these patients had LSM above 8 kPa and 10 kPa, respectively. Among patients with biopsy-proven advanced fibrosis, only 2 had LSM<8 kPa. Increasing the ELF cut-off to 10.5 would reduce the number of false positive results without an increase in false negatives, assuming a TE threshold of 8 Kpa: among 53 patients with ELF ≥10.5 and available biopsy, only 1 with advanced fibrosis had an LSM<8 kPa.

Conclusion: Hierarchical two-step algorithms in unselected cohorts of patients with MASLD with relatively low prevalence of advanced fibrosis require an additional second-line non-invasive test to improve diagnostic accuracy. Using TE after a high ELF score improves the detection of advanced fibrosis.

WED-464-YI

Gaps in screening and management of metabolic dysfunction-associated steatotic liver disease: a retrospective audit of patients at cardiometabolic risk in a secondary care setting

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Background and aims: Significant gaps exist between cross-specialty guidelines and the management of cardiometabolic patients at high risk for metabolic dysfunction-associated steatotic liver disease (MASLD), particularly those referred to secondary specialist settings. A siloed approach and poor communication in secondary care substantially hamper effective MASLD management and prospective actions to decrease disease burden. This study aims to identify and address these practice gaps.
Method: OPTIMA-NASH is a retrospective, longitudinal practice improvement initiative, based on a clinical audit. The study population includes patients seen in Niguarda outpatient clinics over 24 months. Eligible patients had at least one cardiometabolic risk factor (CMR, e.g., prediabetes, type 2 diabetes, overweight or obesity, dyslipidemia, arterial hypertension), or atherosclerotic cardiovascular disease (ASCVD). Data collection focused on calculating MASLD risk scores, including FIB-4 and NAFLD-Fibrosis Score (NFS), and assessing the use of transient elastography (TE).
Results: A total of 854 patients were reviewed, with a mean age of 65.8 ± 15 years and 485 (56.8%) were male. CMR prevalence was: 41.3% diabetes, 27.5% obesity (mean BMI 27.9 ± 4.9 kg/m^2), 29.6% dyslipidemia, 59.3% arterial hypertension. Additionally, 15.6% had ischemic heart disease, 25.1% atrial fibrillation, 2.8% heart failure, 4.8% a history of TIA/stroke, and 10.2% an eGFR <60 ml/min/1.73 m². Overall, 692 (81.0%) patients had 2 or more risk factors, reflecting a very high CMR. Data to calculate the FIB-4 score were available for 311 records. Mean FIB-4 score was 1.7 ± 1.67; 159 patients (51%) had a FIB-4 score >1.3, indicating a need for transient elastography (TE) measurements using Fibroscan. For the NAFLD-Fibrosis score (NFS), data were available in 162 records, mean NFS was −1.224 ± 1.733; 85 (52%) had an NFS ≥1.455. TE was documented for 153 patients, mean TE 8 ± 6.9 kPa. Both FIB-4 and NFS demonstrated moderate accuracy for predicting fibrosis stages ≥F3: AUROCs were 0.768 (95% CI 0.617–0.919) for FIB-4 and 0.739 (95%CI 0.568–0.909) for NFS, respectively, consistent with literature on MASLD. Controlled attenuation parameter (CAP) measurements were available for only 80 patients; mean CAP was 306.5 dB/m ± 49.9; 62 patients (77.5%) had a CAP > 275 dB/m.
Conclusion: In this secondary care setting, a minority of patients with cardiometabolic risk factors were screened for MASLD, highlighting critical areas for improvement in practice. This gap underscores the need for improved protocols and enhanced communication between specialties to facilitate timely screenings and interventions. By addressing these pitfalls, we can better manage MASLD and reduce its associated burden in at-risk populations.

WED-465
Association of hepatic steatosis biomarkers with hepatic steatosis prevalence and risk of developing MASLD fibrosis in patients with type 2 diabetes mellitus in eastern Croatia: a pilot study

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Background and aims: Despite its high prevalence and severe clinical consequences in patients with type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD) is often overlooked in clinical practise. Therefore, the aim of this study was to investigate the prevalence of steatosis and fibrosis in T2DM patients in Eastern Croatia and its association with hepatic steatosis biomarkers and the risk of MASLD fibrosis.
Method: In this pilot study, 52 T2DM patients (29 men and 23 women) aged between 31 and 87 years were included. Liver fibrosis was assessed using 2D shear wave elastography (2D SWE) to measure liver stiffness and liver steatosis was assessed using the ultrasound-guided attenuation parameter (UGAP) method. Blood was drawn for an enzyme-linked immunosorbent assay (ELISA) to determine liver steatosis biomarkers: peroxisome proliferator-activated receptor (PPAR) alpha, PPAR gamma, sterol regulatory element-binding protein (SREBP) 1 and microsomal triglyceride transfer protein (MTTP). In addition, the complete blood count, liver transaminases, coagulogram, proteins, albumins, lipidogram, blood glucose and HbA1c levels were measured. The MASLD fibrosis score was calculated to assess the risk of developing MASLD fibrosis.
Results: 73% of patients had stage F1 fibrosis, while 15% were classified with advanced F4 fibrosis, with a maximum value of 40.28 kPa in one patient. Regarding steatosis, S0 and advanced stage S3 (with a maximum value of 0.83 dB/cm/MHz) were evenly represented (13%) and the other intermediate stages were also almost evenly distributed. The Spearman correlation coefficient showed that there was a significant correlation between fibrosis and steatosis (Rho = 0.311, p = 0.04). However, no significant correlation was observed between 2D SWE and UGAP steatosis with the biomarkers of hepatic steatosis (p > 0.05). Higher plasma glucose (Rho = 0.583 p < 0.001), HbA1c (Rho = 0.370, p = 0.02), triglycerides (Rho = 0.338, p = 0.04), alkaline phosphatase (Rho = 0.352, p = 0.03), gamma-glutamyltransferase (Rho = 0.336, p = 0.04), alanine transaminase (Rho = 0.634, p < 0.001) and lower protein levels (Rho = -0.443, p = 0.01) were significantly associated with increased UGAP steatosis. The Kruskal-Wallis test showed that higher 2DSWE levels were present in patients at high risk of MASLD fibrosis (p = 0.009) and higher PPAR alpha levels were present in patients at intermediate risk of MASLD fibrosis (p = 0.04) compared to patients at low risk of MASLD fibrosis.
Conclusion: Although only a relatively small group of patients were included in our study, liver steatosis and fibrosis were frequently observed, and in a few patients fibrosis and steatosis were extremely high. This strongly emphasizes the urgent need to adopt liver SWE and UGAP, supported by the MASLD fibrosis score, into routine clinical practice to reduce the risk of fibrosis progression, which is a significant health threat worldwide.

WED-466-YI
Serum biomolecules improve liver enzyme-based prediction scores of significant liver fibrosis and fibrotic metabolic dysfunction-associated steatohepatitis

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) with significant fibrosis (i.e. MASH with fibrosis ≥F2) have a higher risk of developing advanced liver disease. The gold standard for identifying MASH and fibrosis remains biopsy based histological evaluation, an invasive and costly procedure. Hence, blood biomarkers-based prediction scores may provide an improved option. Thus, the study aims to establish a serum-based non-invasive score model to predict significant liver fibrosis and fibrotic MASH.
Method: Two comparable cohorts, a derivative and validation, comprising respectively 120 and 118 patients underwent liver biopsy for a suspicion of MASLD at the Gastro-enterology and

Hepatology Department of the Antwerp University Hospital. The NAFLD activity score system was used to determine the histological MASLD features. Beside standard serum biochemistry, serum biomolecules of metabolic, inflammatory, and vascular proteins were measured. Independent predictors of F ≥2 identified by multivariate logistic regression, and the predicted probabilities were used to generate prediction models. The area under the receiver operating characteristic curves (AUROC) of the models and FIB-4 index were compared using the DeLong test. And $p < 0.05$ was considered statistically significant.

Results: The derivation cohort included patients with fibrosis F ≥2 (40%), MASH (40%), and fibrotic MASH (28.3%), while the validation cohort comprised fibrosis F ≥2 (44%), MASH (45.8%), and fibrotic MASH (33.9%). A novel model, Model-2S3 created by unweighted integration of three serum biomolecules and two enzymes. In the derivation cohort, Model-2S3 predicted fibrosis F ≥2 with an AUC of 0.96 (95% CI: 0.93–0.99), maintaining 94% sensitivity and 91% specificity. For fibrotic MASH, Model-2S3 achieved an AUC of 0.90 (95% CI: 0.83–0.95), with 85% sensitivity and 86% specificity. Model-2S3 significantly outperformed FIB4 in predicting fibrosis F≥2 (AUC: 0.83, 95% CI: 0.76–0.90, $P = 0.002$) or fibrotic MASH (AUC: 0.71, 95% CI: 0.61–0.80, $P = 0.001$). Alternatively, Model-E integrating ALT, AST and GGT performed acceptable but also worse than Model-2S3 for prediction of fibrosis F ≥ 2 (AUC: 0.89, 95% CI: 0.83–0.95, $P = 0.008$) and fibrotic MASH (AUC: 0.78, 95% CI: 0.70–0.87, $P = 0.01$). In the validation cohort, Model-2S3 maintained high accuracy, predicting fibrosis F ≥2 with an AUC of 0.95 (95% CI: 0.92–0.99), 84% sensitivity, and 98% specificity. For fibrotic MASH, it achieved an AUC of 0.89 (95% CI: 0.83–0.96), with 85% sensitivity and 87% specificity. In this cohort Model-2S3 also significantly outperformed FIB4 and Model-E in predicting fibrosis F ≥2 and fibrotic MASH.

Conclusion: A composite score of serum biomolecules and enzymes yields high accuracy to predict significant fibrosis or fibrotic MASH. This new model outperformed scores based on routinely available parameters and might be considered as a promising non-invasive tool.

WED-467

Low sensitivity of the 2024 EASL screening criteria for identifying MASLD fibrosis in the NHANES cohort

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Background and aims: The 2024 European Association for the Study of the Liver (EASL) guidelines propose a sequential screening approach using metabolic risk criteria, FIB-4, and transient elastography (TE) to identify patients with metabolic dysfunction-associated steatotic liver disease (MASLD) who require hepatology referral. This study evaluates the diagnostic performance of these recommendations in the NHANES cohort.

Method: Adult participants with complete TE data from NHANES 2017–2020 were included. MASLD was defined as hepatic steatosis (CAP ≥248 dB/m) with at least one cardiometabolic risk factor (CMRF). The EASL screening strategy was applied sequentially: (1) metabolic risk criteria (obesity with ≥1 CMRF, type 2 diabetes [T2D], or raised liver enzymes), (2) age-adjusted FIB-4 thresholds (≥1.3 for age <65 years or ≥2.0 for age ≥65 years), and (3) hepatology referral criteria (FIB-4 > 2.67 or TE ≥8 kPa). Diagnostic performance was assessed for MASLD with fibrosis (TE ≥8 kPa), with subgroup analyses by age and T2D.

Results: Of 7,768 included participants, MASLD and MASLD with fibrosis were present in 45% and 6%, respectively. Applying the EASL criteria sequentially, 45% of the total population met metabolic risk criteria, 7.5% had elevated FIB-4, and 3% qualified for hepatology referral. The overall sensitivity and specificity of the sequential pathway for identifying MASLD with fibrosis were 21% and 98%, respectively. Sensitivity declined from 86% to 29% when age-adjusted FIB-4 thresholds were applied, while specificity improved from 56% to 93%. Subgroup analyses revealed particularly low sensitivity in younger individuals (<50 years, 6%) and those without T2D (16%), whereas specificity exceeded 90% across all subgroups. Sensitivity analyses using higher fibrosis thresholds (MASLD with TE ≥12 kPa) confirmed similarly poor sensitivity (29%).

Conclusion: The 2024 EASL screening criteria exhibit high specificity but poor sensitivity for detecting MASLD with fibrosis, particularly in younger or non-diabetic individuals. The low sensitivity is primarily attributed to FIB-4's poor performance within the sequential algorithm. These findings underscore the need for better-performing non-invasive tests to optimize referral for specialist care.

WED-468

Non-invasive markers to predict biopsy response in people with metabolic dysfunction-associated steatohepatitis and fibrosis: exploratory analysis of a phase 2 trial of glucagon receptor/glucagon-like peptide-1 receptor dual agonist, survodutide

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) clinical trials rely on liver biopsies; thus, the predictive potential of non-invasive tests (NITs) has not been widely investigated. We evaluated the predictive potential of changes in NITs for biopsy outcomes in a phase 2 trial in people with biopsy-confirmed MASH and F1 – F3 liver fibrosis who were treated with survodutide, a novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist.

Method: 295 patients were randomised to once-weekly subcutaneous injections of placebo or survodutide 2.4, 4.8, or 6.0 mg (NCT04771273). This post-hoc analysis involved patients with F2/F3 fibrosis and paired biopsies and NITs (n = 138). We assessed whether % change from baseline after 48 weeks in FibroScan®-aspartate aminotransferase (FAST) score, Agile 3+ (FibroScan-based score), alanine transaminase (ALT), body weight, magnetic resonance imaging proton density fat fraction (MRI-PDFF), controlled attenuation parameter (CAP; FibroScan), vibration-controlled transient elastography (FibroScan), propeptide of type III collagen (PRO-C3), and absolute change in enhanced liver fibrosis (ELF™) score, had predictive potential for 2 biopsy based outcomes: resolution of MASH with no worsening of fibrosis, and improvement of fibrosis with no worsening of MASH. Variables were dichotomized based on cut-off points that were established using the Youden Index. Potential predictors were chosen using the least absolute shrinkage and

selection operator (LASSO) method and threefold cross-validation (CV), adjusted for changes in body weight. The importance of predictors was determined on the absolute value of the regression coefficients of the dichotomized biomarkers. The model's performance was assessed using area under the curve (AUC), with a 95% confidence interval (CI) and a p-value derived from the one-sided Mann-Whitney test.
Results: Only participants receiving survodutide were included in the analysis to avoid a potential confounding effect from the active treatment. Changes in MRI-PDFF (relative importance to the prediction: 100%), ELF (61.9%), and FAST score (50.4%) were predictive of resolution of MASH with no worsening of fibrosis (full dataset: AUC 0.854, 95% CI: 0.78 to 0.93, $p < 0.0001$; AUC based on CV: 0.84). Changes in ELF (100%), ALT (87.2%), PRO-C3 (76.3%), MRI-PDFF (75.6%), FAST Score (72.3%), Agile 3+ (50.5%), and CAP (13.6%) were predictive of improvement of fibrosis with no worsening of MASH (full dataset: AUC 0.811, 95% CI: 0.73 to 0.90, $p < 0.0001$; AUC based on CV: 0.76).
Conclusion: We found evidence for predictive potential of changes in NITs such as MRI-PDFF, ELF, or FAST Score for biopsy outcomes, however predictive models incorporating multiple top NIT candidates are under investigation to enhance model accuracy and refinement.

WED-469
Novel point-of-care, rapid breath test to identify subjects with metabolic-dysfunction associated steatotic liver disease with advanced fibrosis - a pilot study
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Background and aims: There is a clear need for cost-effective, easy-to-use Point of Care (PoC) screening technologies for diagnosing metabolic-dysfunction associated steatotic liver disease (MASLD) and steatohepatitis (MASH), particularly those identifying advanced fibrosis, a key predictor of liver-related mortality. Volatile organic compounds (VOCs) biomarkers in exhaled breath, which reflect altered hepatic metabolism, are promising but current VOC analysis technologies are labor-intensive. NaNose Medical Ltd. is developing a unique nanotechnology-based sensing device, DiaNose, which uses semi-selective chemiresistor sensor array and machine learning to detect "breath fingerprints" without complex VOC concentrations analysis. Sensors' signals data from clinical studies is used to train models to classify disease stages.
Method: The sensor array consists of functionalized metal nanoparticle films over electrodes, detecting VOCs through electric response. DiaNose includes a single-use breath collection unit, a replaceable sensor, and a measurement system. In clinical studies, it collects data from MASLD patients with different fibrosis stages, verified through biopsy or FibroScan tests.
Results: Data from 30 MASLD patients (13 with no/early fibrosis, 17 with advanced fibrosis) were used to develop a classification model. Cross-validation produced accuracies of 85.5% sensitivity, 79% specificity, and 82.3% overall accuracy. Data collection is ongoing to enhance stability and generalization.
Conclusion: Preliminary results indicate DiaNose's potential for non-invasive PoC screening, accurately distinguishing MASLD with early versus advanced fibrosis. This tool could facilitate patient referral, optimize primary care management, and support trial stratification to advance treatment development.

WED-470
AI improves non-invasive diagnosis and screening of advanced MASLD
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Background and aims: The FIB-4 blood test and liver stiffness measurement (LSM) are popular, especially in the screening of advanced liver fibrosis in subjects at risk of MASLD (AASLD and EASL algorithms). Recently, AI has been shown to give a performance of new non-invasive tests (NITs), including usual liver blood markers, like that of proprietary NITs in MASLD (JHep 2025). We assessed whether AI could also improve the performance of FIB-4 and LSM.
Method: We included 1038 patients with MASLD who were split into derivation ($n = 624$) and validation ($n = 414$) sets. The primary endpoint was advanced fibrosis (Kleiner F3+4). The AI used new multi-targeted supervised learning. The new AI versions of FIB-4 and LSM included the same biomarkers adjusted for clinical variables that have been shown to influence NIT accuracy: age, BMI, diabetes for FIB-4 plus IQR for LSM (Fibroscan). Performance was measured by AUROC and the correct classification rate (accuracy). NIT thresholds were set in the derivation set by the Youden index for binary diagnosis and by sensitivity and specificity at 90% for ternary diagnosis. The accuracy of the indeterminate zone was set at 0%.
Results: The results are those of the validation set. 1/ FIB-4. The AUROC for advanced fibrosis increased from 0.757 in its original version to 0.814 ($p = 0.002$) in its AI version called FIB-4A. The binary accuracy increased from 68.8% to 75.6%, respectively ($p = 0.002$). The ternary accuracy increased from 41.1% to 51.0% ($p < 0.001$). The indeterminate rate decreased from 49.0% to 38.6% ($p < 0.001$). 2/ LSM. The LSM AUROC increased from 0.852 in its original version to 0.881 ($p = 0.006$) in its AI version called LSM-A. The binary accuracy increased from 75.6% to 79.2% ($p = 0.024$). The ternary accuracy increased from 59.7% to 65.0% ($p = 0.013$). LSM-A improved LSM reliability by increasing accuracy from 52.6% to 71.1% ($p = 0.039$) in poorly reliable LSM. Aging and diabetes decreased LSM accuracy ($p < 0.001$) but not LSM-A accuracy ($p = 0.755$). 3/ FIB-4A and LSM-A. Their scores directly reflected Kleiner's F-score from 0 to 4 with intra-class correlation coefficient at 0.717 and 0.808, respectively. The accuracy of the AASLD algorithm increased from 66.4% with original NITs to 72.5% ($p = 0.006$) by including FIB-4A and LSM-A. AI significantly decreased the indeterminate rate from 16.4% to 11.6% ($p = 0.019$) and the LSM recourse from 49.0% to 38.6% ($p < 0.001$). This significantly reduces the need for a 2nd fee-paying NIT and for a specialist in all the recommended screening algorithms, including the EASL algorithm. Finally, a new FIABLE algorithm, based on different segmentations of new AI-NITs, significantly improved AASLD algorithm performance.
Conclusion: AI remarkably increases the performance of FIB-4 and LSM. This leads to a significant improvement in LSM reliability, negative influence of age and diabetes, and diagnosis or screening by sequential algorithms of advanced MASLD.

WED-471
Noninvasive fibrosis indices are less effective in predicting significant fibrosis in younger adults with metabolic dysfunction-associated steatotic liver disease
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Background and aims: Although numerous noninvasive indices have been developed to assess significant fibrosis, none have been specifically validated in young adults with metabolic dysfunction-

associated steatotic liver disease (MASLD). This study aims to evaluate the performance of these indices in a younger population.
Method: Retrospective data from patients under the age of 35 who visited the 'Liver Health Clinic' at Armed Forces Goyang Hospital between June 2022 and January 2024 were collected consecutively. Significant fibrosis was defined as a liver stiffness measurement (LSM) ≥7.0 kPa. Patients with alanine aminotransferase (ALT) levels exceeding 80 IU/L were excluded to mitigate the risk of overestimating LSM. MASLD was defined as the presence of hepatic steatosis accompanied by at least one cardiometabolic risk factor.
Results: Among the 972 MASLD patients, 45 had significant fibrosis according to LSM. The mean age of study participants was 23.7 and males were predominant (97.3%). Five noninvasive indices, including FIB-4 index, APRI, FIB-8 index, NAFLD Fibrosis Score (NFS), and BARD score were assessed for their predictive performance. The FIB-4 index demonstrated an area under the curve (AUC) of 0.528, while APRI showed an AUC of 0.659. The FIB-8 index, NFS, and BARD score yielded AUCs of 0.735, 0.603, and 0.469, respectively. Correlation analyses between these indices and LSM revealed coefficients of −0.001 (p = 0.352) for FIB-4, 0.0165 (p < 0.001) for APRI, 0.0380 (p < 0.001) for FIB-8, and 0.0014 (p = 0.125) for NFS. Sensitivity analyses using an LSM cutoff of 8.0 kPa for significant fibrosis showed slightly improved AUCs, with values of 0.591 for FIB-4, 0.666 for APRI, 0.759 for FIB-8, 0.649 for NFS, and 0.531 for BARD.591 for FIB-4, 0.666 for APRI, 0.759 for FIB-8, 0.649 for NFS, and 0.531 for BARD.
Conclusion: Noninvasive fibrosis indices demonstrated inadequate performance in predicting significant fibrosis among young adults with MASLD. These findings underscore the need for developing novel noninvasive indices designed to detect significant fibrosis in this younger population.

WED-472
Vibration-controlled transient elastography scores to predict liver fibrosis in biopsy-proven metabolic dysfunction-associated steatotic liver disease patients with diabetes: a prospective, multicenter study

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Background and aims: Agile 3+ and Agile 4 scores, based on vibration-controlled transient elastography (VCTE), provide non-invasive tools for identifying advanced fibrosis (AF, F≥3) and cirrhosis (F = 4) in metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to evaluate the diagnostic performance of Agile scores in biopsy-proven MASLD patients with type 2 diabetes mellitus (T2DM), a high-risk subgroup.
Method: This prospective multicenter study included 321 MASLD patients with T2DM from five Chinese hospitals between October 2017 and June 2024. The median age was 49.0 years, and 169 patients (52.6%) were male. MASLD was diagnosed based on presence of steatosis, cardiometabolic risk factors, and non-harmful alcohol intake. Liver fibrosis staging was performed histologically, and Agile scores were calculated. Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis and compared with liver stiffness measurement (LSM), fibrosis-4 index (FIB-4), aspartate aminotransferase (AST) to platelet ratio index (APRI), FibroScan-AST score (FAST), and NAFLD fibrosis score (NFS). Sensitivity, specificity, and predictive values of their well-defined dual cut-offs value were tested.
Results: Median Agile 3+ was 0.430 (interquartile range [IQR] 0.199–0.721), and median Agile 4 was 0.045 (IQR 0.014–0.152), while the median LSM was 8.1 (IQR 6.0–12.1) kPa. AF and cirrhosis prevalence were 21.5% (69/321) and 7.2% (23/321), respectively. Agile 3+ achieved an area under the ROC (AUROC) of 0.794 (95% confidence interval [CI] 0.728–0.861) for AF, significantly outperforming APRI (p = 0.036), FAST (p = 0.017), and NFS (p = 0.007). Agile 4 demonstrated an AUROC of 0.876 (95% CI 0.778–0.973) for cirrhosis, significantly higher than APRI (p = 0.005) and FAST (p < 0.001). Agile 4 and Agile 3 + outperformed FIB-4 and LSM in terms of AUROC, percentage of patients with indeterminate results and positive predictive value to rule-in cirrhosis or AF. The percentages of patients in the grey zone were 18.7% and 13.4% for Agile 3+ and Agile 4, respectively. Agile scores yielded fewer indeterminate results and higher rule-in and rule-out rates compared to other non-invasive tests.
Conclusion: Agile scores demonstrated excellent diagnostic accuracy for AF and cirrhosis in MASLD patients with T2DM, providing a reliable and non-invasive alternative for fibrosis assessment in this high-risk population.

WED-475
Plasma FSTL-1 accurately assesses MASH-associated liver fibrosis stage

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Background and aims: Emerging drugs for MASH target at liver fibrosis, especially alleviating F2/F3 liver fibrosis. Reliable non-invasive biomarkers for assessing MASH-associated fibrosis are crucial for clinical assessment and drug development. This study aimed at evaluating the accuracy of plasma Follistatin-like protein 1 (FSTL-1) in assessing MASH-associated fibrosis stages.
Method: Clinical data, plasma and liver biopsy tissues from 115 patients were collected including healthy controls (n = 37) and MASH (n = 78) from 2023 March to 2024 May. The plasma FSTL-1 levels were measured along with the steatosis levels and fibrosis stages based on liver biopsy tissues.
Results: Plasma FSTL-1 levels were significantly higher in MASH patients (0.47, IQR 0.30–0.60) than controls (0.32, IQR 0.16–0.43), showing a 1.5-fold increase. FSTL-1 levels positively correlated with steatosis and fibrosis stages. Among the MASH cohort, 36 patients (46%) had F2 and more, 22 (28%) had F3 and more. Plasma FSTL-1 distinguished fibrosis stages with high accuracy, achieving area under the receiver operating characteristic curve (AUROC) of 0.82 (95% confidence interval [CI], 0.72–0.91) for F ≥2 and 0.93 (95% CI, 0.84–1.00) for F ≥3, indicating that plasma FSTL-1 can accurately assess the MASH-associated liver fibrosis and distinguish participants from F2 and F3 highlighting its relevance in evaluating drug efficacy and facilitating drug discovery for MASH-associated fibrosis.
Conclusion: Plasma FSTL-1 can accurately assess the MASH-associated liver fibrosis and distinguishing liver fibrosis stages in MASH patients, offering a potential drug discovery for MASH-associated fibrosis.

WED-476-YI

Misclassification in non-invasive tests for liver fibrosis is expected: an example predicting liver stiffness in an international cohort

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Background and aims: Vibration-controlled transient elastography (VCTE) is a common tool for diagnosing liver fibrosis and steatosis. In locations where VCTE is not readily available, alternative blood-based scores such as the recently published LiverRisk score might be useful. However, even good alternatives are expected to give deviating results, since they are based on variables with limited predictive power. In this study we illustrate this by predicting VCTE liver stiffness using some of the most common non-invasive biomarkers—both by validating the LiverRisk score, and by developing a new score specifically for this study.
Method: We used an international multicenter cohort of patients with MASLD examined using VCTE. We used ordinal regression on the continuous outcome of VCTE liver stiffness. We predicted this outcome using flexible modelling with age, sex, center, and the most common liver-related blood-based biomarkers (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, platelet count, cholesterol, glucose, albumin, and bilirubin). This modelling approach includes the LiverRisk score as a special case. The discrimination and calibration of LiverRisk and this new model were assessed using the c-index for predicting liver stiffness >8 kPa and a calibration curve. Overall goodness-of-fit was then assessed using R^2 and the mean absolute prediction error (MAPE).
Results: We used 15,196 patients with MASLD without prior diagnosis of decompensated cirrhosis or hepatocellular carcinoma to train the model. The median (interquartile range) liver stiffness was 6.0 kPa (4.7–8.3). The new score showed good discrimination (c-index = 84%) and good calibration according to the calibration curve. Nonetheless, the proportion of explained variation was low (R^2 = 0.38) and the mean absolute prediction error was high (MAPE = 2.66 kPa). The sensitivity and specificity for classifying patients with and without VCTE liver stiffness >8 kPa were 53% and 89%, respectively. The positive and negative prediction values were 63% and 84%. The LiverRisk score understandably performed worse than the new score, mostly due to being developed in a different population (c-index = 74%, R^2 = 0.14).
Conclusion: When using risk scores for referral to specialist care, many patients are expected to be completely healthy, even in a seemingly good score. This is because the variables used in the scores contain limited information about the outcome of interest.

WED-477

Validating non-invasive tests for diagnostic prediction of fibrosis in patients with biopsy-proven MASLD: CORE, LiverRisk, and FIB-4

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Background and aims: Several non-invasive blood-based tests have been proposed for finding advanced fibrosis in patients with known or suspected MASLD. However, also patients with earlier stages of fibrosis (F2) may require and be eligible for approved treatments. Here, we validated the novel risk scores CORE and LiverRisk, compared with the current first-line test FIB-4 for predicting the stage of liver fibrosis according to biopsy in patients with biopsy-proven MASLD.
Method: We used data from patients diagnosed with MASLD at three Swedish university hospitals between 1974–2021 with available biopsy results. We used ordinal regression to map values of each risk score to probabilities of having each fibrosis stage. We used the c-index, the Brier score, and decision curve analysis to compare each score's ability to select patients with fibrosis stage F2 or higher, and F3 or higher.
Results: Among the 964 included patients, 367 (38%) had fibrosis stage F2 or higher, and 155 (16%) had stage F3 or higher. Overall, the scores were better at predicting patients with stage F3+ (c-index & Brier score for CORE: 0.78 & 0.116, LiverRisk: 0.74 & 0.121, FIB-4: 0.81 & 0.107) than patients with stage F2+ (c-index & Brier score for CORE: 0.68 & 0.213, LiverRisk: 0.64 & 0.222, FIB-4: 0.70 & 0.203). The decision curve analysis consistently showed the highest net benefit between true positives and false positives for FIB-4, followed by CORE and then LiverRisk.
Conclusion: In patients with known MASLD and available liver biopsy, FIB-4 was the preferred non-invasive test for predicting advanced fibrosis. All models performed worse to detect fibrosis stage 2 or more, suggesting the need for improved models to define earlier stages of fibrosis. The clinical utility of all scores for referral to subsequent testing with vibration-controlled transient elastography or hepatology referral depends on a so far undetermined risk tolerance for correct versus incorrect referral.

WED-478

Novel multiparametric MRI imaging predicts histologic response in resmetirom versus placebo in the multicentre, international, Maestro NASH phase 3 trial

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Background and aims: Resmetirom was approved by FDA in March 2024 and is indicated for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3). MAESTRO-NASH (NCT03900429) is an ongoing 54-month, randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy of resmetirom in patients with biopsy confirmed non-alcoholic steatohepatitis (NASH) and fibrosis. Dual primary endpoints at Week 52 were achieved with both resmetirom 80 mg and 100 mg: NASH resolution with no worsening of fibrosis or ≥1-stage reduction in fibrosis with no worsening of NAS. All participants also received non-invasive tests, with change in MRI-PDFF a key secondary endpoint. For a subset of patients MRI-derived cT1, a marker of fibro-inflammation, was collected. A reduction in cT1 of −80 ms has been identified as the optimal threshold associated with histological

response. We explored the cT1 responses observed in the Maestro-NASH trial.
Method: Adults with ≥3 metabolic risk factors, liver stiffness ≥8.5 kPa, hepatic fat ≥8%, biopsy-confirmed NASH with F1B-F3 fibrosis, and NAS ≥4 were eligible to participate in MAESTRO-NASH. cT1 was acquired using LiverMultiScan. Average changes in cT1 with increasing dose, and with histological response was assessed and summary descriptive statistics reported. cT1 responders were considered those who had an ≥80 ms reduction in cT1.
Results: 156 patients had cT1 and histology data (mean age: 57 years old, 56% female, mean BMI: 37 kg/m^2). cT1 and PDFF were positively correlated (Spearman's rho ranging between 0.68–0.83) and cT1 increased with increasing fibrosis stage. After 16-weeks of Resmetirom treatment, the mean reduction in cT1 was −48 ms (SD: 101 ms) in the 80 mg group (N = 37) and −78 ms (SD: 88 ms) in the 100 mg group (n = 46). There was minimal change in the in the placebo group (−8 ms, (SD: 56 ms), N = 51). This dose-dependent pattern in cT1 change was maintained at 52 weeks. Additionally, 25% and 36% met the cT1 response criteria in the 80 mg and 100 mg arms, respectively. cT1 reduction was larger in histological responders than non-responders for NASH Resolution in the 100 mg arm (mean change −125 ms versus −46 ms; cT1 responders 53% versus 19%) and for fibrosis Improvement in both 80 mg (mean change −84 ms versus −11 ms) and 100 mg arms (mean change −124 ms versus −74 ms; cT1 responders 70% versus 24%).
Conclusion: A positive association with fibrosis stage and with MRI-PDFF was observed for cT1 in this subset analysis. cT1 demonstrated a dose dependent reduction with Resmetirom treatment, with the greatest reductions in the 100 mg group, and a negligible placebo response. A reduction in cT1 of >80 ms was associated with high likelihood of histological response. These data suggest cT1 may be a suitable test for monitoring response in patients being treated with Resmetirom.

WED-479
Assessment of the metabolic dysfunction-associated steatohepatitis resolution index and component biomarkers in prediction of histology response to denifanstat in the FASCINATE-2 trial

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Background and aims: Denifanstat, a fatty acid synthase inhibitor in clinical development for metabolic dysfunction-associated steatohepatitis (MASH), met statistical significance in histology endpoints in Ph2b FASCINATE-2. Liver biopsy is the currently accepted endpoint in MASH trials for accelerated regulatory approval. However, because of biopsy's invasive nature and variability, there is an important unmet clinical need to identify and test non-invasive biomarkers to more efficiently diagnose, monitor and predict treatment response in clinical trials and in the real-world setting. The MASH Resolution Index (MR-I) has recently been defined by Loomba et al., as a non-invasive biomarker score including liver fat, ALT and AST that predicts MASH resolution (MR) by histology. This analysis aimed to test the performance of MRI-I in predicting MR by denifanstat by retrospective analysis of FASCINATE-2.
Method: 168 patients with biopsy-confirmed F2/F3 MASH were randomized 2:1 to once daily oral denifanstat 50 mg or placebo for 52 wk. Pre- and wk52 liver biopsy slides were read by an expert central pathologist using NASH-CRN criteria. Liver fat by MRI-PDFF was measured pre, wk26 and wk52. ALT and AST also at wk4 and wk13. MR-I was calculated at wk26 and wk52 for each patient, defined as 0.520–0.003 × baseline ALT (U/L) −0.024 × (latest ALT [U/L]- baseline ALT (U/L)) −0.048 × baseline MRI-PDFF −2.571 × ((latest MRI-PDFF - baseline MRI-PDFF)/baseline MRI-PDFF) −0.039 × baseline AST (U/L). Logistic regression (LR) models were used for analysis versus MR.
Results: Wk52 MR-I showed strong performance and predicted week 52 MR with an AUC of 0.72 ($p < 0.05$ LR), 83% negative predictive power (NPV), and 81% specificity. The week 26 MR-I predicted wk52 MR with an AUC of 0.73, 86% NPV, 56% PPV, 78% specificity, 66% sensitivity, $p > 0.05$ (LR). Testing individual biomarkers showed liver fat change at week 26 had strong diagnostic performance (AUC 0.73, $p > 0.05$), notably high NPV of 91% and 83% sensitivity. ALT change as a continuous variable had AUC of 0.60 and 0.68 at wk4 and wk13, with up to 94% specificity for prediction of wk52 MR, $p < 0.05$ (LR). Taken together, these results indicate that MR-I and its components have potential application to enrich for responders to denifanstat.
Conclusion: This retrospective analysis of the FASCINATE-2 Phase 2b trial demonstrated that MR-I can predict MR. In this analysis, MR-I showed potential to predict non-responders. Further analysis and additional non-invasive markers are being pursued specifically at earlier timepoints, to provide non-invasive approaches to predict response to treatment in future MASH clinical studies.

WED-480
Denifanstat-mediated reduction of plasma glycine- and taurine-conjugated bile acids correlates with histological improvements in denifanstat-treated metabolic dysfunction-associated steatohepatitis patients in phase 2b FASCINATE-2 study

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Background and aims: Increased *de novo* lipogenesis (DNL) drives the development of metabolic dysfunction-associated steatohepatitis (MASH). Fatty acid synthase (FASN) is the rate-limiting enzyme in the DNL pathway. In the Phase 2b FASCINATE-2 study, 56% of MASH patients with F2/F3 fibrosis treated with denifanstat, a selective FASN inhibitor, achieved either fibrosis improvement ³ 1 stage or MASH resolution. To identify potential biomarkers that predict histological responses, plasma lipidomic/metabolomic analyses were performed. Glycine- and taurine-conjugated bile acids play a crucial role in emulsifying and solubilizing dietary fats in the small intestine. In addition to their digestive functions, these conjugated bile acids act as endocrine hormones, mediating gut-liver crosstalk. Elevated serum bile acid levels have been associated with metabolic disorders, such as MASH and type 2 diabetes. This study evaluated the correlation between bile acid changes and histological improvements in MASH patients treated with denifanstat.
Method: MASH patients with biopsy confirmed F2/F3 fibrosis and NAFLD Activity Score ≥4 were enrolled in FASCINATE-2 for 52 weeks treatment. Comprehensive lipidomic and metabolomic analyses were conducted at several visits in the study (OWL Metabolomics).
Results: In the lipidomic/metabolomic analyses, ten abundant plasma bile acids were measured in MASH patients, and glycine- and taurine-conjugated bile acid pools (G- and T-BAs) showed significant reductions following 52 weeks of denifanstat treatment (-27% and −45% vs. placebo +5% and +7%, respectively, $p < 0.001$). Notably, five specific G/T-BAs demonstrated significant reductions in patients with histological responses (³ 1-stage fibrosis improvement or MASH resolution) compared to non-responders or placebo patients. Furthermore, significant reductions in these five G/T-BAs were evident by week 26 in denifanstat-treated patients who

achieved histological improvements by week 52. Among these G/T-BAs, glycodeoxycholic acid and taurodeoxycholic acid exhibited rapid and significant decreases as early as weeks 4 and 13 in histological responders treated with denifanstat, with no significant decreases shown in non-responders or placebo patients.
Conclusion: Identifying reliable biomarkers for response prediction is crucial for advancing precision medicine. In MASH patients treated with denifanstat, glycine- and taurine-conjugated bile acids were significantly reduced at 26 weeks in histological responders for both fibrosis regression and MASH resolution, suggesting that this could potentially be leveraged as a response biomarker in patients treated with denifanstat.

WED-481
Advanced metabolic-dysfunction associated steatotic liver disease fibrosis: low number-needed-to screen in multiple lines of care
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Background and aims: Non-invasive liver tests (NITs) can detect advanced fibrotic MASLD and reduce unnecessary referrals. Yet data comparing numbers-needed-to-screen (NNS) in multiple lines of care are scarce. Therefore we introduced NLA2, the first Dutch MASLD care path, encompassing primary, secondary and tertiary clinics.
Method: Patients at cardiometabolic risk for MASLD were recruited from GPs, regional clinics and a UMC, whilst excluding other liver diseases. Simultaneous FIB4, MAF5, Enhanced Liver Fibrosis (ELF)-test and vibration-controlled transient elastography (VCTE/ FibroScan®) allowed testing of NIT combinations. FIB4 ≥3.25 and/or Liver Stiffness Measurement (LSM) ≥8.0 kPa indicated potential advanced fibrosis, prompting referral to hepatology. Referral patterns were compared to regular care between 2016 and 2024 using a predefined evaluation standard.
Results: 655 participants entered NLA2, 270 from primary, 156 from secondary and 229 from tertiary care. After excluding patients with MetALD or other liver diseases, 597 were analyzed. Median age was 60 years (51–68), 45.9% were women, 51.4% had obesity and 45.2% had T2DM. 73.9% of participants had CAP ≥ 248 dB/m, suggesting ≥ S1 steatosis. 15.5% had LSM ≥8.0 kPa, yielding a NNS of 6.7. NNS decreased across lines of care: 12.1, 5.1 and 5.2 for primary, secondary and tertiary care respectively, inversely related to cardiometabolic comorbidities (mean number 2.1, 2.3, 2.9). ELF was available for 535 participants. 20.0% had ELF ≥9.8, yielding NNS of 5.0. FIB4 stratifies 64% as low risk for advanced fibrosis and 36% as intermediate/high risk. MAF5 stratifies 40% as low risk for advanced fibrosis and 60% as high risk. In a 2-tiered algorithm in case of MAF5 ≥1, VCTE as second test would refer 6.4%; using ELF would refer 11.7%. In a 2-tiered algorithm in case of intermediate FIB4 (1.3–3.25), VCTE as second test would refer 13.1%; using ELF would refer 13.5%. Of 96 patients at risk for advanced fibrosis, 72 were referred to hepatology. 465 patients were referred to hepatology via regular care between 2016 and 2024. Compared to regular care, NLA2 improved correct referrals 4-fold (RR 4.03; 95% CI 2.53–6.41). Unnecessary referrals were reduced 2-fold (RR 0.44; 95% CI 0.27–0.69).
Conclusion: The first Dutch MASLD care path study shows incrementally lower NNS for potential advanced fibrosis detection across multiple lines of care and a significantly improved referral pattern for fibrotic MASLD. We found a marked difference in referral-rate between different NIT combinations.

WED-482
Leveraging natural language processing (CogStack) to analyse FibroScan data: a seven-year exploration (2016–2023) of socioeconomic disparities, ethnic variations, and fibrosis trends
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Background and aims: Non-invasive liver health assessments, such as FibroScan, are increasingly valuable for identifying fibrosis and liver damage across diverse populations. This study leverages CogStack, an advanced data retrieval and analysis platform, to evaluate FibroScan data. The primary aims were to analyse trends in the deprivation index and ethnic diversity among individuals undergoing FibroScan and correlate these variables with the severity of fibrosis.
Method: This retrospective study analysed FibroScan results from electronic health records (EHR) collected between 2016 and 2023 at King's College Hospital's liver outpatient clinic. Data processing was conducted using CogStack, which enabled efficient extraction of both structured and unstructured clinical information. Collected patient demographics included age, gender, ethnicity, and deprivation index scores. Liver stiffness measurements (LSM) and Controlled Attenuation Parameter (CAP) values were analysed to assess fibrosis and steatosis trends over time.
Results: A total of 24,908 FibroScan results were analysed through CogStack. The catchment areas for the patients included Lewisham (25.89%), Lambeth (27.21%), Southwark (29.70%), and Bromley (17.21%). The cohort had a slight male predominance, with 53.3% male and 46.7% female patients, and a mean age of 45 years. The majority of patients were White (42.85%), followed by Unknown (22.56%), Black (20.90%), Asian (8.30%), Other (5.51%), and Mixed (0.30%) ethnicities. The mean liver stiffness measurement (LSM) was 8.38, with 28% of patients showing high LSM values indicative of significant fibrosis. The mean CAP value was 313.68, suggesting a trend towards hepatic steatosis in a significant proportion of patients. For our data, we had 9302 patients index of multiple deprivation (IMD) data (37.35% of the total cohort), with 67.83% of patients being in the fifth decile or below. For these the mean LSM was 8.15, with an interquartile range (IQR) of 4.5 to 7.9.
Conclusion: This study underscores the utility of CogStack for extracting and analysing large-scale clinical data to identify disparities and trends in liver health. Findings highlight the need for targeted public health interventions addressing high-risk populations defined by socioeconomic and ethnic factors.

WED-483
Development of a deep learning-based model for predicting liver-related events in steatotic liver disease using specific health checkup data
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Background and aims: Steatotic liver disease (SLD) affects approximately 30% of the population, posing challenges in risk stratification. This study aimed to develop a predictive model for liver-related events (LREs) using Health Checkup data, which annually screens 7.6 million individuals in Japan.
Method: From the JMDC database, 1,449,032 SLD patients were identified after excluding those with chronic liver diseases or a history of LREs or cardiovascular events. Data were split into a training set (1,049,322 patients) and a test set (449,710 patients). Predictive

models, including DeepSurv, Random Survival Forest (RSF), and Cox proportional hazards (CoxPH), were developed and evaluated using Harrell's C-index. Risk stratification and SHAP (SHapley Additive exPlanations) analyses were performed with the best-performing model.
Results: The median follow-up was 4.5 years, with cumulative LRE rates of 0.03% at 3 years, 0.07% at 5 years, and 0.16% at 10 years. The DeepSurv model (C-index: 0.893) outperformed RSF (C-index: 0.879), CoxPH (C-index: 0.875), and conventional metrics like Fatty Liver Index (C-index: 0.339). Risk stratification revealed significantly higher LRE rates in the high-risk group (0.658%/10 years) compared to intermediate-risk (0.058%/10 years, $p < 0.0001$) and low-risk groups (0.009%/10 years, $p < 0.0001$). SHAP analysis identified age, AST, ALT, GTP, BMI, and smoking as key predictors.
Conclusion: The DeepSurv model demonstrated superior predictive performance and enabled effective risk stratification for LREs in SLD patients.

WED-484
The culprits behind methotrexate-proposed hepatotoxicity are modifiable risk factors

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Background and aims: Methotrexate (MTX), a cornerstone in managing rheumatoid arthritis (RA) and psoriatic arthritis (PsA), is often discontinued due to hepatotoxicity concerns. Emerging evidence suggests a multifactorial etiology involving modifiable risk factors such as metabolic syndrome. This study aimed to identify specific risk factors underlying MTX-related hepatotoxicity and examine the utility of non-invasive liver fibrosis scores to rule out patients at risk of liver fibrosis, thus minimizing unnecessary MTX discontinuation.
Method: This prospective study included 179 patients (108 women, 71 men; median age 61 years, range 53–67 years) with RA (n = 123) or PsA (n = 56), categorized by MTX treatment duration. Liver assessments were carried out using acoustic radiation force impulse (ARFI) and Fibroscan® (fibrosis measured in kilopascal (kPa) and steatosis grade measured by controlled attenuation parameter (CAP)). Participants underwent comprehensive blood tests, anthropometric measurements, and questionnaires. Non-invasive fibrosis scores (e.g., FIB-4, APRI) were calculated and compared to imaging results.
Results: There were no signs of liver fibrosis on Fibroscan® (median: 4.6 kPa, range 3.85–5.85) or ARFI (median: 2.8 kPa, range 2.2–3.6) despite many Fib-4 and APRI scores indicating the presence of fibrosis. On the other hand, several patients had varying degrees of liver steatosis on Fibroscan® (CAP median: 242.5 dB/m, range 213.5–278.0; Steatosis Grade: S2) which may explain this discrepancy. We found statistically significant correlations between steatosis and metabolic factors including higher body weight (CI:0.226–0.523, $p < 0.0001$), waist circumference (CI:0.174–0.483, $p < 0.0001$), triglycerides (CI:0.112–0.432, $p < 0.0014$), fasting glucose (CI:0.013–0.347, $p = 0.004$), and lower HDL-cholesterol (CI:-0.446 to – 0.129, $p = 0.0007$). Interestingly, higher Alcohol consumption, analysed using B-PEth showed no significant correlation with steatosis (CI:–0.019 to 0.314, $p = 0.08$). Neither MTX dose nor duration showed any significant correlation with steatosis or fibrosis grade (CI:–246–0.108, $p = 0.437$).
Conclusion: A majority of patients on MTX do not have liver fibrosis but rather varying degrees of steatosis, suggesting metabolic dysfunction-associated steatotic liver disease (MASLD) as a modifiable risk factor emphasizing the importance of addressing MTX-related hepatotoxicity. Steatosis in these patients can be detected using simple non-invasive tests such as the FIB-4 index reducing the need for specialized personnel or instrumentation.

WED-485
US markers and necroinflammation, steatosis, and fibrosis in metabolic dysfunction-associated steatotic liver disease: the iLEAD study

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Background and aims: Attenuation coefficient (AC) and shear-wave speed (SWS) are established US markers for assessing patients with metabolic dysfunction-associated steatotic liver disease (MASLD), while shear-wave dispersion slope (DS) is not. The purpose of this study was to assess the relationship between the multiparametric US imaging markers DS, AC, and SWS and liver histopathologic necroinflammation in patients with MASLD.
Method: This international multicenter prospective study enrolled consecutive patients with biopsy-proven MASLD between June 2019 and March 2023. Before biopsy, all participants underwent multiparametric US, and measurements of DS, AC, and SWS were obtained. Multivariable linear regression analyses were performed to assess the association of clinical variables and imaging markers with pathologic findings. The diagnostic performance of imaging markers for determining inflammation grade, steatosis grade, and fibrosis stage was assessed using the area under the receiver operating characteristic curve (AUC).
Results: A total of 124 participants (mean age, 53 years ± 15 [SD]; 62 males) were evaluated. In multivariable regression, lobular inflammation was associated with DS (regression coefficient, 0.06; $P = 0.02$), alanine aminotransferase level (regression coefficient, 0.002; $P = 0.002$), and Hispanic or Latino ethnicity (regression coefficient, –0.68; $P = 0.047$), while steatosis was associated with AC (regression coefficient, 3.66; $P < 0.001$) and fibrosis was associated with SWS (regression coefficient, 2.02; $P < 0.001$) and body mass index (regression coefficient, 0.05; $P = 0.02$). DS achieved an AUC of 0.72 (95% CI: 0.63, 0.82) for identifying participants with inflammation grade A2 or higher (moderate to severe inflammation). AC showed excellent performance for identifying participants with grade S1 (mild) or higher steatosis (AUC, 0.92 [95% CI: 0.87, 0.97]), while SWS

showed excellent performance for identifying participants with fibrosis stage F2 or higher (clinically significant fibrosis) (AUC, 0.91 [95% CI: 0.86, 0.96]). Of the three US markers, SWS showed the highest AUC (0.81 [95% CI: 0.74, 0.89]) for the diagnosis of metabolic dysfunction-associated steatohepatitis.
Conclusion: Of the three US imaging markers (DS, AC, and SWS), DS was most associated with lobular inflammation grade at histologic examination and demonstrated fair diagnostic performance in distinguishing moderate to severe lobular inflammation.

WED-486
First construction and validation of new circulating markers (NITs) to assess the risk of early-fibrosis (eF) occurrence in outpatients with type-2 diabetes (T2D) and elevated transaminases
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Background and aims: An unmet need in MASLD is a single NIT predicting together the time-dependent steatosis (S) and inflammatory activity (I) and the fibrosis stage (F) occurring later. Here, we constructed such SIF-FibroTest combining SteatoTest-2, NashTest-2 and FibroTest, separately previously validated in 402 consecutive T2D-outpatients with elevated transaminases (QuidNash-cohort). The histological comparator was based on a modified 5tier-CRN score, with F0-F1A-F1C being no-bridging-fibrosis, F1B early fibrosis (eF), significant fibrosis stages (sF) still being the standard CRN F2-to-F4. This higher granularity for the diagnosis of eF was already used in the phase-3 trial of the resmetirom treatment, which demonstrated a superiority to placebo in improving non-cirrhotic stages by at least one-stage with NASH-resolution.
Method: We characterized the profiles of F0-F1A-F1C patients compared to those with eF, including confounding factors (CFs). Among these 402 subjects, 32%were F0-F1A-F1C at biopsy, 31%eF, 17% F2, 28%F3 and 9%F4. Secondly, we constructed the SIF-FibroTest calibrated for the diagnosis at predicting eF at baseline and the F trajectories according to I, S, age, and BMI. SIF-FibroTest was compared head-to-head and intention-to-diagnose at baseline with SIF-VCTE one combining VCTE for eF, controlled-attenuation-parameter (CAP) for S, and AST for I. CFs were identified by logistic-regression odds-ratio (OR), F-trajectories used cumulative-hazard ratio (HR) function, and Cox-models for the occurrence of sF and AUROCs for performances.
Results: In the F0-profiles, prevalence of Nash-activity score (NAS)≥1 was already 91% and higher in eF versus F0 (OR = 2.7; 95% 1.7–4.1; p = 0.001). F0-profiles were similar (all p > 0.50) to those of eF: age median 57years, male-sex (39% vs 35%) and BMI (31 kg/m^2). Versus F0-profiles, SteatoTest-2 was elevated in eF (OR = 7.1; 1–4.3; p = 0.04), and sF (OR = 32;4.7–82; p = 0.003). Higher steatosis-grades estimated using biopsy or SteatoTest-2 were associated with earlier sF occurrence, and NashTest-2 later. Higher steatosis-grade (HR95% CI; 1.3;1.1–1.5;p = 0.0005) and higher BMI accelerated eF-occurrence (HR = 1.03; HR95% CI; 1.01–1.05; p = 0.001). SIF-FibroTest (0.77; 95% 0.73–0.82) and SIF-VCTE AUROCs (0.76; 0.71–0.80) had a non-significant difference (equivalence-p = 0.08).
Conclusion: If confirmed by independent studies, NITs calibrated for eF could replace liver biopsy for surveillance and approval of anti-fibrosis treatments in T2D outpatients with elevated transaminases.

WED-487
The blood-based SteatoTest-2 score identifies a previously invisible early steatosis phenotype
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Background and aims: Steatosis is a major liver feature of the steatosis-associated liver disease (SLD) definition. There is a consensus on using hepatic proton density fat fraction (PDFF) as a reference for assessing the diagnosis performance of circulating liver steatosis non-invasive circulating biomarkers (NITs). However, Steatosis grade S1 had been defined arbitrarily as PDFF≥5% to 33%. As PDFF has a low 1.2–1.6% measurement error, we aimed to identify if an early-steatosis (ES) phenotype (S1A) defined as PDFF from 3.2–6.4% following Kim et al recommendations (APT 2023) could be identified in a general population with or without risk of MASLD and MetALD, as well as in outpatients with type-2 diabetes (T2D) with biopsy. Then, we constructed and validated a new NIT for an earlier identification of SLD. S1B was defined as PDFF from 6.4%-17.4%, S2 S3 remained with PDFF 17.4–22.1% and ≥22.1% respectively.
Method: For this purpose, we first post-hoc analyzed apparently healthy participants of the UK-biobank (n = 31,715) with repeated PDFF and used a proxy of the validated SteatoTest-2 (ST2proxy) to assess the prevalence of ES in UKB participants (n = 343,064) among MASLD and MetALD, according to the number of cardiometabolic risk-factors (CF 1–4/5) and alcohol intake (verylow-increased). Characteristics of subjects with S0, S1A and S1B as well as overall mortality were compared using, uni- and analyses (separate logistic regression by sex) and AUROCs to validate the specificity of the phenotypes S1A vs S0 and vs S1B subjects.
Results: In UKB, in 16,322 women the prevalence of S0/S1A/S1B were 45/33/22% and in15,403 men 22.5/42.5/35%). Between the 20 subsets stratified by MASLD, MetALD, CF and alcohol intake all the S1A prevalences ranged significantly. The range was 9–25% in women, and 17–31% in men. The multivariate analysis among in subjects without S2S3 found that only hypertension Hazard-Ratio was significantly associated with 10 years overall mortality in women (HR; 95% CI = 1.80;1.19–171;p = .04) and men (1.36;1.01–0.048; p = 0.048), and glucose (1.40;1.02–1.94; p = 0.04), triglycerides (1.40;1.03–1.90; p = 0.03) increases only in men. In 145 T2D with PDFF, the prevalence of S0/S1A/S1B were 0/12/88%. ST-2TD permitted to diagnose the stage S1A vs S2B with a significant AUROC = 0.77; 95% CI 0.60–0.87; p < 0.0001.
Conclusion: With the limitation of a European origin context of use, these results strongly suggest than subjects with early steatosis stage S1A have a phenotype at risk of MASLD.

WED-488
Weight loss-related changes in MRI-derived measures of body composition and liver health: a large-scale analysis from the UK biobank
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Background and aims: Amid rising global obesity rates and recent advances in weight-loss therapies, measuring body composition and the resolution of ectopic fat relative to weight loss could refine treatment strategies to enhance liver, cardiometabolic, and skeletal muscle health. This study aimed to investigate weight loss-related changes in visceral and subcutaneous adipose tissue, skeletal muscle

volume, and the associated changes in liver fibro-inflammation and fat content using MRI, in a large-scale cohort from the UK Biobank.
Method: Participants (N = 3,919) from the UK Biobank with whole-body Dixon MRI scans from two visits, spaced 1–3 years apart (mean 2.6 years), were included. MRI data were processed automatically to derive volumetric visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle (SM) in the abdominal region. Liver fat content (liver steatosis from proton density fat fraction) and liver fibro-inflammation (cT1) were assessed using LiverMultiScan. Participants were categorized into two groups based on relative weight change between visits: ≥5% weight loss and <5% weight loss (causes of weight loss were not investigated). Within-group comparisons were conducted using the paired Wilcoxon signed-rank test, while between-group comparisons were assessed with the Wilcoxon rank-sum test.
Results: In the ≥5% weight loss group (N = 415, mean age 64 years, male 47%, BMI 27 kg/m^2, baseline VAT 3.9 litres (L), SAT 7L, SM 5.4L, LFC 3.6%, cT1 703 ms), significant reductions from baseline were observed: LFC −25%, VAT of −27%, SAT of −21%, and SM of −3.4% (all $p < 0.001$). Liver cT1 decreased by 1.2% (10 ms), which was not clinically significant. In the <5% weight loss group (N = 3,294, mean age 63 years, male 51%, BMI 26 kg/m^2, baseline VAT 3.2L, SAT 6L, SM 5.5L, LFC 3%, SM 5.5L, cT1 689 ms), no significant reductions were observed in any of the body composition or liver metrics. Between-group comparisons showed significant differences across all metrics ($p < 0.001$).
Conclusion: Individuals who lost ≥5% weight demonstrated substantial reductions between imaging visits in liver fat, VAT, SAT, and skeletal muscle volume, and compared to the <5% weight loss group. Reductions in liver fat were not accompanied by parallel improvements in metrics of liver fibro-inflammation. While a weight loss of ≥5% significantly improves MRI adiposity-related measures, targeted therapeutic strategies and patient stratification prior to intervention may be necessary to minimize muscle loss, and reduce liver steatosis and its sequela of fibro-inflammation.

WED-489

Similar prevalence of MASLD and liver fibrosis when screening high-risk patients identified in primary care versus outpatient clinics in secondary care

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Background and aims: Suboptimal awareness and insufficient knowledge about MASLD and its progressive stages (MASH and advanced fibrosis) still lead to significant underdiagnosis. The 'Global Research Initiative for Patient Screening on MASH' (GRIPonMASH) Consortium aims to facilitate and investigate care path implementation at primary and secondary care level.
Method: In this prospective multicenter observational study, we aim to screen 10.000 individuals with cardiometabolic risk factors, but no prior liver disease diagnosis, in 10 European countries. High-risk is defined as having type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), obesity or arterial hypertension. Patients qualifying as high-risk are identified at both primary care centers and at outpatient clinics. In this preliminary analysis we report descriptives of the screened populations and results of vibration-controlled transient elastography (VCTE) measurements with FibroScan. MASLD was assumed if controlled attenuation parameter (CAP) ≥275, as all included patients have cardiometabolic risk factors.
Results: Thus far, 412 individuals from 5 countries (NL, BE, DE, ES, PT) have been included, of whom 56% were recruited at primary care centers and 44% in outpatient clinics (i.e. internal medicine, diabetology, endocrinology). The median age was 60 (IQR: 16) years in primary care versus 57 (17) years at the outpatient clinic, 42% vs. 52% was female, mean weight was 93 (± SD: 20) vs. 96 (± 20) kg and mean BMI 32 (± 6) vs. 33 (± 6) kg/m2 respectively. The majority of the population was Caucasian (75%). In primary care, the primary diagnosis for inclusion was arterial hypertension (33%), followed by T2DM (32%), obesity (30%) and MetS (5%). At the outpatient clinic, this was T2DM (41%), obesity (30%), arterial hypertension (28%) and MetS (2%). The level of liver steatosis measured by CAP was similar between patients recruited in primary care vs. the outpatient clinic: mean 285 (± 57) vs. 285 (± 53) dB/m. The prevalence of MASLD was 59% and 58%, respectively. Liver stiffness measurement (LSM) by VCTE was also similar: median 5.3 (IQR 2.9) vs. 5.3 (2.6) kPa. In primary care 83% had a low risk of fibrosis (<8.0 kPa), 13% were at risk for significant fibrosis (8.0–12.0 kPa) and 4% had advanced fibrosis (>12.0 kPa). Results in the outpatient clinic were again similar with 82%, 12% and 6% respectively. The most striking difference between the recruitment locations was the higher use of insulin at the outpatient clinic.
Conclusion: In this preliminary analysis in a first subset of the GRIPonMASH cohort, the prevalence of MASLD and advanced fibrosis was similar for high-risk patients screened after identification in primary care and at the outpatient clinic. The GRIPonMASH project is supported by the Innovative Health Initiative Joint Undertaking, its members and its contributing partners under grant agreement No 101132946.

WED-490

Ultrasound-derived visceral adipose tissue: an easily obtainable adiposity index strongly associated with metabolic dysfunction-associated steatotic liver disease and metabolic parameters

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Background and aims: Emerging evidence suggests that adiposity indices beyond body mass index (BMI) are better predictors of metabolic complications, including metabolic dysfunction-associated steatotic liver disease (MASLD). Among these indices, visceral adipose tissue (VAT) has garnered attention, but the clinical translation of available techniques (magnetic resonance imaging and computed tomography) remains constrained due to their intrinsic limitations. Ultrasound (US)-based VAT measurements offer a feasible alternative. However, only a few studies evaluating this approach have been reported. Here we aimed to evaluate the associations of US-measured VAT with metabolic parameters, liver enzymes and hepatic steatosis in comparison with those of BMI and waist circumference (WC).
Method: Patients enrolled at Fondazione Policlinico Universitario Campus Bio-Medico of Rome for the All-Liver Interventional Global

Network (ALIGN) screening study were included. Inclusion criteria were age 18–75 years, and history of hepatic steatosis and/or diabetes and/or obesity, without other causes of chronic liver disease. US-measured VAT was assessed as the distance between the inner surface of the anterior rectus muscle and the anterior aortic wall. Steatosis was defined by ultrasound derived fat fraction (UDFF). Correlations and linear regression analyses were performed to assess the relationship between VAT, metabolic parameters, liver enzymes, UDFF, and FibroScan-AST (FAST) score.

Results: 837 patients were included [mean age 56 years (SD 11.5), 60% male], with a median BMI of 31.1 kg/m² (IQR 27.8–34.4). Higher US-measured VAT tertiles were associated with an increased prevalence of diabetes ($p = 0.002$), hypertension ($p < 0.0001$), elevated triglycerides ($p < 0.0001$), and liver enzymes [AST ($p = 0.005$), ALT ($p = 0.001$)]. The correlations of US-measured VAT with metabolic and hepatic parameters were almost always stronger than those of BMI and WC: HbA1c ($p = 0.019$ vs BMI), triglycerides ($p < 0.0001$ vs BMI; $p = 0.0004$ vs WC), ALT ($p = 0.002$ vs BMI; $p = 0.026$ vs WC), UDFF ($p = 0.00005$ vs BMI; $p = 0.00091$ vs WC), and FibroScan-AST (FAST) score ($p = 0.035$ vs BMI). At multivariate linear regression, VAT (beta = 1.33, $p < 0.001$) was the only adiposity index associated with UDFF, along with triglycerides (beta = 0.01, $p = 0.008$) and hypertension (beta = 1.52, $p = 0.021$). Notably, for any given BMI, higher VAT tertiles were associated with a progressively greater mean UDFF percentage (T2 vs T1: + 33.07%; T3 vs T1: + 62.17%; T3 vs T2: + 22.26%).

Conclusion: US-measured VAT is an easily obtainable measure that strongly correlates with metabolic parameters and UDFF, outperforming BMI and WC. If validated in larger cohorts, the measurement of VAT can be proposed to complement liver ultrasound examination for baseline assessment and monitoring of patients with suspected/known MASLD.

WED-491

Longitudinal validation of the AGA, AASLD and EASL care pathways for metabolic dysfunction-associated steatotic liver disease (masld) in a prospective cohort of individuals with type 2 diabetes

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Background and aims: Multiple international societies recommend a care pathway with sequential testing with FIB-4 and vibration-controlled transient elastography (VCTE) for populations at-risk for MASLD, including those with type 2 diabetes (T2DM). However, there are limited data on the longitudinal performance of these pathways in patients with systematic follow-up assessment. We aimed to validate longitudinal care pathway assessment in a prospectively recruited cohort with T2DM at risk for MASLD with 2-year follow up using magnetic resonance elastography (MRE), the most accurate non-invasive biomarker of fibrosis.

Method: This prospective study enrolled adults age ≥50 years with T2DM recruited from primary care and endocrinology clinics. Participants underwent a standardized clinical research visit with MRI-PDFF, MRE and VCTE and follow up assessment. Participants with alcohol intake exceeding AASLD guidance for MASLD were excluded. The outcomes were the diagnostic performance of the clinical pathway for MRE ≥ 3.3 kPa based on recently published recommendations supporting pharmacologic treatment at this threshold.

Results: 188 patients (40% men) with baseline and follow up visits separated by a mean (SD) of 2.1 (0.75) years were included. The mean (±SD) age and BMI were 64.3 (±7.7) years and 31.1 (±4.8) kg/m^2, respectively. At baseline 148 (79%) of individuals were classified as low risk; 92 with FIB-4 <1.3 and 56 with FIB-4 1.3–2.67 and VCTE <8 kPa. The false negative rate for detecting significant fibrosis warranting treatment in patients classified as low risk was 7.6% and 21% of the cohort would qualify for specialty referral. 90% of false negatives were related to FIB-4 <1.3. Among the 148 low-risk individuals on baseline assessment, 137 (93%) remained low risk and the false negative rate decreased to 3.4%. Follow up of the false negative participants at baseline demonstrated that only 20% remained misclassified, 40% had an increase in repeat FIB-4 with appropriate classification at follow up and 40% had liver stiffness decrease below the significant fibrosis threshold indicating improvement.

Conclusion: Longitudinal validation of multi-society guidance in a well-phenotyped, prospectively recruited cohort of adults with T2DM revealed that repeat assessment at 2-years enhanced performance to detect patients with significant fibrosis who may be eligible for treatment and require specialty care by reclassifying false negative FIB-4 assessments.

WED-492

Liver fibrosis is a strong predictor of all-cause mortality in patients with metabolic dysfunction-associated steatotic liver disease independent from metabolic syndrome

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Background and aims: The impact of metabolic syndrome (MetS) on mortality in metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear. This study examines the association between MetS and mortality in MASLD patients and evaluates liver fibrosis as a potential predictor.

Method: A population-based cohort study was conducted using data from the United States National Health and Nutrition Examination Survey III, including 9,217 participants with complete datasets. Participants were classified into four groups — no steatotic liver disease (SLD), MASLD, metabolic dysfunction-associated alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD) — based on the criteria recently published in the EASL-EASD-EASO clinical guidelines for the management of MASLD. Participants were stratified into two groups based on the presence or absence of MetS using IDF criteria. In the MASLD group, liver fibrosis was assessed using the FIB-4 index: FIB-4 ≤1.3 indicated no fibrosis, 1.3–2.67 intermediate risk, and >2.67 advanced fibrosis. Cox regression analysis was performed, with results reported as percentages and hazard ratios (HR) with 95% confidence intervals (CI).

Results: Over a median follow-up period of 26.4 years, a total of 3,521 mortality events were recorded among all participants. Of the 9,217 participants, 5,615 had no SLD and 3,602 had SLD, with 3,323

classified as having MASLD. Among these 3,323 MASLD patients, 1,859 had MetS, while 1,464 did not. The proportions of patients with high FIB-4 scores were 1.8% in the MASLD(+)/MetS(+) group and 0.8% in the MASLD(+)/MetS(-) group. After adjusting for multiple variables, the risk of all-cause mortality was not significantly elevated in either the MASLD(+)/MetS(+) or MASLD(+)/MetS(-) groups compared to the healthy control group, with HR of 1.19 (95% CI: 0.98–1.45) and 0.97 (0.83–1.14), respectively. However, MASLD patients with advanced liver fibrosis demonstrated a significantly increased risk of all-cause mortality, independent from MetS status, with HRs of 1.51 (1.06–2.13) for the MASLD(+)/MetS(+) group and 1.89 (1.42–2.52) for the MASLD(+)/MetS(-) group. Additionally, MASLD patients with an intermediate fibrosis risk and MetS(+) had a higher risk of all-cause mortality (HR: 1.30, 1.13–1.50). In contrast, MASLD patients with intermediate fibrosis risk but without MetS, as well as those without liver fibrosis independent from MetS status, showed no increased all-cause mortality risk compared to healthy participants.

Conclusion: MASLD, independent from MetS status, was not associated with an increased risk of all-cause mortality in NHANES. In contrast, advanced liver fibrosis estimated by FIB-4, independently predicted all-cause mortality irrespective of MetS status. Identifying high-risk subjects with FIB-4 may help to select those eligible for the most intensive treatment.

WED-493

Evaluating noninvasive tests for significant fibrosis in a population-based MASLD cohort: insights from NHANES 2017–2020

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Background and aims: Resmetirom is FDA-approved for metabolic dysfunction-associated steatotic liver disease (MASLD) with significant (F2) to advanced (F3) fibrosis. While current AASLD guidance recommended Vibration-Controlled Transient Elastography for treatment consideration, limited availability highlights the need for noninvasive tests (NITs) using common laboratory parameters. Most existing NITs were developed in tertiary referral centers and are not optimized for screening significant fibrosis in general populations. This study compares among ALADDIN-F2-Lab, FIB-4, NAFLD Fibrosis Score (NFS), SAFE, and Liver Risk Score for identifying significant fibrosis or higher in a population based cohort.

Method: The National Health and Nutrition Examination Survey (NHANES) 2017–2020 database was used. NHANES survey design weights, strata, and clusters ensured nationally representative estimates. Adults (≥18 years) with steatotic liver disease (CAP ≥248 dB/m) and at least one cardiometabolic risk factor were included. Alcohol intake was calculated from survey responses, and patients with alcohol intake ≥20 g/day for females, ≥30 g/day for males, viral hepatitis, or missing liver stiffness measurement (LSM) were excluded. Significant fibrosis was defined as LSM ≥8 kPa. NITs including ALADDIN-F2-Lab, FIB-4, NFS, SAFE Score, and Liver Risk Score were categorized into low, intermediate, and high-risk groups using published cutoffs.

Results: Among 4,022 participants with MASLD, 16.0% (SE 1.4%) had significant fibrosis (≥8 kPa). ALADDIN-F2-Lab, FIB-4, and Liver Risk Score classified the majority of participants as low risk, at 80.4%, 74.7%, and 96.1%, respectively, making them suitable for community-based screening. Among these, ALADDIN-F2-Lab demonstrated the highest sensitivity (36.5%), followed by FIB-4 (32.5%) and Liver Risk Score (10.2%). NFS displayed a comparable sensitivity (33.8%) but identified only 33.4% as low risk. SAFE Score achieved the highest sensitivity (85.5%) but classified only 30.8% of participants as low risk. For high-risk classification, ALADDIN-F2-Lab (83.7%), FIB-4 (76.1%), NFS (80.9%), and Liver Risk Score (94.2%) demonstrated excellent specificity. ALADDIN-F2-Lab achieved the highest PPV (69.6%) due to fewer patients being classified as high risk.

Conclusion: While ALADDIN-F2-Lab demonstrated the highest PPV among NITs for high-risk classification and SAFE achieved superior sensitivity, no NIT showed sufficient sensitivity (<50%) to reliably identify the majority of patients with significant fibrosis (LSM ≥8 kPa) in a general population cohort. This highlights the challenge of applying NITs derived from tertiary centers to broader, community-based settings. Reassessing existing cutoffs and optimizing NITs for use in general populations may improve their utility as first-line screening tools for significant fibrosis or higher. Until such adjustments are made, their adoption in clinical practice should be approached with caution.

WED-494

Development and validation of two NIS2+®-based models for the detection of MASH resolution and fibrosis improvement

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[INSERT WED-494F01 HERE]NIS2+® is a blood-based biomarker developed for at-risk MASH (MAS =4; F = 2) detection. NIS2+® changes over time have previously shown significant association with histological improvement. We aimed to develop and validate predictive models for EP1 and EP2 based on demographic data and successive NIS2+® measurements.

Method: Pts included in the RESOLVE-IT phase 3 trial (NCT02704403) with MASH, MAS = 4 and F 1–3 at baseline and NIS2+® available at all 8 trial visits between baseline and end-of-study (EOS) were selected (N = 703). This cohort was randomly split in training (N = 280, 40%) and test (N = 423, 60%) sets. Seven demographic features at baseline and 56 features describing NIS2+® changes over time were used as potential predictors. For each endpoint, a logistic Lasso regression model was developed in the training set, proceeding to a selection of features; 23 features retained in the model for EP1 (M1) and 8 in the model for EP2 (M2). For each model, low (Lc) and high (Hc) cutoffs were derived in the training set to respectively reach a sensitivity (Sen) and specificity (Spe) of 80%, creating intermediate risk zones (IRZ: Lc ≤ NIS2+® < Hc). Performance of M1 and M2 were validated in the test set, and evaluated for decreasing number of NIS2+® measures

collected between baseline and EOS and shorter duration of follow-up.
Results: Mean follow-up was 19 months. Prevalences of EP1 and EP2 ranged 21%-23% in both training and test sets. M1 reached an AUC of 0.85 in training, 0.81 in test. At Lc (0.41), M1 reached a Sen of 80%, Spe of 67% and NPV of 93% in the test set, while at Hc (0.52), Spe was 79%, Sen 68% and PPV 46%. Importantly, only 12% of pts were classified in the IRZ. M2 achieved an AUC of 0.78 in training, 0.74 in test. At Lc (0.48), M2 showed a Sen of 72%, Spe of 61% and NPV of 88% in the test set, while at Hc (0.56), Spe was 78%, Sen 53% and PPV 41%; 18% of patients were in the IRZ. Similar diagnostic performance was observed when using ≥4 measures of NIS2+® between baseline and EOS with high concordance of classification (kappa >0.75). Decreased AUCs were observed when using only 3 NIS2+® measures vs 8 (M1: 0.78 vs 0.81, p = 0.07; M2: 0.71 vs 0.74, p = 0.02). AUCs increased with increasing duration of follow-up, reaching compelling performance after only 13 months of follow-up with 4 NIS2+® measures (M1: AUC = 0.75, M2: AUC = 0.73).
Conclusion: We developed and validated 2 NIS2+®-based models with high performance in ruling-in/out MASH resolution and F improvement, allowing a potential use for monitoring treatment response. While a ~1-year follow-up could potentially allow for early detection of histological improvement, a design with 4 measures over ~1.5 years using Hc is recommended.

WED-495
Liver stiffness measurement as a tool for identifying risk of hepatic-related hospitalizations: insights from a large real-world cohort
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Background and aims: Chronic liver disease affects a significant portion of the population, but only a minority will progress to a severe form that impacts morbidity and mortality. As a result, there is an ongoing need for non-invasive tools to risk stratify chronic liver patients. The long-term implications of elevated liver stiffness in routine care are not well described. This study retrospectively evaluated a large cohort of patients who underwent liver stiffness measurement (LSM) at a single tertiary liver referral centre and examined how liver stiffness correlated with liver-related hospitalizations.
Method: Patients undergoing transient elastography were identified from a prospective database. Basic demographic and clinical variables were collected and data regarding hospitalizations were extracted from the electronic health record.
Results: A total of 10,723 patients were included in the study. The cohort had a mean age of 51.7 years (SD 15.3, range 16–96), comprising 58.8% males and 41.2% females. The largest proportion of diagnoses was 'Other' (38.4%), followed by SLD (37.6%), viral (18.5%), cholestatic (2.9%), and AIH (2.6%). The mean deprivation index was 4.1 (SD 3.0, range 1–10), with higher scores indicating greater socioeconomic disadvantage. Participants were followed for a mean of 3.8 years (median: 4.2 years, IQR: 0.3–6.2 years). The majority of patients had LSM <8 kPa 6510 (60.7%), while 1603 (15%) had LSM > 15 kPa. Increasing liver stiffness was strongly associated with age and male sex. The probability of at least one hospital admission with liver disease as the primary cause increased with increasing liver stiffness: from 0.058 in those with LSM <8 kPa to 0.366 in those with LSM > 15 kPa (p < 0.001). While the probability of at least one admission with liver disease as the primary cause was highest in those with the highest LSM, 376 patients with LSM <8 kPa met this criterion, compared to 587 patients with LSM > 15 kPa.
Conclusion: Liver stiffness measurement serves as a valuable non-invasive tool for risk stratification in chronic liver disease in routine clinical practice. It is significantly correlated with liver-related hospitalizations though a substantial number of liver related hospitalisations still occur in those patients at the lowest risk. This study supports the use of LSM in clinical practice to better identify high-risk chronic liver patients and serves to highlight opportunities to link patients to care even following favourable risk stratification.

WED-496
Anthropometric measures and mortality risk in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD): a population-based cohort study
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Background and aims: As the primary anthropometric measure in metabolic dysfunction-associated steatotic liver disease (MASLD), waist circumference (WC) may more accurately reflect the visceral fat distribution and metabolic risks than body mass index (BMI). This study aimed to evaluate and compare the prognostic value of BMI, WC, and WC-related indices including waist-hip ratio (WHR), body shape index (BSI), and weight-adjusted-waist index (WWI) in individuals with MASLD.
Method: Four large-scale cohorts with well-characterized MASLD participants with comprehensive demographic, anthropometric, and clinical data were analyzed. The first cross-sectional cohort from the National Health and Nutrition Examination Survey (NHANES 2017–2020) assessed the association between anthropometric measures and liver stiffness/controlled attenuation parameter values. The second cohort, from NHANES III (1988–1994), followed 51,793 person-years and evaluated mortality risk across these measures using multivariate Cox proportional hazards regression and restrictive cubic spline. External validations were conducted using the Kailuan (317,501 person-years) and UK Biobank cohort (40,302 person-years).
Results: The Pearson correlation coefficient of WC with hepatic steatosis and fibrosis was better than that of BMI. WC and WC-related indices, but not BMI, indicated a significant mortality risk gradient among individuals with MASLD. The finding was consistently demonstrated across both sex and racial/ethnic subgroups. External validation further supported the application of WC-related indices. There was a dose-dependent distribution of the prevalence of MASLD and fibrosis across the quartiles of WC-related indices. Notably, low

BMI and high WC-related indices portended the highest mortality risk.
Conclusion: WC and WC-related indices are better parameters in prognosticating MASLD than BMI. The BMI-related 'obesity paradox' may be a misnomer resulting from the use of an incorrect metric. WC should be measured more routinely among individuals with MASLD.

WED-497
Steatotic liver disease as a mortality risk enhancer in the presence of metabolic syndrome
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Background and aims: Steatotic liver disease (SLD) is an overarching term to encompass the various aetiologies of steatosis, including metabolic-dysfunction associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD). However, the impact of metabolic syndrome (MetS) on the association between SLD and mortality risk remains uncertain. This study aims to compare all-cause and cause-specific mortality across SLD subtypes in individuals with or without MetS.
Method: A population-based cohort study was conducted from the United States National Health and Nutrition Examination Surveys (NHANES III). A total of 9,217 participants with complete data were included. Participants were categorized into four groups: no SLD, MASLD, MetALD, and ALD based on the cardiometabolic factor, liver steatosis and alcohol consumption according to the 2024 EASL–EASD–EASO Clinical Practice Guidelines. These groups were further stratified into eight subgroups based on the presence or absence of MetS, defined according to the International Diabetes Federation criteria.
Results: Over a median follow-up of 26.4 years, 3,521 mortality events occurred, including 985 cardiac-related, 850 cancer-related, and 474 diabetes-related deaths. After full adjustment, SLD with MetS was significantly associated with an increased risk of all-cause mortality compared with healthy controls, particularly in the MetALD and ALD groups. In contrast, no significant association was found between SLD subtypes without MetS and all-cause mortality risk or cause-specific risks. When stratified by MetS presence, ALD, MetALD, and MASLD were all significantly associated with increased mortality risk compared to the no SLD group in the presence of MetS, which was primarily driven by increased cancer-related and diabetes-related mortality risk. However, this association was not observed in the population without MetS.
Conclusion: This study reveals that the significant association between SLD subtypes and mortality risk is mediated by MetS. To enhance risk stratification and to improve long-term health outcomes, it is crucial to distinguish between MASLD, MetALD, and other SLD types, and to control metabolic status while reducing alcohol consumption.

WED-498
Hepatic collagen percent by morphometry correlates with non-invasive tests in metabolic dysfunction associated steatotic liver disease
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Background and aims: Hepatic % collagen can provide an accurate assessment of hepatic fibrosis. Although non-invasive tests (NITs) for fibrosis correlate with semi-quantitative pathologic staging of hepatic fibrosis, this has not been done for other NITs. Our aim was to associate % collagen with commonly used NITs in metabolic dysfunction associated steatotic liver disease (MASLD).
Method: Liver biopsy slides of MASLD patients were stained with Sirius red; % collagen and % morphometric hepatic fat quantification were evaluated using computer-assisted morphometry. The histologic stages of fibrosis (F0-F4) and grade of steatosis (S0-S3) were evaluated using semi-quantitative scoring. Serum samples collected at the time of biopsy were used to measure FIB-4, enhanced liver fibrosis (ELF), Hepatis Steatosis Index (HSI), Fatty Liver Index (FLI) and liver stiffness measurement (LSM) by transient elastography.
Results: There were 660 MASLD patients [age 46 ± 12 years, 28% male, 93% obese (BMI > 30), 36% type 2 diabetes, 52% hyperlipidemia, 59% hypertension, 43% MASH, 47% with PNPLA3 rs738409 CG or GG genotype (linked to higher risk), 60% histologic F0/F1, 19% F2, 13% F3, 7% F4; mean (SD) FIB-4 score 1.18 (1.64) with 75% having FIB-4 <1.30 (low-risk); mean (SD) ELF score 9.1 (1.3) with 72% having ELF <9.8 (low-risk)]. The mean (SD) % collagen was 3.74 (3.90) % and mean (SD) % fat was 11 (10) %. There was a strong association between % collagen with histologic stage of fibrosis (trend $p < 0.0001$). In particular, pooled together, patients with advanced fibrosis (F3-F4) had significantly higher % collagen than patients with mild or moderate fibrosis (F0-F2): 7.20 (5.87) % vs. 2.87 (2.58) % in F0-F2 ($p < 0.0001$). Among NITs, there were significant correlations of % collagen with FIB-4 ($r = +0.28$) and ELF ($r = +0.28$) scores as well as LSM ($r = +0.33$) (all $p < 0.0001$). Patients with elevated ELF (≥9.8) had higher % collagen than those with low-risk ELF: 5.79 (5.32) % vs. 3.70 (4.39) %, $p = 0.0001$. Similarly, patients with elevated FIB-4 (≥1.30) had higher % collagen than those with low-risk FIB-4: 6.18 (5.70) % vs. 3.03 (3.06) %, $p < 0.0001$. Also, patients with elevated LSM (≥10 kPa) had higher % collagen than those with low-risk LSM: 7.48 (5.56) % vs. 4.36 (3.66) %, $p = 0.0004$. Finally, patients with high-risk PNPLA3 rs738409 genotype (CG/GG) had higher % collagen than those with the CC genotype: 3.78 (3.50) % vs. 3.16 (3.10) %, $p = 0.0148$. The morphometric % fat correlated with histologic steatosis grade ($r = +0.52$) but less strongly with HSI ($r = +0.16$) ($p < 0.0001$).
Conclusion: In MASLD patients, morphometric assessment of histologic steatosis and fibrosis correlate with semi-quantitative assessment by histology as well as commonly used NITs to include FIB-4, ELF, and liver stiffness by transient elastography.

MASLD – Experimental and pathophysiology

TOP-426-YI

Lipidomics crosstalk with hepatic stellate cells and macrophages in people with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a complex metabolic disorder characterized by excessive fat accumulation in the liver. This study aimed to elucidate lipids crosstalk with hepatic stellate cells (HSCs) and macrophages in MASLD progression.
Method: Untargeted lipidomics were employed to analyse lipid profiles in plasma, plasma nanoparticles (PNs) and liver tissue from MASLD patients and normal controls. In vitro, HepG2 cells were stimulated with the identified lipids with potential significance between the groups. Gene and protein expression were assessed by Western blot and RT-PCR. EVs isolated from lipid-stimulated HepG2 cells were co-cultured with primary human macrophages and cytokines' secretion was measured. PNs isolated from MASLD patients and controls were co-cultured with primary human HSCs, and aSMA expression was evaluated by RT-PCR.
Results: Lysophosphatidylcholine (LPC 16:0) was elevated in plasma but reduced in PNs and liver tissue in MASLD. PNs from MASLD patients showed reduced sphingomyelin (SM) and increased ceramide (Cer), with SM levels correlating with MASLD severity. Plasmalogens decreased in plasma, PNs, and liver tissue, whereas their precursor (1-O-alkyl-2-acylglycerol) was elevated in liver tissue. Cardiolipins were significantly depleted.
HepG2 cells treated with LPC 16:0, upregulated inositol-requiring enzyme 1(IRE1), sphingomyelinases (SMase1 and SMase2), choline/ethanolamine phosphotransferase 1(CEPT1) and ethanolamine phosphotransferase 1(EPT1), the key enzymes for plasmalogen synthesis. LPC 16:0-induced EVs from HepG2 were then used to stimulate primary human macrophages from healthy controls. IL-1b and IL-6 were significantly upregulated compared to controls ($P < 0.05$). Furthermore, PNs derived from MASLD patients activated primary human HSCs, isolated from controls, by upregulating aSMA, whereas PNs derived from healthy controls did not.
Conclusion: Circulating LPC 16:0 induced endoplasmic reticulum (ER) stress in vitro and triggered reactive oxygen species (ROS) accumulation, resulting in progressive plasmalogen depletion even though the synthesis were increased. The lipid synthesis was regulated by LPC 16:0 inducing EVs, - enriched in Cer but depleted of SM – released from hepatocytes to promote a pro-inflammatory response in macrophages and activate HSCs, contributing to a pro-fibrotic effect in MASLD.

TOP-427

Characterizing the response to high-dose gene therapy in non-human primates with a healthy or fibrotic liver at single nucleus resolution

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Background and aims: Adeno-associated viral (AAV) vector-mediated gene therapies present a direct approach to treat liver disease, especially for rare genetic disorders. Candidate gene therapies are often tested in healthy non-human primate (NHP) models, however, due to the essentiality of the affected genes to hepatocyte metabolism, patients are more likely to have a liver that has experienced prolonged damage. Therefore, testing in NHPs with healthy livers may not fully recapitulate the patient response to a gene therapy. Here we investigate how a NHP with an inflamed and fibrotic liver would respond to an AAV gene therapy.
Method: African Green monkeys, one healthy and one fed a high fat, cholesterol and fructose diet for 82 weeks to induce metabolic dysfunction-associated steatohepatitis (MASH), were administered about 2×10^{13} vg/kg of a hepatocyte-targeted AAV gene therapy encoding a red fluorescent protein (RFP) alongside a 6-day immunosuppression protocol. Both NHPs were confirmed to be negative for AAV serotype-specific neutralizing antibodies prior to treatment. Single nucleus RNA-Sequencing (snRNA-Seq) was performed on liver biopsies at 2 weeks and 4 weeks after the AAV infusion.
Results: Differences between the healthy and MASH NHP were observed through histology and blood panels. The liver of the healthy NHP showed normal histology while the MASH NHP's liver histology showed steatosis, inflammation and extensive perisinusoidal fibrosis. Both the healthy and MASH NHP showed a transient increase in serum ALT that peaked at 7 days post-AAV infusion and returned to baseline levels within 14 days. ALT reached 342 U/L in the healthy NHP and 559 U/L in the MASH NHP. Bilirubin did not increase throughout the duration of the study. In both the healthy and MASH NHP, hepatocytes comprised the largest cell population in the liver, followed by endothelial cells. Two weeks following the AAV infusion, the most abundant cell type was a macrophage-like population in the MASH NHP. By 4 weeks, hepatocytes were once-again the most abundant cell type in the liver of the MASH NHP. The 2-week RFP-positive cells in the MASH NHP appeared primarily to be hepatocyte-macrophage doublets, suggesting active phagocytosis of transduced hepatocytes. In contrast, in the healthy NHP, the RFP-positive cells were primarily hepatocyte singlets.
Conclusion: In a NHP model, a healthy liver and a MASH liver showed dramatically different responses to AAV-mediated gene therapy. Steatohepatitis is associated with an exaggerated immune response. Caution should be exercised when extrapolating the findings of a hepatocyte-directed gene therapy in healthy NHPs to patients with liver disease.

TOP-428

Bispecific small interfering RNA targeting YAP1/WWTR1 as a novel therapeutic agent for metabolic dysfunction-associated steatohepatitis

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is the leading cause of liver fibrosis worldwide, but the efficacy of approved drugs is limited. It is well known that YAP (Yes-associated protein, encoded by *YAP1*) and TAZ (transcriptional coactivator with PDZ-binding motif, encoded by *WWTR1*) contribute to fibrogenesis in the liver, but there are no approved therapeutic agents targeting YAP/TAZ directly. This study aimed to establish bispecific small interfering RNA (bsiRNA) targeting *YAP1*/*WWTR1* (bsiYW), in which one antisense oligonucleotide binds to specific regions of both genes, and to explore the therapeutic potential and mode of action of bsiYW for MASH.

Method: In vitro studies involved transfecting HepG2, a human liver cancer cell line, and AML12, a mouse normal liver cell line, with negative control siRNA (siNC), siRNA targeting *YAP1* (siY) or *WWTR1* (siW), and bsiYW, followed by gene expression analysis, psiCHECK and Oil Red O (ORO) staining. Each siRNA was chemically modified and encapsulated in lipid nanoparticles (LNP) or conjugated with N-acetylgalactosamine (GalNAc). Each formulation was administered bi-weekly for 8 weeks to mice fed a choline-deficient L-amino-acid-defined high-fat diet (CDAHFD) for 12 weeks. Gene and protein expressions, biochemistry, histology, and metabolome analyses were then performed.
Results: RNA-seq and psiCHECK revealed that bsiYW has no fatal off-target genes. bsiYW synergistically suppressed the transcriptions of YAP/TAZ-responsive genes, CCN family member 1, 2, and ankyrin repeat domain-containing protein 1 mRNA, and the ORO-positive area, compared to siY and siW in HepG2 and AML12. bsiYW/LNP suppressed the expression of *Yap1* and *Wwtr1* in both parenchymal cells (PCs) and non-PCs in the liver of mice. A single dose of bsiYW/LNP suppressed the expression of YAP and TAZ by more than 50% at both the gene and protein levels in the liver of CDAHFD-fed mice for at least 3 weeks. Repeated doses of bsiYW/LNP synergistically suppressed the levels of hepatic triglycerides (TG) compared to siY and siW in CDAHFD-fed mice. bsiYW/LNP also significantly suppressed the levels of hydroxyproline (HYP) and collagen 1 in the liver, as well as plasma alanine aminotransferase, in CDAHFD-fed mice in comparison with vehicle. Metabolome analysis showed that hepatic free fatty acids, especially polyunsaturated fatty acids, were significantly increased by bsiYW/LNP in comparison with vehicle, despite a significant reduction of TG. Hepatic TG and HYP were also decreased by bsiYW/GalNAc in CDAHFD-fed mice, whereas the expressions of *Yap1* and *Wwtr1* were decreased only in PCs in mice.
Conclusion: Dual silencing of *YAP1* and *WWTR1* synergistically suppressed the YAP/TAZ pathway in vitro and in vivo. bsiYW ameliorated hepatic steatosis and fibrosis in CDAHFD-fed mice depending on the hepatocytes-derived mechanisms, such as remodeling of lipid composition, at least in part. These findings suggest that bsiYW could be a novel therapeutic approach for MASH.

TOP-441

CD8+ T cells are pro-inflammatory, cytotoxic, and clonally expanded in the early stages of fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH)

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by hepatic accumulation of immune cells and can lead to fibrosis. We previously found increased number and activation of peripheral blood CD8$^+$ T cells in patients with MASH compared to steatosis and healthy controls. In cirrhosis, clonally expanded, phenotypically exhausted, CD8 T cells are found in the liver. However clonality and activation status of CD8 T cells in early stages of MASH fibrosis remain unclear and may give unique insights into pathogenesis. We characterised the phenotype and T cell receptor repertoire of CD8 T cells in blood, liver and adipose tissue sampled simultaneously from patients ranging from health to non-cirrhotic fibrosis.
Method: We performed antibody-augmented single cell RNA and T cell receptor sequencing on immune (CD45$^+$)-enriched cell populations sampled from liver, blood, subcutaneous, and visceral adipose tissue sampled during bariatric surgery in 18 individuals with F0 -F3 fibrosis (gallbladder surgery for healthy). Histological assessment of MASLD and fibrosis was conducted by a specialist pathologist according to the NASH CRN.
Results: Unsupervised clustering of 129,500 cells from all individuals and tissues revealed 29 distinct clusters. Cell-cell communication was higher in disease than health with greatest incoming signalling in clusters containing CD8 T cells. VDJ sequencing showed many CD8 T cells in these high-signalling clusters were clonally expanded (suggesting peptide-specific activation) at higher numbers in patients with greater fibrosis. The same clones were found in liver and adipose suggestive of migration between tissues. Pathway and leading-edge analysis in expanded clones showed expression of cytotoxic (eg granzyme and perforin) and inflammatory (TNFa/NFKB signalling) genes. We annotated potential epitopes of expanded clones based on CDR3 sequencing (excluding common viral targets) and identified known liver, diabetes, and obesity-related epitopes which may be relevant to MASH and some unannotated epitopes that require further characterisation.
Conclusion: Clonal expansion of CD8 T cells with cytotoxic and pro-inflammatory expression profiles occurs early in MASH-related fibrosis and may be a key pathogenic factor in progressive disease. This has important implications for understanding pathogenesis and may influence diagnosis, risk-stratification and even treatment of MASH and fibrosis.

TOP-442-YI

Somatic mutation in early stage metabolic-dysfunction associated steatotic liver disease (MASLD)

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Background and aims: The contribution of somatic mutation to end-stage metabolic-dysfunction associated steatotic liver disease (MASLD) has recently been discovered. Enlarging hepatocyte clones, sequestered by fibrosis, independently acquire recurrent somatic mutations in genes encoding regulators of lipid metabolism. The heterogeneity of MASLD has been reflected through inter-patient variability in the mutational landscape from a modest number of donors with cirrhosis to date. The temporal accrual of such mutations during, and their causative role in MASLD disease progression, remain unknown.
Method: Using whole-exome NanoSeq, a single DNA molecule sequencing protocol, DNA from archival fresh-frozen needle biopsies of 20 patients with MASLD fibrosis stages F0-F3 was sequenced to a cumulative duplex coverage of 3,164dx. Donors had median follow-up of 12 years post-biopsy; 10 donors experienced MASLD progression, 10 had stable liver disease. Genes under positive selection pressure were identified using *dNdScv*, a statistical model comparing ratios of non-synonymous somatic mutations to evolutionarily neutral synonymous mutations. Genes were considered to have significant excess of non-synonymous mutations after correction for multiple hypothesis testing with a q-value of <0.1.
Results: The pattern and density of somatic mutations varied extensively between individuals, even in this early disease stage,

though we observed minimal correlation of mutation burden to age or fibrosis stage with this limited cohort size. 9 genes were found to have a significant excess of non-synonymous somatic mutations, indicative of positive selection. These included lineage-defining, highly hepatocyte-specific genes such as Albumin (*ALB*) and transferrin (*TF*), with a pattern of short insertion and deletion ('indel') excess, hypothesised to relate to high gene expression. Recurrent variants in genes recognised as drivers in end-stage MASLD were found to be under positive selection, including *ACVR2A, TNRC6B* and *CIDEB*. A potentially novel driver gene was identified in a metabolic pathway responsible for conjugation of lipophilic compounds.

Conclusion: We provide evidence of positive selection of somatic variants across the MASLD disease spectrum. Recurrent somatic mutagenesis of genes implicated in lipid metabolism suggest hepatocytes develop adaptive pathways in attempt to escape their lipotoxic environment prior to development of advanced liver disease. Deep-targeted sequencing across a wider cohort spanning the disease spectrum will now be conducted, with long-term outcome data to allow clinical correlation.

TOP-443

Paneth cells regulate intestinal lymphangiogenesis and lipid metabolism in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Paneth cells (PC) are involved in the regulation of intestinal microbiota, and their function in intestinal lymph- and angiogenesis has been recently described. Uptake of dietary lipids is largely dependent on intestinal lymphatic vessels, and impairments in their density or function may result in significant depletion of lipids in the liver. In this study, we assessed the effects of PC deficiency in a model of metabolic dysfunction associated steatotic liver disease (MASLD).

Method: We induced functional inactivation of PC in male and female mice ($Sox9^{lox/lox}VilCre^{ERT2}$) by intraperitoneal injection of 1 mg/day of tamoxifen for three consecutive days. One week later, all mice, PC-deficient, and control littermates were randomly subjected to a high sucrose/fructose - high fat (60% lard) (HFD) or standard (SD) diet for 16 weeks. Intraepithelial leakage of FITC-albumin was measured *in vivo* using laser-probe endomicroscopy. Several tissues were harvested for histological examination, molecular biology analyses, and imaging mass cytometry (IMC). Fecal samples were collected at both the start and end of the experiment to assess intestinal dysbiosis.

Results: All mice fed HFD gained weight compared to SD, but the weight gain in PC-deficient-HFD was significantly lower than in HFD-controls. Consistent with these findings, the severity of hepatic steatosis was significantly lower in PC-deficient-HFD compared to HFD-control mice. IMC of liver tissue revealed lower levels of collagen deposition and steatosis associated with fewer macrophages and neutrophils activation/infiltration in PC-deficient-HFD than in control-HFD mice. In vivo, microscopy showed a lower disruption of intestinal vascular barriers in PC-deficient-HFD than in HFD-control mice. The intestinal expression of distinct lymphangiogenic genes (VEGFC, VEGFR3, Prox1) was reduced in the PC-deficient HFD or SD. The alpha diversity of the fecal microbiota showed no significant differences based on gender or PC deficiency in the SD groups. Nevertheless, the beta diversity showed significant differences in PC-deficient fed SD after 16 weeks. Furthermore, we found significant alpha- and -beta diversity associated with decreased *Bacteroidota* and increased *Firmicutes* in HFD and PC-deficient mice.

Conclusion: PC deficiency attenuated the severity of steatosis and fibrosis in mice, suggesting their regulatory role on intestinal lymphatics contributing to the pathogenesis of MASLD. Thus, Paneth cells may represent a novel target for intervention in MASLD.

FRIDAY 09 MAY

FRI-323

Redundant yet distinct role of Vacuole membrane protein 1 and transmembrane protein 41B in regulating hepatic lipoprotein secretion and autophagy in metabolic dysfunction-associated steatohepatitis

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Background and aims: Vacuole membrane protein 1 (VMP1) and transmembrane protein 41B (TMEM41B) are two endoplasmic reticulum (ER)-resident scramblases with important roles in autophagy and lipoprotein secretion. Hepatic loss of VMP1 or TMEM41B leads to defective autophagy and rapid development of metabolic dysfunction-associated steatohepatitis (MASH) in mice. Previous studies showed that overexpression of VMP1 or TMEM41B alleviates steatosis in MASH diet-fed or ob/ob mice. However, whether VMP1 and TMEM41B regulate lipoprotein secretion in MASH complementarily or independently is unknown.

Method: Liver-specific VMP1 knockout ($Vmp1^{LKO}$), TMEM41B KO ($Tmem41b^{LKO}$), VMP1 and TMEM41B double knockout ($Vmp1/Tmem41b^{DKO}$), TMEM41 KO/VMP1 knockin ($Tmem41b^{LKO}/Vmp1^{LKI}$), VMP1 KO/TMEM41B KI ($Vmp1^{LKO}/Tmem41b^{LKI}$) and ATG5 KO ($Atg5^{LKO}$) mice were generated. VLDL secretion, liver histology, biochemical assays, hepatic lipidomics, and autophagy were analyzed. VMP1 and TMEM41B protein levels were examined in human liver tissues from healthy and MASLD patients.

Results: $Vmp1^{LKO}$, $Tmem41b^{LKO}$, and $Vmp1/Tmem41b^{DKO}$ mice at one-month-old fed on a chow diet severely impaired VLDL secretion, resulting in massive microsteatosis, increased hepatic triglyceride, inflammation and fibrosis. Vmp1/Tmem41bDKO mice did not further impair VLDL secretion compared with single KO mice. Lipidomics analysis of liver tissues showed decreased phosphatidylcholine and phosphatidylethanolamine and increased neutral lipids. Cellular fractionation studies revealed that VMP1 and TMEM41B localized at the mitochondrial associate membrane (MAM). Electron microscopy analysis showed decreased mitochondria-ER contact in VMP1 and TMEM41B deficient hepatocytes. Hepatic loss of VMP1 or TMEM41B led to markedly increased levels of LC3-II and p62/SQSTM1, indicating impaired autophagic flux, unaffected by the double deletion of VMP1 and TMEM41B. Restoration of VMP1 in $Tmem41b^{LKO}$ mice partially corrected VLDL secretion but not autophagy. Restoration of TMEM41B in $Vmp1^{LKO}$ mice partially corrected VLDL secretion and autophagy. Intriguingly, $Atg5^{LKO}$ mice developed hepatomegaly without affecting VLDL secretion. Moreover, VMP1 and TMEM41B protein levels decreased in human liver samples with MASLD.

Conclusion: Loss of hepatic VMP1 or TMEM41B decreases MAM and phospholipids content and VLDL secretion resulting in the development of MASH independent of autophagy. VMP1 and TMEM41B may have redundant but distinct mechanisms regulating lipoprotein secretion and autophagy.

FRI-324

Fgl2-C3aR axis mediated NETs promote intravascular coagulation and liver fibrosis in MASLD progression

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Background and aims: Procoagulant imbalance was observed in metabolic dysfunction-associated steatotic liver disease (MASLD) patients with liver fibrosis, but the role of coagulation in MASLD-associated fibrosis remains largely unclear. Neutrophil extracellular traps (NETs) served as an essential factor in immuno-thrombosis. Here, we aim to study the role of NETs-mediated complement and coagulation activation in MASLD progression and the underlying mechanism.
Method: NETs were depleted by intraperitoneal injection of DNase-1. Wild type (WT) and *fgl2*$^{-/-}$ C57BL/6 mice were treated either with 60% high fat diet (HFD) or methionine/choline-deficient (MCD) diet to induce MASLD-associated fibrosis. RNA-Seq of hepatic tissues or liver leukocytes were conducted in WT and *fgl2*$^{-/-}$ mice. Bone marrow neutrophils from WT and *fgl2*$^{-/-}$ mice were subjected to palmitic acid (PA) and LPS *in vitro*.
Results: Abundant neutrophil accumulation and NETs formation were observed in MASLD progression. NETs depletion improved liver fibrosis, inflammatory response and lipid accumulation both in HFD and MCD models. Meanwhile, decreased coagulation activation, including lower level of plasma thrombin-anti-thrombin complex (TAT) and hepatic fibrin deposition was observed following DNase-1 treatment. Highly expressed on hepatic neutrophils, fibrinogen-like protein 2 (FGL2) colocalized tightly with NETs area. Fgl2 knockout inhibits NETs formation and coagulation activation in MASLD progression. Combined with RNA-Seq analysis, *in vivo and in vitro* experiment identified that NETs formation was regulated by FGL2-C3aR axis. Treatment with C3aR antagonist alleviated NETs formation, coagulation activation and liver fibrosis *in vivo*.
Conclusion: NETs mediated coagulation dysregulation promotes MASLD progression. In depth, NETs formation was regulated by FGL2-C3aR axis.

FRI-325-YI

Sorafenib alleviates portal hypertension associated with metabolic dysfunction-associated liver disease by attenuating hepatic sinusoidal capillarization

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Background and aims: Portal hypertension (PHT) commonly arises from cirrhosis, but non-cirrhotic portal hypertension (NCPH) associated with metabolic dysfunction, -associated steatotic liver disease (MASLD), presents unique challenges. Recent studies have shown that PHT can precede liver fibrosis and may act as a driving factor in the development of MASLD, as evidenced by both animal models and clinical cases where portal pressure was elevated in the absence of advanced fibrosis. Sorafenib (Sora) is the first-line therapy for advanced hepatocellular carcinoma and has shown some efficacy in treating liver fibrosis. This study aims to investigate the therapeutic potential of Sora to ameliorate MASLD-associated PHT, focusing on its impact on hepatic sinusoidal capillarization.
Method: A high fat diet (HFD, 60% calories from fat) was used to induce MASLD-associated PHT in C57BL/6J mice. Sora (10 mg/kg) vs vehicle alone was administered by gavage (200μl, q.d.) from week 10 to week 12 of HFD feeding to evaluate its effects on portal pressure. Histopathological assessments, electron microscopy (EM), RT-PCR and Western blot were performed to analyze sinusoidal capillarization and underlying mechanisms.
Results: Sora treatment significantly reduced portal pressure (5.42 ± 0.54 vs 4.55 ± 0.35 mmHg, p = 0.008, n = 6) and decreased the spleen-to-body weight ratio, an indirect indicator of portal pressure (0.0022 ± 0.00014 vs 0.0019 ± 0.0003, p = 0.029). H&E and Masson staining showed that Sora reduced luminal narrowing and occasional occlusion in portal vein branches, and decreased perivascular fibrosis compared to the control group. EM demonstrated that Sora counteracted the loss of sinusoidal fenestrae, upregulated liver sinusoidal endothelial cell markers (Lyve1, Stab1, Stab2, Msr) and downregulated normal venous endothelial markers (CD31, CD34, endomucin, apelin) indicating mitigation of sinusoidal capillarization.
Conclusion: Sorafenib demonstrates potential in alleviating MASLD-associated PHT by attenuating hepatic sinusoidal capillarization, offering a promising therapeutic approach for managing non-cirrhotic PHT in MASLD.

FRI-333

Exercise protects against semaglutide-induced muscle loss in obese Ldlr-/-.Leiden mice

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Background and aims: Semaglutide, a glucagon-like peptide-1 receptor agonist, is an antidiabetic medication that has recently been approved for treatment of obesity as well. While the benefits of semaglutide for weight management are encouraging, concomitant muscle loss can be a potential drawback. Here, we evaluated the metabolic effects of semaglutide, exercise and the combination thereof in a translational model of obesity and the Metabolic Syndrome.
Method: Ldlr-/-.Leiden mice received a high fat diet (HFD) for 20 weeks to induce obesity, insulin resistance and hyperlipidemia. Mice were subsequently left untreated (control) or were treated for 14 weeks with semaglutide, exercise (running-wheel) or the combination thereof. Body weight, lean body mass (EchoMRI) and plasma parameters were evaluated during the study and liver, muscles, adipose tissue depots, hearts and brain were collected at end-point for future histological analysis and transcriptomics.
Results: Already after 2 weeks of treatment, semaglutide either alone (−21%), or in combination with exercise (−23%) significantly decreased body weight, while exercise monotreatment tended to slightly reduce body weight (with −3%, p = 0.056). Semaglutide monotreatment significantly reduced both fat mass (-43%) and lean body mass (−11%), while in combination with exercise fat mass was significantly decreased (−50%), but loss of lean body mass could be prevented. Semaglutide treatment either alone, or in combination with exercise significantly improved blood glucose, plasma insulin, cholesterol and triglyceride levels as well. All these changes remained until the end of the study. Tissue analyses are currently ongoing.
Conclusion: Using a translational model of obesity and the Metabolic Syndrome, we demonstrated that semaglutide has beneficial metabolic effects, but combination with exercise is required to prevent muscle loss.

FRI-334

Adaptative immune activation as a biomarker of Metabolic dysfunction- associated steatotic liver disease severity

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Background and aims: Metabolic dysfunction- associated steatotic liver disease (MASLD) is a multifactorial disease in which several stresses factor, that contribute to the overall pathophysiology MASLD severity and is related to the immune system activated. The cascade of inflammatory events in MASLD has been marked as type 3 inflammatory response, characterized by fibrosis and production of cytokine IL-17A. The inflammatory trigger that initiates inflammation is MASLD includes tissue-resident-innate-like T cells, increasing gut permeability, Mucosal-associated invariant T (MAIT) cells respond to bacterial antigens contributing to liver fibrosis in IL-17A/TNF-α dependent manner. Increase intake of dietary components like toxic lipid species, danger-associated molecular patterns, and gut derived pathogens associated molecular patterns (PAMPS) activate recruited myeloid cells, leading to the secretion of effector cytokines (as TNF-α, IL-1β, TGFβ, and IL-6). Finally for liver inflammation, adaptative immune cells such as $CD4^+$, Th17 cells, $CD8^+T^-$ and B cells, on this phase there are an extensive hepatocyte cell death and deposition of extracellular matrix by activate hepatic stellate cells. The main objective of these study was evaluated immunological profile of MASLD severity.

Method: Patients with metabolic criteria were evaluated by hepatic elastography, and, saliva was collected to analyzed by Fourier-transformed infrared spectroscopy (FTIR, at 4000 and 400 cm^{-1}). Also, IMC, hematologic biochemic with differential count, biochemical (coagulopathy profile, glucose, urea, creatinine, uric acid, Bilirubin, ALT, AST, ALP, GGT, cholesterol, triglycerides, HDL, LDL, and HbAc1) were collected. The study of the immune response analysis through FTIR were at IgG (1560–1464), IgA (1285–1237), and IgM (1160–1028), IFN-γ (1061–1044), TNF-α (1243–1217), IL-6 (1436–1428). For statistical analysis SPSSv26 was employed, Shapiro -Wilk normality test were performed, analyzed by U-Mann-Whitney, or T-Student, and Spearman correlation were employed ($p < 0.05$, statistical significant).

Results: On this study we included 19 patients with MASLD, 3 was male and 16 was female, with media age 45 years ± 7.6 years. Eight patients was S2 and 11 patients was S3. The CAP, Lymphocytes and HbAc1 were significant increase on S3 in comparison with S2. There were not any other differences on any other parameters. Regarding to the immunological findings we found a significant increase on IgA, IgG, TNF-α, and IL-6. We found a correlation between levels of CAP and kPa, lymphocytes, IMC, TNF-α, IgA, the IMC was not significant correlation to TNF-α, IgA.

Conclusion: The changes on immunoglobulins related to adaptative immune and mucosal response (IgG and IgA), and correlation to overexpression with TNF-α, and IL-6, on saliva is related to the increase on lymphocytes regarding to the MASLD severity, and disease progression.

FRI-335

Therapeutic potential of a GHRH analog in experimental MASLD

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Background and aims: Tesamorelin, an analog of growth hormone-releasing hormone (GHRH), has shown promise in improving metabolic health by reducing visceral adiposity and enhancing lipid profiles in patients with HIV. Its potential in MASLD patients lies in its ability to target underlying metabolic dysregulation and alleviate liver steatosis, addressing key drivers of liver disease progression. The aim of this work was to evaluate the effects of this treatment in murine models of MASLD.

Method: To understand the effect of Tesamorelin (TheraTechnologies), we used two different animal models of MASLD: CDAC-HFD (n = 36) (45% fat, 0.1% methionine, no choline, 1% cholesterol) and HFHCC (42% fat, high sucrose, 1.25% cholesterol + glucose/fructose in the drinking water) (n = 40). For both experiments, animals were fed the MASLD-inducing diet or chow for 20 weeks, being treated with Tesamorelin (0.7 mg/Kg, IP, daily) or vehicle for the last 4 weeks. Phenotypic, histologic and biochemical data were collected for experiments.

Results: In CDAC-HFD fed animals, Tesamorelin was associated with a reduction in eWAT/body weight (1.3 ± 0.4 vs 0.8 ± 0.4%; $p < 0.05$) and liver/BW (10.1 ± 0.5 vs 9.1 ± 0.6; $p < 0.05$). Also, we observed a decrease in ALT (225 ± 81 vs 119 ± 78 U/L; $p < 0.01$) and AST (445 ± 152 vs 346 ± 102 U/L; $p = 0.1$) levels, and in the number of liver nodules per mouse (3.8 ± 3.8 vs 1.1 ± 1.0 U/L; $p < 0.05$) and collagen deposition. However, there were no significant differences in the NAFLD activity score. HFHCC-fed animals under Tesamorelin demonstrated a reduction in body weight gain (1.7 ± 2.4 vs −2.5 ± 2.4%; $p < 0.001$), and obesity measured by the Lee index (0.35 ± 0.01 vs 0.33 ± 0.01; $p < 0.05$). It was also associated with a decrease in circulating LDL (1.9 ± 0.5 vs 1.0 ± 0.4 mmol/L; $p < 0.001$) and HDL (6.3 ± 1.0 vs 4.4 ± 1.2 mmol/L; $p < 0.001$) particles, ALT (210 ± 120 vs 177 ± 81; p = ns), AST (585 ± 460 vs 411 ± 310 U/L; p = ns) and a 70% improvement in HOMA-IR. Histologically, there was evidence of reduced NAS and fibrosis.

Conclusion: Tesamorelin administration induced a reduction of adipose tissue with consequent weight loss. Also, it improved liver enzymes, lipid profile and insulin resistance. Further experiments are needed to better understand and isolate peripherical GH effects from IGF-1-mediated liver protection.

FRI-336-YI

Genetic variation in GPAM and protection against histologic severity in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Recently, a novel genetic locus in the mitochondrial glycerol-3-phosphate acyltransferase (*GPAM*) has shown an association with liver biochemistries and steatosis by imaging. Since the causal variant in *GPAM* is unknown, we applied statistical fine mapping to identify lead SNPs in *GPAM* and subsequently tested their association with histologic disease severity in a large biopsy-confirmed metabolic dysfunction-associated steatotic liver disease (MASLD) cohort.

Method: We performed statistical fine mapping using FINEMAP and SuSiE at the *GPAM* locus for associations with liver biochemistries in UK Biobank (n = 361,194). We tested the association of the lead variants from the target loci with histologic severity in the NASH CRN cohort (n = 3,049). We used logistic regression to assess the relationship between the *GPAM* polymorphism and fibrosis stage as a continuous variable, advanced fibrosis (≥ F3), and NAS ≥ 4. We adjusted for age, sex, body mass index, type 2 diabetes, and the first 10 principal components of ancestry.
Results: Fine mapping identified 8 polymorphisms at the *GPAM* locus with posterior probability of association > 0.1, representing two independent genomic loci. Variants within each locus were in complete linkage disequilibrium and GWAS of ALT in the UK Biobank identified rs55875049 and rs10797429 as the lead SNPs from these two *GPAM* loci. In the UK Biobank, the minor allele frequency for rs55875049 and rs55875049 are 19% and 27%, respectively. In adults (n = 2,149), *GPAM* rs55875049 was protective against increased fibrosis stage (OR 0.82, 95% CI: 0.75–0.90, p = 5.08E-05), advanced fibrosis (OR 0.78, 95% CI: 0.65–0.94, p = 0.007), and NAS ≥ 4 (OR 0.78, 95% CI:0.66–0.92, p = 0.003); rs10787429 was also protective against NAS ≥ 4 (OR = 0.86, 95% CI: 0.74–1.00, p = 0.04), but not against fibrosis stage (OR = 0.94, 95% CI: 0.87–1.02, p = 0.16), or advanced fibrosis (OR = 1.0, 95% CI: 0.85–1.17, p = 0.97). The direction and strength of associations were similar after adjusting for *PNPLA3* genotype. In children (n = 900), *GPAM* rs55875049 was not associated with fibrosis stage, advanced fibrosis, or NAS ≥ 4 (p > 0.05 for all). GPAM rs10787429 was protective against fibrosis stage (OR 0.91, 95% CI: 0.82–1.02), p = 0.098) and advanced fibrosis (OR 0.73, 95% CI: 0.54–1.00, p = 0.04), but not NAS ≥ 4 (OR 1.28, 95% CI: 1.02–1.60, p = 0.03).
Conclusion: We identified rs55875049 and rs10797429 as the lead SNPs from two independent *GPAM* loci potentially associated with MASLD. *GPAM* rs55875049 showed strong protection against fibrosis and steatohepatitis in adults but not children with MASLD. *GPAM* rs10787429 showed protection against fibrosis in children but not in adults. These findings provide additional insight into the genetic basis of MASLD.

FRI-337

ETX-312, a GalOmic siRNA for the treatment of MASH, effectively improves the MASH phenotype of GAN DIO-MASH mice alone or in combination with emerging therapies

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a chronic liver disease with remaining high unmet need despite recent therapeutic advances. e-therapeutics used its HepNet computational platform to identify a novel, liver-expressed target gene implicated in MASH and designed a potent GalOmic siRNA to silence its expression in hepatocytes. ETX-312 previously demonstrated efficacy alone and in combination with a THR-beta agonist or GLP-1 receptor agonist in the Gubra-Amylin NASH diet-induced obese (GAN-DIO) mouse model. The aim of this study was to assess the liver histopathological effects of ETX-312, alone or in combination with additional emerging MASH treatments, in the GAN-DIO mouse model.
Method: Male C57BL/6 mice were fed the GAN diet high in fat, fructose, and cholesterol for 32 weeks prior to study start. A liver biopsy was collected 4 weeks prior to study start for confirmation of liver pathology and mice randomized based on quantitative liver fibrosis staining. ETX-312 was administered alone or in combination with a GLP-1/GIP receptor (GLP-1R/GIPR) agonist or an FGF-21 analogue for 16 weeks. Body weight was measured weekly and histopathological pre-to-post individual assessment of NAFLD activity score (NAS) was performed. Other terminal endpoints included quantitative liver histology and plasma biomarkers of MASH.
Results: ETX-312 treatment, alone and in combination with relevant clinical comparators, led to a marked improvement in NAS driven by a reduction in steatosis and inflammation. 95% of DIO-MASH mice treated with ETX-312 monotherapy had at least a 1-point improvement in NAS, with 60% achieving at least a 2-point improvement, surpassing both the GLP-1R/GIPR agonist and FGF-21 analogue comparators arms. Combination of ETX-312 with GLP-1R/GIPR agonist or FGF-21 analogue resulted in additive improvement in NAS compared to either therapy alone. In both ETX-312 combination groups, all DIO-MASH mice had at least a 2-point improvement in NAS, with up to 5-point improvement observed. DIO-MASH mice treated with ETX-312 demonstrated lower rates of fibrosis progression comparable to the effects observed in the FGF-21 analogue and GLP-1R/GIPR agonist groups. Beneficial effects of ETX-312 on fibrosis were further supported by a statistically significant reduction in collagen staining of liver biopsies and significant improvements of the plasma biomarkers TIMP1 and PIIINP.
Conclusion: High unmet need remains despite recent advances in treatments of MASH. These results highlight the potential of ETX-312 as an effective treatment for MASH as a monotherapy with a desirable quarterly subcutaneous dosing regimen; or as part of a combination regimen, to further improve the efficacy of emerging therapies. ETX-312 has been selected for clinical development and is being evaluated in IND-enabling studies, with an IND submission planned for 2025.

FRI-338

Genetic predisposition for hepatic fat accumulation impacts the uptake of fatty acids through fatty acid translocase in a human stem cell-based in vitro model

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Background and aims: Several single nucleotide polymorphisms relevant to metabolic dysfunction-associated steatohepatitis (MASH) - PNPLA3 rs738409 C > G, TM6SF2 rs58542926 C > T, GCKR rs1260326 C > T, and MBOAT7 rs641738 C > T - have been combined into a polygenic risk score for hepatic fat content (PRS-HFC). While earlier research by our group has validated the PRS-HFC in an *in vitro* model of hepatic cells differentiated from human skin-derived precursors (hSKP-HPC), the underlying mechanisms driving this genetic predisposition remain to be elucidated. We hypothesized that genetic predisposition for hepatic fat accumulation can influence the active uptake of fatty acids (FAs) and aimed to investigate this in the hSKP-HPC-based *in vitro* model.
Method: 92 hSKP cell lines were genotyped and classified according to their PRS-HFC (risk category ($RC)_{low}$, $RC_{intermediate}$, RC_{high}). Of both RC_{low} and RC_{high}, five cell lines were selected and differentiated to hSKP-HPCs. The cell cultures were exposed for 24 hours to a 'MASH' mix consisting of oleic acid, palmitic acid, fructose, lipopolysaccharide and tumor necrosis factor alpha, or vehicle-matched control medium. Both conditions also contained linoleic acid, which was present as a supplement in the differentiation medium. Intracellular lipids were stained with BODIPY™ 493/503 and quantified using flow cytometry. Active uptake of FAs was evaluated using the BODIPY™ FL C_{16} probe. Further, the expression of genes related to FA uptake was assessed.
Results: In the control condition, lipid accumulation was 4.6-fold higher for RC_{high} cultures compared to RC_{low} (p = 0.0051). In concordance with mRNA expression data, where a 3.8-fold higher expression of *cluster of differentiation 36* (CD36, fatty acid translocase) was found (p < 0.0001), active uptake of FAs was significantly

increased in the RC_{high} category compared to RC_{low} (1.6-fold, $p < 0.0001$). Gene expression of *solute carrier family 27 member 5*, encoding fatty acid transport protein 5, was unaltered between RCs. After exposure to the 'MASH' mix, the lipid load in the RC_{high} cultures was 3.5-fold higher than in the RC_{low} cultures ($p = 0.0004$). The mRNA expression of CD36 was markedly reduced in the RC_{high} cultures compared to their control condition (0.32-fold, $p < 0.0001$), and similarly modulated in the RC_{low} cultures (0.66-fold, $p = 0.0962$). On the functional level, this was reflected by a reduction in active FA uptake in RC_{high} (0.70-fold, $p < 0.0001$) and RC_{low} cultures (0.79-fold, $p = 0.039$). Nevertheless, CD36 expression and active uptake remained respectively 1.85-fold ($p = 0.0296$) and 1.45-fold ($p < 0.0001$) higher in RC_{high} than in RC_{low} cultures.

Conclusion: Increased FA uptake through fatty acid translocase might be one of the mechanisms through which genetic predisposition contributes to hepatic fat accumulation. In the current *in vitro* study, this effect was predominantly observed in the control condition, suggesting a possible role for differential FA transport during early stages of steatosis development.

FRI-339

Identifying health-to-disease transitional biomarkers in 3D human organotypic models of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH)

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) affects two billion adults worldwide and precedes the inflammatory condition metabolic dysfunction-associated steatohepatitis (MASH). Current diagnostic and therapeutic approaches are limited by a lack of cell-type specific biomarkers that distinguish transitional states between health, MASLD, and MASH. This study aimed to identify such biomarkers by using novel 3D human spheroid models of MASLD and MASH pathogenesis that recapitulated the cellular complexity within patient livers.

Method: We developed a human hepatic spheroid model composed of biliary epithelial cells (BECs) and hepatocytes (HepaRG116^{TM}), stellate, monocyte (Kupffer cell analogue), and endothelial cells (all from Biopredic International; BPI). 5000 cells/spheroid were seeded in William's E medium supplemented with general purpose serum (BPI). From day 3, spheroids were given maintenance and metabolism medium (MMM; BPI). From day 7, spheroids were treated with oleate (MASLD model) or a nutrient-excess and pro-inflammatory cocktail of lactate, pyruvate, octanoate and ammonia (LPON; MASH model). Controls were cultured in MMM. Media and cell lysates were collected at 0, 24, 48, and 72 h. HepaRG116^{TM} cells were used as a 2D comparator system. Pathogenic cell states were assessed by confocal microscopy with the Opera Phenix Plus Imaging System (Revvity) and validated with MASLD/MASH patient RNA-seq data (SteatoSITE.com). Image quantification was performed with Harmony (Revvity) or Fiji/ImageJ software. Lipid dynamics were assessed by holographic tomography (HT) (Nanolive) and CellPose/Cell Profiler software. Molecular profiling was achieved by SDS-PAGE/Western blotting, and cell health markers (ALT, AST, and L-lactate) were measured by enzyme-linked immunosorbent assays. Statistics were performed with GraphPad Prism 10 software.

Results: MASH spheroids showed extensive lipid accumulation, elevated ALT, AST, and L-lactate levels, and inflammatory activation of monocytes, resembling *in vivo* MASLD-MASH pathogenesis. Nanolive HT revealed lipid loading in MASH hepatocytes and BECs, and reduced BEC proliferation, compared to 2D MASLD and control models. Immunoblotting revealed increased epithelial (ZO-1 and E-Cadherin) and reduced mesenchymal (N-Cadherin, SNAIL1, alpha-SMA, and Vimentin) biomarkers in 2D MASH compared to both MASLD and control models. Confocal imaging of spheroids identified cell-type specific phenotypes for hepatocytes, monocytes, and stellate cells in 2D and spheroid MASH models over time. Patient RNA-seq data validated the cell type signatures identified in our MASLD and MASH models.

Conclusion: This study sought to tackle the need for reliable and specific molecular profiling for MASLD or MASH patients. Our human hepatic spheroid model provides a unique platform for studying real-time progression from health to MASLD and MASH at the cellular level and for putative biomarker discovery.

FRI-340-YI

Brain dysfunction is ameliorated by alpha 2A adrenergic receptor antagonism in experimental metabolic dysfunction-associated steatotic liver disease through vasodilatory and anti-inflammatory effects

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Background and aims: Brain dysfunction in terms of cognitive impairment and neurobiological changes is a recognised complication of metabolic dysfunction-associated steatotic liver disease (MASLD), and treatments for this condition are lacking. We have previously shown that antagonising the alpha 2A adrenergic receptor (ADRA2A) ameliorates liver inflammation, portal hypertension and disease progression in MASLD. This study aimed to investigate the potential of ADRA2A antagonism to treat brain dysfunction in MASLD and to explore the potential beneficial mechanisms.

Method: Two animal models of MASLD were evaluated in this study. Male C57BL/6NTac mice were fed a modified Amylin-liver non-alcoholic steatohepatitis (AMLN) diet or a standard diet (controls) for 36 weeks. Male Sprague Dawley rats were fed a high-fat, high-cholesterol (HFHC) diet or a standard diet (controls) for 16 weeks. Half of the MASLD animals in both protocols received the ADRA2a antagonist Yohimbine, in their drinking water for the final 10 weeks. Neurobehavioural tests were conducted in all animals. In the AMLN model, we also examined brain perfusion and conducted proteomic analyses of the cerebral cortex. In the HFHC model, we assessed inflammation in the liver, systemic circulation and brain.

Results: ADRA2a antagonism ameliorated impaired memory and depressive-like behaviour in both MASLD models, and also anxiety-like behaviour in the AMLN model. ADRA2a antagonism increased total cortex perfusion in the AMLN model and prevented an inhibition of pathways leading to vasodilation in the cerebral cortex, through Ca^{2+}-Calmodulin-NOS1 signalling. In the HFHC model, ADRA2a antagonism decreased systemic and liver inflammation and ameliorated signs of neuroinflammation by reducing levels of pro-inflammatory cytokines in the hypothalamus and cerebrospinal fluid.

Conclusion: Ten weeks of ADRA2a antagonism in two rodent MASLD models ameliorated cognitive dysfunction. This seemed to be through two mechanisms: 1) increased cerebral perfusion through facilitation of vasodilatory pathways and 2) decreased liver, systemic and brain inflammation.

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miRNA isoforms are differentially expressed with increasing disease activity and fibrosis in metabolic dysfunction-associated steatotic liver disease

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Background and aims: microRNA isoforms (isomiRs) may contribute to the differential functions of miRNAs, thus providing a novel class of druggable targets. Their expression and relationship to disease severity in MASLD is unknown. We therefore aimed to assess: (1) the isomiR landscape in MASLD, (2) its relationship to histological features, and (3) its role in disease biology.
Method: Snap-frozen liver tissue at the time of liver biopsy was obtained (MASL = 19, MASH = 47, MASH-cirrhosis = 11, control without liver disease = 2). Small RNA (sRNA) was sequenced and characterized for post-transcriptional modification, resulting in sRNA isoforms. Two independent approaches were used to relate isomiRs to histological activity and fibrosis stage: differential expression analysis (DEA) selecting isomiRs with adjusted $p < 0.05$ and by machine-learning (ML) methods with 10x k-fold cross-validation. TargetScan was used to determine their gene targets and to identify potential regulatory networks. The results were validated in an independent cohort.
Results: 7 classes of sRNA were identified with miRNA (74.5%) and piRNA (11.3%) representing the majority; 66% of miRNA were isomiRs. mir122, mir143, mir21 and let7a and let7b were the most common miRNA with both templated and non-templated additions of nucleotides. 1824 and 7818 sRNAs were differentially expressed with high activity (NAS > 4) and advanced fibrosis (AF), (stage 3–4). miRNA had the largest upregulated (n = 621) and downregulated (n = 141) species with AF. The data were split in a training and validation set for ML (glmnet + SVM) identification of high NAS and AF yielding an AUROC of 0.75 and 0.79 respectively. These differentially expressed isoforms were mapped to differentially expressed genes linked to 33 pathways including insulin- and PPAR-signaling, cholesterol metabolism and fibrosis. Specific isoforms of mir122 and mir21 targeting specific pathways e.g. -GAGTGTG 5′ isomiR122 for cholesterol metabolism and -TAGCTTA 5′ isomiR21 for modulation of integrin-cell surface interactions and response of TGF-β were identified. Gene targets were further validated in an independent data set.
Conclusion: These data expand the druggable genome by identifying novel sRNAs correlated to MASLD severity that can modulate specific pathways linked to disease activity and fibrosis providing foundational data for a new array of potential RNA-therapeutics.

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Exploring the repurposing of Telmisartan for the treatment of MASLD: characterization of its antisteatotic mechanism of action

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Background and aims: Metabolic dysfunction-associated steatotic liver (MASL), the initial stage of metabolic dysfunction-associated steatotic liver disease (MASLD), is directly involved in the progression to steatohepatitis. Moreover, individuals with MASL are already at increased risk of cardiovascular disease (CVD). Thus, the repurposing of Telmisartan, an angiotensin II type I receptor (AGTR1) antagonist approved to prevent cardiovascular events, as a treatment for MASL could represent a promising strategy to mitigate further clinical complications.
Method: Two-month-old female Sprague Dawley rats were randomized into three groups (n = 8 each): control diet and water; high-fat plus 10% drinking fructose (HFHFr); or HFHFr diet plus telmisartan 10 mg/kg/day in the final month.
Five days post-fertilization (dpf) zebrafish larvae with transgenically expressed fluorescent labels on hepatocytes (Tg[2.8fabp10a:GFP]) were randomly distributed into 4 groups until 10 dpf: standard-fed controls (ST), overfed plus 3% glucose (OF+GL), OF+GL plus Telmisartan at 0.4μM (Tel0.4μM) or OF+GL plus Telmisartan at 2μM (Tel2μM). Telmisartan was added from 8 to 10 dpf. For mutant zebrafish experiments, CRISPR/Cas9-induced mutated larvae and controls were distributed 50:50 to untreated or treated tanks at 5 dpf, with all tanks fed OF+GL. At 10 dpf we acquired whole-body and liver images of live larvae, and quantified lipids using a deep neural network. Fragment length analysis was used to ascertain the presence/absence of mutations.
Results: In the rodent model, Telmisartan reduced intrahepatic triglycerides (TG), % Oil Red O area (x0.34 and x0.22 vs. HFHFr, respectively), and perigonadal white adipose tissue weight (x 0.78) without affecting calorie intake or body weight. Hepatic lipid uptake, blood TG levels and β-oxidation markers were not modified by the drug treatment. In contrast, phosphoenolpyruvate carboxy kinase (PCK1) protein levels were restored (x2.07), and lipogenesis markers like ATP citrate lyase protein levels (x 0,64), fatty acid synthase (x 0,52) and stearoyl-CoA desaturase (x 0,59) mRNA levels were downregulated. Treatment with 2 μM Telmisartan reduced liver fat content (x 0.78) in a OF+GL challenged zebrafish larvae. The antisteatotic effect of Telmisartan was attenuated in larvae with CRISPR/Cas9-induced mutations in its targets (*agtr1* or *pck1*).
Conclusion: Telmisartan treatment attenuates steatosis in two dietary-induced MASLD models, potentially through the AGTR1 blockade and restoration of PCK1 levels. Our findings strongly encourage further clinical research to explore the repurposing of Telmisartan for the treatment of MASLD. Grants: PID2023-146140OB-I00, funded by MICIU/AEI/10.13039/501100011033 and FEDER-UE, and 2021SGR-00345. Swedish Heart-Lung Foundation (20230518), Swedish Research Council (2023-02556).

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Anti-steatosis effect of telmisartan in a MASL-dietary rat model does not associates to changes in faecal bile acid metabolome

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Background and aims: We have previously shown that pemafibrate administration prevents steatosis development in an experimental model of simple metabolic-associated steatotic liver disease (MASL) in Sprague-Dawley (SD) rat (*Biomed&Pharmacother* 177 (2024) 117067), further inducing significant changes in faecal bile acid (BA) metabolome. As we have found that telmisartan also prevents steatosis in the same experimental model, we were interested in determining its possible effect on faecal BA metabolome.
Method: Female Sprague-Dawley rats were randomly distributed into 3 groups (n = 8 each): (1) control (CT; standard rodent chow); (2)

high-fat diet with 10% w/v fructose in drinking water (HFHFr); (3) HFHFr plus telmisartan at 10 mg/Kg/day (Telmi). Rats were fed the HFHFr diet for three months, while the Telmi group received high fat diet supplemented with the corresponding drug for the last month. At the end of the treatment, rats fasted for 2 h were sacrificed and liver tissue and faecal content were collected and properly stored. The concentrations of 10 BA (cholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, ursodeoxycholic acid, α-muricholic acid, β-muricholic acid, hyocholic acid, hyodeoxycholic acid, and murideoxycholic acid) in rat faeces were determined by ultra-high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS), as described previously (Biomed&Pharmacother 177 (2024) 117067). Liver expression of pertinent genes related to primary BA synthesis was determined.
Results: After 3 months of dietary intervention, HFHFr showed increases in the following faecal bile acid concentrations: Total BA (x1.4 vs CT), cholic acid (x8.5 vs CT), chenodeoxycholic acid (x2.8 vs CT), Total Secondary BA (x1.3 vs CT), ursodeoxycholic acid (x7.8 vs CT), deoxycholic acid (x1.4 vs CT), and hyocholic acid (x2.6 vs CT). These changes were similar in intensity and direction to the changes induced by the HFHFr diet we have previously described (Biomed&Pharmacother 177 (2024) 117067). Although telmisartan treatment partially restored the liver expression of *cyp7a1* (x4.0 vs HFHFr), a gene coding for the main enzyme regulating primary bile acid synthesis, it did not significantly modify the faecal concentration of any of the BA analyzed.
Conclusion: Anti-steatosis effect of Telmisartan in a SD rat MASL dietary model do not associate with significant changes in faecal BA metabolome. Grants: PID2023-146140OB-I00, funded by MICIU/AEI/10.13039/501100011033 and FEDER-UE, and 2021SGR-00345.

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Sexual dimorphism of Sprague-Dawley rats in the liver inflammatory/fibrotic response to a high in sucrose and fat, choline-deficient, L-amino acid CDAA diet

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Background and aims: We have shown the efficacy and security of bempedoic acid and pemafibrate in an experimental model of simple metabolic dysfunction-associated steatotic liver in Sprague-Dawley (SD) rat (*Biomedicines* 10 (2022) 1517, *Biomed&Pharmacother* 177 (2024) 117067). We aim to characterize an appropriate SD rat model of metabolic dysfunction associated steatohepatitis (MASH) to test the efficacy and security of these drugs in an advanced stage of metabolic dysfunction-associated steatotic liver disease.
Method: Male and female SD rats were randomly distributed into 2 groups each: (1) control (CT; standard rodent chow, n = 8), and (2) CDAA (n = 16). Half the animals were fed the CT and CDAA diets for three months, and the remaining for an additional 2 moths. At the end of each period, the animals were sacrificed and serum and liver and perigonadal white adipose tissues were obtained. Zoometric, liver histology (Oil-Red O -ORO-, Haematoxylin-Eosin -HE-, and Sirius Red -SR-), serum and liver triglyceride (TG) and cholesterol (C) concentrations, serum analytes, liver hydroxyproline (LHP) content and expression of genes related to inflammatory, redox and fibrotic processes were determined.
Results: After 3 months, CDAA-male SD rats showed liver steatosis (increased liver content of C and TG, and ORO staining), inflammation (increased serum - alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase- and liver – tumor necrosis factor alpha (TNFalpha), F4.80, interleukin (IL) 6, IL1b - expression of inflammatory markers, and HE staining), and fibrosis (increased LHP and fibrotic - collagen type I alpha 1 chain (COL1A1), TIMP metallopeptidase inhibitor 1 (TIMP1), tissue growth factor beta (TGFbeta), actin alpha 2, smooth muscle (ACTA2)-markers, and SR staining). These changes were maintained at 5 months without a significant increase in their intensity. On the contrary, 3 and 5 months CDAA-female SD rats, although presenting liver steatosis, and mild changes in inflammatory markers, did not show clear signs of liver fibrosis, specially as assessed by LHP content and SR staining. Significant differing responses to the CDAA diet related to sex were observed for serum TG, C, insulin, ALT, AST, alkaline phosphatase, and growth differentiation factor 15 concentrations, histological assessment, and liver tissue expression of TNFalpha, F4.80, IL6, COL1A1/2, TIMP-1, TGFbeta, and ACTA2.
Conclusion: There is a clear sexual dimorphism in the response of SD rats to a CDAA diet, with males developing MASH after three months of continuous CDAA diet supplementation, while females not showing any clear increase in liver fibrotic markers after five months of CCDA diet supplementation.
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Quantifying the periportal and lobular fat distribution in metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis with artificial intelligence detection of portal tracts and macrovesicular steatosis

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Background and aims: Portal Tracts (PTs) are important features to identify when assessing liver histology slides because their morphology, location and related disease features are intrinsic to pathologists' evaluation of the tissue. Identification is also needed to determine biopsy adequacy (>6 PTs required). In addition, measures of steatosis, inflammation and fibrosis are generally reported as averages across the tissue - scored by eye rather than computationally. This averaging results in loss of potentially important information on heterogeneity of distribution of pathological features. To address the first two issues, we have developed an AI detection model for segmenting individual PTs. To show how this can also resolve the "averaging" issue, we have accurately quantified the distribution of steatosis in relation to portal and lobular regions.
Method: Our AI model detects individual features of PTs (bile duct, hepatic artery and portal vein) and associated tissue (foreground and connective tissue). Based on spatial analysis of these features, PTs and lobular regions can be identified. PT segmentations were then paired with segmentations of fat droplets to measure steatosis. Around each PT, concentric zones of ~100 microns thickness were identified to generate metrics across portal, lobular and periportal regions. The model was applied to Haematoxylin and Eosin stained WSIs from Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD) [N = 249] and Metabolic dysfunction-Associated Steatohepatitis (MASH) [N = 104] datasets. Steatosis was measured using the percentage of steatotic tissue in proportion to the total tissue area (Fat Fraction - FF). Comparisons were measured using Mann-Whitney and Kruskal-Wallis tests.
Results: Our model accurately identified steatosis in interface, portal and lobular regions across WSIs. When comparing the FF in portal regions, there was a significant ($p < 0.05$) low level of steatosis in MASLD [0.16%] and MASH [0.20%]. In lobular regions, there was a significant ($p < 0.001$) difference of steatosis between MASLD [4.9%]

and MASH [7.2%]. When delineating periportal regions, there were low levels of steatosis in the closest zone to the PT (Zone 1) in both MASLD and MASH [2.25% vs 2.69%] with increasing levels of steatosis in zones 3–4 [5.2% vs 6.75% and 5.3% vs 7.2% in MASLD and MASH respectively]. Significant differences ($p < 0.01$) in steatosis were apparent between MASLD and MASH in all zones apart from zone 1. When compared to steatosis scores from expert pathologists, there was no significant difference between MASLD and MASH.
Conclusion: PT characterisation is imperative for histological scoring and establishing sample adequacy of liver biopsies. Our AI model can also generate visual overlays on WSIs to assist pathologists by producing automated quantifications of steatosis across whole biopsies. Quantitative measurements of steatosis are not only more accurate and reproducible endpoints but may help differentiate between MASLD and MASH cases.

FRI-350
Effect of high-intensity interval, moderate continuous and voluntary training on body composition, hepatic steatosis and myosteatosis in a preclinical model of metabolic dysfunction-associated steatotic liver disease
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Background and aims: MASLD is defined as hepatic steatosis combined with different levels of inflammation and fibrosis. Recently, myosteatosis has been shown to be linked to the severity of MASLD in preclinical models. On the other hand, physical exercise could be beneficial for decreasing lipid content in the liver and in the skeletal muscle. This study aims to investigate if physical exercise could reduce myosteatosis and the severity of MASLD in a preclinical model, and which training modality would be the most effective.
Method: High fat diet (HFD)-fed fat aussie (FOZ) mice were used as a preclinical model of MASLD. Mice were divided into five groups: control treadmill (CTRL TM, n = 3), control wheel (CTRL W, n = 3), high intensity interval training (HIIT, n = 6), moderate continuous training (MCT, n = 4) and free wheel training (W, n = 3). After 12 weeks of HFD, mice were trained 5 times per week for 8 weeks on a treadmill or during nights on the wheel. Before and after training, body composition and density of the dorsal muscle (DM) and the liver were assessed by micro-computed tomography (µCT-scan). Mice were sacrificed at 20 weeks of HFD. Hindlimb muscles and liver were collected for further analysis. The MASLD activity score (MAS) was determined based on the degree of inflammation, hepatocyte ballooning and steatosis in the liver.
Results: At this point of the study, there is not enough individuals to conclude any comparisons between groups. However, each group can be analyzed individually before and after training. After HIIT, weight was increased ($p = 0.014$) and DM density was decreased ($p = 0.024$). After MCT, DM density and liver density were both increased ($p = 0.019$ and 0.003 respectively). MAS score and its parameters taken individually were not changed by HIIT or MCT so far. Results from the groups CTRL W and W are not available for the moment but will pe presented on the poster.
Conclusion: HIIT and MCT did not reverse the severity of MASLD based on the MAS score. According to the µCT-scan results, HIIT seems to worsen the myosteatosis whereas MCT seems to improve lipid infiltration in the liver and in the DM. Further analysis needs to be conducted to enhance statistical power and to understand the underlying mechanisms of lipid accumulation in the liver and in the skeletal muscles.

FRI-351
Qushi Huayu formula and some of its compounds directly promote the growth of Roseburia intestinalis to alleviate metabolic dysfunction-associated steatotic liver disease
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing global health concern, strongly influenced by gut dysbiosis. In our prior clinical trial, Qushi Huayu (QSHY), a traditional Chinese medicine, demonstrated efficacy in treating MASLD and correcting gut dysbiosis. This study aims to identify the efficacy response-associated microbial species (RAMS) linked to QSHY intervention and to explore the formulation compounds responsible for modulating RAMS.
Method: We conducted a metagenomic analysis of 44 patients, including high-response individuals (relative decreases in serum alanine transferase > 40% or liver magnetic resonance imaging-derived proton density fat fraction > 30% from baseline at week 24) treated with QSHY or a control (n = 22 per group). RAMS associated with QSHY intervention were verified via fecal microbiota transplantation (FMT) from patients pre- and post-treatment into recipient mice. A high-fat, high-sugar (HFHS) diet-induced model of steatohepatitis (MASH) was used for in vivo evaluation. Compounds from QSHY and cecal contents of MASH mice were analyzed using chromatography-q exactive-orbitrap high resolution mass spectrometry (UHPLC-Q-Orbitrap HRMS) at multiple time points (4, 6, 8, 12, and 24 hours) after continuous QSHY intragastric administration (1.7 g/kg for six weeks, n = 5 per time point). The direct effects of QSHY and its compounds on RAMS were assessed using in vitro co-culture assays.
Results: QSHY significantly increased the abundance of *Roseburia intestinalis* (*R. intestinalis*) in high-response MASLD patients post-intervention. The relative abundance of *R. intestinalis* was negatively correlated with liver fat content, liver injury markers, and insulin resistance. FMT from post-QSHY MASLD patients improved liver lipid deposition and elevated *Roseburia* abundance in recipient mice. Colonization with *R. intestinalis* alleviated hepatic steatosis, inflammation, and metabolic dysfunction in HFHS diet-induced MASH mice. A total of twenty compounds were identified in both QSHY and the cecal contents of MASH mice after six weeks of continuous QSHY intragastric administration. QSHY and eight compounds were found to directly promote *R. intestinalis* growth.
Conclusion: QSHY corrects intestinal dysbiosis in patients with MASLD. QSHY and some of its compounds directly promote the growth of *R. intestinalis*, offering potential therapeutic effects for MASLD.

FRI-352-YI
Spatial multiplex analysis reveals distinct senescence patterns and cellular interactions in mouse models of MASLD and MetALD
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Background and aims: Hepatocellular senescence, arising from cellular injury, leads to cell cycle arrest in metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic alcohol-related liver disease (MetALD), affecting the tissue microenvironment, including interaction with neighboring hepatocytes, their

distribution, and localization. This study aims to characterize senescence-associated cellular patterns in steatotic liver disease (SLD) to explore their potential role in mediating disease progression.
Method: MASLD and MetALD rodent models were established in wild-type C57BL6/J mice. For MASLD, mice were fed with Choline-Deficient, L-Amino Acid-Defined, High-Fat Diet (CDAHFD) for 8 & 12 weeks and Western Diet (WD) for 7 & 16 weeks. For MetALD, mice received WD plus 10% ethanol in drinking water for 4 weeks plus ethanol binge (6 g/kg) 24 hours before sacrifice. Liver tissues underwent multiplex immunofluorescence (mIF) staining followed by single-cell analysis with CellProfiler and MATLAB/CytoMAP.
Results: The MASLD models demonstrated varying levels of steatosis and inflammation, accompanied by an increased senescence phenotype (elevated SA-beta galactosidase activity, p53, and p21, along with decreased Lamin B1 and phosphorylated Retinoblastoma). Notably, the CDAHFD exhibited more pronounced effects than the WD. Additionally, mIF-based single-cell analyses revealed that DNA damage and senescence were specific to hepatocytes, showing significant results in WD ($p21: p < 0.002$; gamma-H2A.X: $p < 0.04$) and CDAHFD ($p21: p < 0.02$; gamma-H2A.X: $p < 0.006$). Senescent hepatocytes were primarily located in the peribiliary zones, while DNA-damaged and proliferating hepatocytes predominantly occurred in the parenchymal region. The DNA-damaged hepatocytes in the parenchyma (WD: $p < 0.04$; CDAHFD: $p < 0.002$) were often surrounded by proliferative hepatocytes (WD: $p < 0.04$; CDAHFD: $p < 0.03$). This suggests that, in MASLD, senescent hepatocytes in the peribiliary areas may inhibit the proliferation of adjacent cells, whereas DNA-damaged hepatocytes in the parenchyma could promote hepatocellular proliferation in their vicinity. In contrast, the MetALD model was significantly associated with hepatocellular senescence ($p < 0.02$) despite the absence of substantial DNA damage. In this case, senescent hepatocytes were primarily localized in the perivenous region and surrounded by proliferative hepatocytes. This distribution pattern likely reflects the influence of alcohol on the localization of senescent cells.
Conclusion: Hepatocellular senescence is ubiquitous among MASLD (WD and CDAHFD) and MetALD. Refined spatiotemporal patterns of hepatocellular senescence, DNA damage, and proliferation in MASLD and MetALD illuminate the intricate progression of SLD, deepen our understanding of disease mechanisms, and highlight zone-specific therapeutic targets for future interventions.

FRI-353-YI

Tirzepatide reduces diet-induced senescence and NETosis-mediated liver fibrosis in mice

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Background and aims: Lipofuscin was found to accumulate in senescent cells and was reported in liver biopsies from patients with liver fibrosis of various etiologies. However, the relationship between lipofuscin and liver fibrosis has not been elucidated. Tirzepatide (TZP), the latest FDA-approved anti-diabetic drug, was recently shown to improve liver fibrosis in patients with obesity. Adopting a mouse model of liver fibrosis with robust lipofuscin accumulation, we aimed to examine if TZP can alleviate liver fibrosis by intercepting senescence and neutrophil activation.
Method: C57BL/6J mice were fed either control diet or choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for up to 10 weeks with TZP (or vehicle) treatment commenced concurrently. Livers were collected and processed for histological staining, bulk RNA sequencing (RNA-seq), immunostaining and western blotting to examine differences in fibrosis severity, lipofuscin accumulation, neutrophil activation and markers of senescence.
Results: Mice developed liver fibrosis starting from week 7 of CDAHFD feeding, while lipofuscin accumulation in hepatocytes was visible as early as at week 2. A strong and significant positive correlation ($r = 0.85$, $p < 0.001$) was observed between liver collagen deposition and lipofuscin accumulation. Among differentially expressed genes revealed by RNA-seq analysis, chemokine- and cytokine-related genes were upregulated in the liver of CDAHFD-fed mice. Further Gene Ontology analysis showed a significant enrichment in neutrophil migration, chemotaxis, and activation pathways. Immunostaining confirmed that more neutrophils infiltrated into the liver of CDAHFD-fed mice. Notably, neutrophil extracellular trap formation (NETosis) occurred mainly in neutrophils that clustered around lipofuscin-laden cells. Mice defective in NETosis (*Vav1-Cre Padi4$^{fl/fl}$*) showed less severe liver fibrosis when fed CDAHFD, indicating a crucial role of NETs in liver fibrosis development. Treatment of TZP decreased lipofuscin accumulation and liver fibrosis, in conjunction with a reduction of chemokine- and cytokine-related genes mediating neutrophil activation. CDAHFD-induced senescence markers, including p21 and p16, senescence-associated secretory phenotype-related genes, loss of hepatocyte identity and increase in polyploidisation in lipofuscin-laden cells, were also reversed by TZP.
Conclusion: TZP reduces senescence, including lipofuscin accumulation, and liver fibrosis in CDAHFD-fed mice. These findings highlight the potential to repurpose TZP for liver fibrosis implicating lipofuscin accumulation in a non-diabetic context.

FRI-354-YI

A dynamic human liver acinus-on-a-chip to model health-to-disease (MASLD-MASH) transitions

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Background and aims: The transition from healthy liver to metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH) involves complex interactions between hepatocytes, nonparenchymal cells (NPCs), and extracellular matrix (ECM). These processes are poorly captured in standard static 2D cultures. Microfluidic Organ-Chip platforms offer physiologically-relevant microenvironments integrating mechanical forces, fluid dynamics, and cell-cell/cell-matrix interactions. We developed a novel 5-cell-type human liver acinus-on-a-chip to model hypoxia and inflammation-driven transitions from healthy liver to MASLD and MASH.
Method: Using Emulate™ S1-Chips the 5 cell-types of the human liver acinus were co-cultured under dynamic flow. HepaRG116™ cells (hepatocyte:cholangiocytes) were seeded into the S1-Chip upper channel; and monocytes (Kupffer cell analogue), stellates', and endothelial cells in the lower channel. Chips were incubated under flow (30µL/h) for 7 days before challenge with MASLD (Oleate) or MASH (LPON: Lactate, Pyruvate, Octanoate & Ammonia) inducing media for 72 h. Supernatant samples were collected at 0, 24, 48 and

72 h. Lipid accumulation, pro-inflammatory markers, and ECM remodelling were assessed with ELISA, Western blotting, and confocal imaging. Results were compared with conventional, static 2D monolayer and 2.5D Transwell® models.
Results: The liver acinus-on-a-chip displayed self-organization (cell-cell/cell-matrix interactions) with robust biocompatibility/viability. MASLD-MASH conditions induced progressive lipid accumulation and inflammation-driven ECM remodeling. The acinus-chip outperformed conventional systems in recapitulating in vivo-like (patho)physiological/ responses in albumin, ALT, and L-lactate (cell stress) secretion. Pro-inflammatory IL-6 levels and hypoxia-inducible factor 1-alpha nuclear localization were elevated in MASH conditions, aligning with published patient data.
Conclusion: The acinus-on-a-chip model offers a unique physiologically-relevant liver microenvironment to study the pathogenic progression from healthy-MASLD-MASH. It offers enhanced predictive insights compared with static models, enabling temporal tracking of cellular behaviour and secreted factors. Future studies will employ temporal-omics analyses to identify biomarkers and elucidate disease mechanisms - validated against patient data - which could aid diagnostic and therapeutic strategies in chronic liver disease.

FRI-355
Single-cell transcriptomics reveals THR-β agonist treatment increases macrophage proportion and inhibits complement pathway in mice with metabolic dysfunction-associated steatohepatitis
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Background and aims: Thyroid hormone receptor (THR)-β agonist resmetirom has been approved by the U.S. FDA as the first drug for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). However, the effects of THR-β agonist treatment on different liver cell types and their interactions in the MASH context remain poorly understood.
Method: To explore the effects of the THR-β agonist HSK31679 on liver cell types and their interactions in MASH, we used a mouse model induced by a western diet. Mice were divided into two groups (n = 3 per group). Group A received HSK31679 (5 mg/kg) by gavage, while Group B received the solvent as a control. The treatment lasted for 28 days, after which liver tissue was subjected to single-cell sequencing.
Results: Seven liver cell subsets were identified: hepatocytes, liver macrophages, hepatic stellate cells, liver endothelial cells, B cells, dendritic cells, and plasma cells. Compared to the model group, the proportion of hepatocytes decreased in the HSK31679 treatment group, while proportions of liver macrophages, hepatic stellate cells, liver endothelial cells, B cells, dendritic cells, and plasma cells increased. Notably, liver macrophages showed the most significant increase. Gene ontology enrichment analysis revealed activation of the alternative and classical complement activation pathways in macrophages of the model group, which were suppressed in the HSK31679-treated group. In addition, communication between various liver cell subsets was enhanced in the HSK31679-treated group, particularly between hepatocytes and liver macrophages, hepatic stellate cells, liver endothelial cells, B cells, and dendritic cells. Communication between liver macrophages and other cells (hepatocytes, hepatic stellate cells, and endothelial cells) was also strengthened.
Conclusion: Treatment with the THR-β agonist HSK31679 in MASH mice resulted in an increased proportion of liver macrophages and suppressed complement activation pathways in these cells. Additionally, communication between liver cell subsets, particularly between hepatocytes and macrophages, was enhanced.

FRI-357
Liver disease activity measured with quantitative MRI is associated with major liver and cardiovascular events: a prospective cohort study
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Background and aims: Individuals with metabolic-dysfunction associated liver disease (MASLD) experience higher rates of mortality and morbidity. Our aim was to investigate the prognostic value of MRI-derived biomarkers of liver disease activity and liver fat in assessing the risk of experiencing major liver events, at the population level and in individuals with MASLD.
Method: UK biobank participants aged 40–70 years were scanned between 2016 and 2022. LiverMultiScan was used to measure inflammation via iron-corrected T1 (cT1, ms), and liver fat content (LFC, %). Outcomes were all-cause mortality, new-onset major liver and cardiovascular events, and non-infective liver disease-related related hospitalization from hospital and death records. Hazard ratios were reported, adjusted for age, sex and body mass index (BMI), and repeated in a subset of participants with MASLD for cT1 and LFC as continuous, normalised variables and thresholded at clinically relevant cutoffs. (cT1 between 800 ms and 875 ms, cT1 above 875 ms, LFC between 5% and 10% and LFC above 10%).
Results: 45,262 participants had available cT1 data (mean age 65 years, 52% female, 18% BMI ≥30 kg/m^2, 99% with LFC available) with a median follow-up time of 4 years (3–5). 11,560 met the diagnostic criteria for MASLD (mean age 65 years, 40% female, 40% BMI ≥30 kg/m^2). The median time to liver events was 27 months (13–42), and to CVD events was 27 months (14–41). Overall incidence rates per 1000 person-years were 0.4 for liver events (0.5 in MASLD sub-group) and 2.5 for liver hospitalization (4.7 in MASLD); 11 for CV events (14 in MASLD); and 3.2 for all-cause mortality (3.5 in MASLD). As a continuous variable, liver cT1 was associated with major liver events (HR 1.9 [1.6, 2.4]), liver hospitalisation (1.6, [1.5, 1.7]), CVD events (1.1 [1.0, 1.2]) and all-cause mortality (1.2, 1.1, 1.3). Liver fat was associated with liver hospitalization (1.5 [1.4, 1.6]). In the MASLD subset, continuous cT1 and LFC were associated with major liver events (cT1 2.3 [1.5, 3.4], LFC 1.5 [1.0, 2.1]). and liver hospitalisation cT1 between 800 and 875 ms was associated with liver hospitalisation (HR 3.2 [2.4, 4.4]), major liver events (2.6 [1.1, 6.2]), and all-cause mortality (1.7 [1.1, 2.3]). cT1 above 875 ms was associated with major liver events (14.5 [5.8, 36.6]) and liver hospitalisation (6.4 [4.0, 10.2]). LFC between 5 and 10% and LFC above 10% were associated with liver hospitalisation (1.7 [1.3, 2.2], 3.1 [2.4, 4.1]).
Conclusion: In a large-scale prospective study, MRI metrics of liver impairment are associated with liver hospitalisation and liver events in the general population and in a MASLD sub-set. Liver disease activity measured by cT1 is more strongly associated with risk of new-onset liver events than liver fat. cT1 is also associated with new-onset major cardiovascular events and all-cause mortality.

FRI-358
Anti-inflammatory effects of a chemokine receptor mimicking peptide in obesity-associated MASH and atherosclerosis in Ldlr −/− Leiden mice
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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is one of the most prevalent chronic liver diseases, which is closely associated with obesity, dyslipidemia and

atherosclerotic cardiovascular disease. Inflammation is one of the driving forces in MASLD and atherosclerosis progression. Therefore, in this study, we investigated the potential anti-inflammatory effect of a novel peptide-based chemokine receptor ectodomain mimic, msR4M-L1, as a treatment for obesity-associated MASLD and atherosclerosis. msR4M-L1selectively inhibits the MIF/CXCR4 axis and blocks pro-inflammatory MIF activity *in vitro* and *in vivo*, an atypical chemokine known to play a role in both MASLD and atherosclerosis progression. The peptide has high proteolytic stability and spares the dichotomic CXCL12/CXCR4 and cardioprotective MIF/CD74 axis.

Method: Ldlr−/− Leiden mice were fed a high-fat diet (HFD) for 10 weeks to induce obesity dyslipidemia, atherosclerosis and MASLD features and subsequently treated for 14 weeks with msR4M-L1 (3x/week via i.p.) or vehicle (3x/week saline via i.p.) while continuing HFD feeding. Endpoints included plasma lipids, lipoprotein profile and histological analysis of MASLD and atherosclerosis in the aortic root as well as single nuclei RNA sequencing (snRNAseq) of aorta.

Results: After 24 weeks of HFD feeding, Ldlr−/− Leiden mice developed obesity, increased white adipose tissue weight, systemic low-grade inflammation, plasma dyslipidemia, MASLD and atherosclerosis. msR4M-L1 slightly increased body weight compared with the HFD-vehicle group, without affecting food intake or adiposity, an observation sparking future mechanistic studies. The peptide did not affect MASLD or atherosclerotic lesion size but improved circulating inflammatory factors and the vascular inflammatory status by increasing atheroprotective vascular macrophage populations and eliciting an anti-inflammatory transcriptional signature. These systemic and vascular anti-inflammatory effects of msR4M-L1 were associated with an increase in the number of smooth muscle cells (SMCs) within atherosclerotic plaques, contributing to a more stabile plaque phenotype.

Conclusion: Specifically targeting the MIF/CXCR4 axis attenuated HFD-induced low-grade inflammatory state and improved atherosclerotic plaque composition by increasing plaque-stabilizing SMCs, suggesting an overall atheroprotective role.

FRI-359

A 5-week treatment with the GLP-1/GIP/glucagon triple receptor agonist retatrutide demonstrates multiple metabolic benefits and strong reduction in liver steatosis in a diet-induced obese MASH mouse model

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Background and aims: Retatrutide is a novel triple agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1 and glucagon receptors that demonstrated significant body weight loss and liver fat reduction in patients with obesity. Our aim was to evaluate the effectiveness of retatrutide in the AMLN-diet induced obese MASH mouse model, a preclinical model routinely used for preclinical drug development.

Method: C57BL/6JRj mice were fed the AMLN-diet for 35 weeks to induce obesity and MASH, before a 5-week treatment with vehicle or retatrutide 15 nmol/kg s.c. Q3D. A group of age-matched/control chow fed mice was included as negative control. Body weight, food/water intake, whole body composition and energy expenditure were monitored during the treatment period, then blood and liver were collected for biochemistry and histology analysis after 5 weeks of treatment.

Results: As expected, 5-week treatment with retatrutide strongly reduced body weight by 31% ($p < 0.0001$ vs. vehicle) with significant reduction in fat and lean mass. The weight loss was also associated with a strong inhibition of food and water intake during the first days of treatment and a significantly greater energy expenditure at the end of the treatment period. Compared with vehicle, retatrutide significantly reduced fasting blood glucose and plasma insulin, leading to a 69% lower HOMA-IR index of insulin resistance ($p < 0.0001$ vs. vehicle). Retatrutide did not alter plasma transaminases levels and fasting plasma triglycerides, but reduced total cholesterol levels (−37%, $p < 0.01$). Compared with vehicle, retatrutide markedly decreased liver mass (−44%, $p < 0.0001$) and strongly reduced hepatic fatty acids, triglycerides and total cholesterol content (-66%, – 75% and 45%, all $p < 0.001$). Although the 5-week treatment period did not reduce hepatic inflammation and portal fibrosis, histology analysis also showed a 2-fold lower steatosis score with retatrutide ($p < 0.0001$ vs. vehicle).

Conclusion: In the AMLN-diet induced obese MASH mouse model, a 5-week treatment with retatrutide demonstrates multiple metabolic benefits and a strong reduction in liver steatosis. This preclinical data set will help to further assess the efficacy of novel therapies targeting obesity and MASH versus retatrutide as reference.

FRI-360

Sex-based differences in immune response and liver damage in MASLD-associated sepsis: role of neutrophil extracellular traps

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD), the most prevalent liver disease worldwide, is characterized by liver damage, fibrosis, and inflammation. Its progressive form, MASH, has been recently confirmed as an independent risk factor for sepsis, a life-threatening systemic response to bacterial infection. In sepsis, the participation of neutrophils remains unclear. While neutrophil extracellular traps (NETs) function to remove pathogens, excessive NETs release has been proposed to contribute to organ damage during sepsis. However, the role of NET formation and their clearance in experimental MASLD and following sepsis, as well as potential sex-based immune response differences, have not been reported.

Method: MASLD was induced in 8- to 10-week-old wild-type (WT) C57BL/6J male and female mice using a high-fat, choline-deficient diet (HFCD) with 60% kcal from fat and 0.1% methionine. After four weeks on the HFCD, mild sepsis was induced via intraperitoneal injection of lipopolysaccharide (LPS, 10 mg/kg, LD50). Mice were sacrificed 6- or 16-hours post-injection. Liver damage was assessed by ALT levels. Serum levels of inflammatory cytokines IL-6 and TNF-α, neutrophil elastase (NE), liver tissue IL-1β, and citrullinated histone H3 (H3cit, a marker of NET formation) were measured by ELISA. Inflammatory gene expression was analyzed by qPCR. Immunofluorescence was used to detect NETs in hepatic tissue, acquired in a Leica Stellaris 8 dive confocal microscope, and analyzed with ImageJ/Fiji.

Results: Following LPS administration, hepatic damage (ALT) peaked earlier in male MASLD mice compared to MASLD females, while chow-fed mice of either sex showed no liver damage. Inflammatory cytokines at the 6-hour mark were significantly elevated in males compared to females, both in serum protein levels and liver mRNA expression. However, 16 hours post-LPS, MASLD males exhibited reduced liver damage compared to MASLD females, which displayed persistent hepatic injury that correlated with increased presence of NETs in liver as compared to MASLD males. In accordance, higher H3cit levels in tissue, confirmed the increased presence of NETs in the livers of MASLD females.

Conclusion: This study highlights significant sex-based differences in immune response and liver damage in MASLD-associated sepsis. In

similar MASLD conditions, while males displayed an earlier inflammatory response with quick resolution at later stages, females showed a persistent injury paralleled by enhanced NET formation and aggravated hepatic damage. Our results suggest NET formation as participating mechanism in the susceptibility to sepsis observed in female MASLD patients, underscoring the study of NETs as potential target for personalized strategies in sepsis treatment.

FRI-365

DR10624, a novel FGF21R, GCGR, and GLP-1R tri-agonist, demonstrated extraordinary efficacy in B6-Alms1-del mice, a spontaneous MASH model of mice with obesity, hyperglycemia, and dyslipidemia phenotype

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Background and aims: DR10624 is a novel long-acting tri-specific therapeutic protein with agonistic activity against FGFR1c/Klothoβ coreceptor (FGF21R), Glucagon receptor (GCGR), and GLP-1 receptor (GLP-1R). In non-clinical studies, DR10624 has shown extraordinary potency in terms of reduced body weight, normalized blood lipids, and improved glycemic control, making it a promising candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH).

Method: Thirty-five B6-Alms1-del mice, a spontaneous metabolic dysfunction-associated steatohepatitis (MASH) model of mice, were selected for a 6-week study. The mice were randomly divided into five groups of seven: G1 (normal control), G2 (model control), G3 (Semaglutide 30 nmol/kg), G4 (DR10624 3 nmol/kg), G5 (DR10624 10 nmol/kg), and G6 (DR10624 20 nmol/kg). Blood samples were collected at week 3 and 6 to assess liver function and lipid profiles. At the end of the study, liver weights were recorded, liver lipid content (TC and TG) were analysed. Liver tissues from the left, middle, and right lobes were paraffin-embedded for hematoxylin and eosin (H&E) staining to assess the NAFLD Activity Score (NAS) and Picrosirius Red (PSR) staining to evaluate fibrosis.

Results: DR10624 showed dose-dependent liver protection and antihyperlipidemic effects, evidenced by significantly reduced ALT, AST, Choloesterol, and LDL-C levels. Both Semaglutide and significantly reduced liver weight, liver index, and hepatic TC and TG, but DR10624 was more effective at all dose levels. DR10624 (3, 10, and 20 nmol/kg) significantly reduced steatosis, inflammation, and ballooning, leading to a lower NAS score compared to the model control ($p < 0.0001$). While Semaglutide (30 nmol/kg) reduced inflammation and the overall NAS score, DR10624 exhibited superior effects in reducing steatosis and ballooning. Compared to the normal control, all groups (model control, Semaglutide, and DR10624) exhibited mild fibrosis. However, the model control group had a higher proportion of grade 2 fibrosis and a lower proportion of grade 0 fibrosis. Both Semaglutide and DR10624 reduced the proportion of grade 2 and 1C fibrosis and increased the proportion of grade 0 fibrosis, indicating improved fibrosis. While both treatments were effective, DR10624 appeared to have a slightly weaker antifibrotic effect than Semaglutide, as evidenced by a higher proportion of lower-grade fibrosis.

Conclusion: DR10624 significantly improved liver pathology in B6-Alms1-del mice, a spontaneous MASH model of mice. It also effectively reduced body weight, improved liver and blood lipid profiles, and ameliorated liver function, which all outperformed Semaglutide. DR10624's preclinical study demonstrated its great potential as a possible best-in-class biotherapy for the treatment of MASH patients.

FRI-366

Integrated analysis of the liver tissue proteome and transcriptome in metabolic dysfunction-associated steatotic liver disease (MASLD) reveals an evolving pathophysiological milieu that may support identification of novel therapeutic targets

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Background and aims: Greater understanding of pathophysiological changes as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) progresses to cirrhosis will inform the identification of new therapeutic targets. Previous studies have compared the hepatic transcriptome with the circulating proteome, but have been unable to simultaneously survey transcriptomic and proteomic changes within the liver itself. This is the first large-scale multi-omics study to carry out comprehensive analyses of the evolving liver proteome and transcriptome across the full spectrum of MASLD.

Method: Simultaneous extraction of mRNA and proteins was conducted from the same tissue sample in a cohort of 122 well-characterised, histologically confirmed, MASLD cases selected from the European SLD (NAFLD) Registry. Using untargeted LC-MS/MS proteomics, we measured the expression of 4,815 hepatic proteins and conducted global RNA-sequencing, detecting 35,390 mRNA signals in total. These datasets were then integrated with publicly available scRNA-sequencing data to explore correlations between genomic and proteomic expression changes and the expression of potential therapeutic targets during MASLD progression.

Results: We demonstrated a considerable positive correlation between protein and mRNA expression (Spearman's Rho = 0.5, *p*-value = 2.2e-16). The markers exhibiting the strongest correlation were significantly enriched in metabolic processes, with many highly localised to hepatocytes. Proteins linked to lipid, retinol and cholesterol metabolism (AKR1B10, TM7SF2 and SULT2A1) were observed to increase with worsening fibrosis. We also identified proteins enriched in carbohydrate, lipid, homocysteine and glycine metabolism (GALK1, PLIN1, GNMT and BHMT) to decrease particularly at the cirrhotic stage, indicating strong metabolic changes within hepatocytes throughout disease progression. In addition, tissue remodelling and progenitor cell markers (CAPG, TAGLN, FBLN5 and KRT7) were highly correlated between transcriptomic and proteomic levels increasing with advancing fibrosis. We then carried out differential expression analysis comparing milder

(fibrosis stages 0–2) and advanced disease (fibrosis stages 3–4) to investigate significance. We discovered 26 candidates to be differentially expressed at both the transcriptomic and proteomic levels, 9 of which were amongst the most correlated, with an additional 17 proteo-transcriptomic markers significantly changing in advanced MASLD.
Conclusion: The current study provides new insights into the changing proteo-transcriptomic profile of the liver throughout the pathophysiological evolution of MASLD. It suggests optimum treatment targets/drug mechanisms of action may change as the disease progresses and has clinically relevant implications that will help guide future drug development.

FRI-367
Pathophysiological mechanisms involved in liver steatosis in metabolic dysfunction-associated steatotohepatitis over time : a bulk RNAseq data analysis
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Background and aims: Liver steatosis results from metabolic dysregulations of lipid homeostasis. Drugs targeting lipid metabolism are being evaluated in clinical trials with inconsistent results. We suggest that steatosis pathophysiology evolves with MASLD progression resulting in a mismatch between the deregulated mechanisms and the drug used. Our aim is to analyze the evolution of gene expressions of key lipid metabolism genes during MASH progression in mice.
Method: *Foz/foz* mice (FOZ) were fed normal diet (ND) (3.39 kcal/g, 16% of lipids) or high-fat diet (HFD) (5.24 kcal/g, 60% of lipids). Liver tissue was harvested at baseline (control group, N = 5) and after 4 (HFD = 4), 12 (HFD = 8) or 32 (HFD = 6) weeks. Liver samples were scored histologically (SAF score) using hematoxylin & eosin staining. Total RNA from liver samples was extracted using Qiagen® mini kits prior to bulk RNA sequencing. Sequencing data were normalized according to timepoint and diet (RStudio). Differentially expressed genes (DEG) and enrichment analysis reported by the Normalized Enrichment Score (NES) of FOZ HFD mice were compared at each timepoint with the control group.
Results: Maximal liver weight to body weight ratio was reached at 32 weeks ($p < 0.001$). Insulin resistance assessed by the HOMA-IR index was present at 4 weeks of HFD ($p < 0.01$). Liver histology showed the whole MASH spectrum with transcriptomics changes over time. At week 4, steatosis was observed with 284 DEG notably involved in fatty acid biosynthetic process (NES = 13.9, padj = 1.2e-4), lipid transport (NES = 9.7, padj = 8.0e-8), lipid storage (FES = 21.5, padj = 3.0e-6) and fatty acid oxidation (FAO) (NES = 9.4, padj = 0.02). At week 12, steatohepatitis was observed with 469 DEG involved in 504 enriched pathways including lipid transport (NES = 14.7, padj = 3.6e-15), lipid storage (NES = 24.2, padj = 1.66e-7) and FAO (NES = 22.2, padj = 2.7e-7). At week 32, fibrosing steatohepatitis was observed with 750 DEG involved in 1167 enriched pathways including lipid transport (NES = 11.3, padj = 6.3e-21), lipid storage (NES = 24, padj = 1.4e-15) and FAO (NES = 11, padj = 7.4e-7). At the gene level, the lipid metabolism key regulator Pparɣ was downregulated in a time-dependent manner: Log2FC = – 1.6, padj = 9e-5 at week 4; Log2FC = –1.8, padj = 9e-6 at week 12 and Log2FC = –2.35, padj = 6.6e-9 at week 32. Fatty acid oxidation related genes are all downregulated at week 12, such as Obp2a (Log2FC = –3.17, padj = 0.003) and Acaa1b (Log2FC = –1.64, padj = 9.9e-9). Lipid storage genes expression also greatly change over time. Both Cidec and Fitm1involved in lipid droplet homeostasis are significantly downregulated at week 12 (Log2FC = –2.13, padj = 3e-6; Log2FC = –1.37, padj = 1.68e-7 respectively) and at week 32 (Log2FC = – 2.7, padj = 2e-5; Log2FC = –1.02, padj = 2e-4 respectively).
Conclusion: Gene expression of key-lipid metabolism genes significantly change over time during MASH occurence. These shifts in gene expression of potential therapeutic targets may significantly influence the response to MASLD treatments.

FRI-368
Harnessing mouse genetic diversity to identify novel genetic determinants of MASLD to MASH transition
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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD), and its more severe form, metabolic dysfunction associated steatohepatitis (MASH), are a public health burden with high unmet therapeutic need. About one quarter of the general population has MASLD, but only about 20% of these patients will progress to develop MASH. The specific pathways involved in the MASLD-to-MASH transition are not fully elucidated. In a previous study we found large variability in MASLD/MASH susceptibility between genetically different mouse strains and identified highly sensitive and completely resistant strains. We used this information to design a 4-way F2 genetic cross to map novel quantitative trait loci (QTL) involved in disease susceptibility and find novel potential therapeutic targets.
Method: We performed a 4-way intercross of the strains with the highest (PWK/PhJ), intermediary (C57BL/6J and 129S1/SvlmJ) and lowest (CAST/EiJ) susceptibility to MASLD/MASH. 500 genetically unique F2 mice (250 males and 250 females) from this cross were fed a "western" style diet (WD) and were housed at thermoneutrality (30°C) for 17 weeks to induce metabolic dysfunction and MASLD/MASH. We measured activity, food intake, energy expenditure and respiratory exchange ratio (by the CLAMS system at week 0 and 13), body composition (by EchoMRI at week 0, 7 and 15) and body weight (bi-weekly). Plasma and urine were collected at week 0, 7 and 15. We quantified several disease biomarkers in the plasma (including ALT, AST, cholesterol and TIMP-1), performed histological analysis of the livers to quantify steatosis and fibrosis, as well as liver RNA-seq and proteomics.
Results: Analysis of the evolution of the body weight and body composition revealed a large variation in body weight and body fat gain in the F2 population, with a subset of mice being completely resistant to body fat gain. Unbiased hierarchical clustering of liver disease phenotypes identified 4 different clusters covering the whole spectrum of MASLD/MASH severity. Analysis of the transcriptomes allowed to identify distinct gene expression signatures that characterize different stages of MASLD and MASH severity. We found several genetic loci associated with obesity phenotypes and liver disease. By combining QTL analysis on clinical phenotypes (cQTL), transcriptome (eQTL) and proteome (pQTL), and validating the results in large human cohorts, we are now refining a list of novel candidate genes involved in MASLD and MASH susceptibility.
Conclusion: The F2 mouse population that we generated covers a very wide range of genetic susceptibility to resistance to MASH. In combination with human genetic data our data is an ideal tool to discover causative genes of both susceptibility to MASLD and the transition to MASH that are generalizable to humans.

FRI-369-YI

Lysine-specific demethylase 1 modulates hepatic lipid metabolism in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent condition affecting approximately 30% of adults worldwide. It is characterized by hepatic steatosis, obesity, type 2 diabetes, and hypertension. Emerging evidence suggests that epigenetic alterations play a pivotal role in the development of MASLD. Lysine-specific demethylase 1 (LSD1) stands out as a key player in regulating chromatin structure and transcriptional control through the demethylation of histone 3 lysine 4 or lysine 9. Transcriptomic and proteomic analyses have revealed alterations in lipid metabolism gene expression profiles, indicating the involvement of LSD1 in MAFLD pathogenesis.
Method: To investigate the role of LSD1 in MAFLD development, we employed a high-fat diet mouse model. Systemic and hepatocyte-specific LSD1 inhibition were achieved using a LSD1 inhibitor or liver-specific conditional transgenic LSD1 mutation, respectively, after administration of adeno-associated virus (AAV). RNA-seq from these livers and adipose tissue showed a dysregulation in the chemokine expression profile. Additionally, primary hepatocytes were isolated to further explore the functional significance of LSD1 in MAFLD.
Results: Liver histology demonstrated a significant reduction in steatosis, accompanied by notable weight loss and healthy liver enzyme values after systemic LSD1 inhibition. Notably, hepatocyte-specific LSD1 inactivation also resulted in diminished fat accumulation, although to a lesser extent compared to systemic pharmacological LSD1 inhibition. Transcriptomic analysis of liver tissue from systemic LSD1-inhibited mice revealed marked alterations in lipid metabolism, particularly in genes involved in lipid transportation. Furthermore, chemokine expression profiles were reduced after LSD1 inhibition that favors the decrease in steatosis. Moreover, single nuclei-RNA sequencing from liver-specific LSD1 inactivation revealed an imbalance in proteostasis and stress response.
Conclusion: This study underscores the crucial role of LSD1 in MAFLD development. By altering hepatic lipid metabolism, proteostasis and chemokine expression profile.

FRI-370

Hepatoprotective effects of efruxifermin treatment in GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background and aims: Efruxifermin (EFX, a long-acting FGF21 analogue) is currently in phase 3 clinical development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). This study aimed to investigate the therapeutic benefits of EFX on metabolic, biochemical, histopathological and transcriptomic profile in the Gubra Amylin NASH (GAN) diet-induced obese (DIO) and biopsy-confirmed mouse model of MASH with liver fibrosis.
Methods: Male C57BL/6 mice were fed GAN diet, high in fat, fructose and cholesterol for 36 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice with NAFLD Activity Score (NAS $\geq$ 5) and fibrosis stage F2–F3 were included and stratified into treatment groups. EFX (1 mg/kg) or vehicle was administered subcutaneously once weekly for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other endpoints included quantitative liver histomorphometry, blood and liver biochemistry and liver RNAsequencing.
Results: EFX promoted vehicle-corrected weight loss of approx. 14% and improved hepatomegaly as well as liver (triglycerides, total cholesterol) and plasma (transaminases, total cholesterol, LDL/HDL cholesterol) biomarkers. EFX promoted a $\geq$2-point statistically significant improvement in NAS, driven by reductions in steatosis and lobular inflammation scores. These findings were supported by quantitative liver histology of steatosis (lipid-laden hepatocytes, lipid droplet size) and inflammation (CD45, galectin-3). EFX did not improve fibrosis stage, albeit reduced histological markers of fibrosis (PSR, Collagen 1a1) in addition to hepatic stellate cell marker (α-SMA) for fibrogenesis. Finally, EFX induces transcriptomic regulation and reduced gene expression involved in inflammation and extracellular matrix production.
Conclusion: EFX treatment improved metabolic and biochemical parameters, as well as histological markers of steatosis, inflammation and fibrosis/fibrogenesis. In addition, EFX improved histopathological NAFLD Activity Score, with longer treatment intervention needed for observing fibrosis stage improvement. The therapeutic effects of EFX highlight the translatability and applicability of the GAN DIO-MASH mouse model in preclinical drug discovery.

FRI-371-YI

Serum lipidome heterogeneity in MASH patients identifies DNA damage as predominant hit in one subtype

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Background and aims: The heterogeneity of metabolic-associated steatotic liver disease (MASLD), linked to genetic and environmental factors and comorbidities difficulties finding effective treatments. Among the diversity of MASLD, dysregulation of pathways involved in lipid and lipoprotein metabolism play a prominent role. Thus the aims were: 1) to classify patients with MASH according to the serum lipidome of five models of diet-induced MASH, identifying the most prevalent profile; 2) to identify the involvement of the predominant hit in the metabolic dysregulation according to the classification of the serum lipidome, proposing targets for treatment.
Method: Serum lipidome analysis was performed on five diet-induced mouse models of MASH (52 weeks of Choline deficient high-fat diet (HFD); 52 weeks of HFD; 10 weeks of HF/H Sucrose; 17 weeks of HF H Cholesterol (1.5%) and diethylnitrosamine (DEN) followed by 26 weeks of HFD. Serum lipidome was also analyzed in a cohort of biopsy-proven MASH patients (n = 324) and metabolically healthy individuals (n = 302). The 25 most representative metabolites of each mouse model were used to classify MASH patients according to the altered mechanism dividing the patients into five categories. Hepatic lipidome, hepatic proteome analysis, mitochondrial complex activity and serum parameters were analyzed in the biopsy-proven Biobizkaia MASLD cohort (n = 103).
Results: Of the 324 patients, the greater number (n = 109) fell into the DEN-HFD category, the predominant hit being DNA damage (DD) and related DD response. The serum lipidomic signature of "DD-related MASH" was associated with changes in species of sphingolipids and phospholipids. To validate the role of DD in MASH, the Biobizkaia cohort was divided into MASH patients with levels of the DD marker pH2AX above the mean and below the mean. MASH patients with higher pH2AX levels had a worse metabolic status, increased hepatic triglyceride (TG) and dygliceride (DG) species and inefficient fatty acid oxidation despite increased mitochondrial complex IV activity. Accordingly, proteome analysis of patients with MASH and high DD showed remodelling of pathways involved in lipid and lipoprotein metabolism, as well as those involved in the cell cycle. The metabolic and cell cycle regulator E2F2, increased in MASLD, promoted DD and DDR in primary cultures of hepatocytes while its deficiency protected against DD. Upon DD the intracellular lipid deposition promoted by E2F2 overexpression was abolished when hepatocytes were treated with the DDR inhibitor ceralasertib by increasing FAO.
Conclusion: DD is a driving mechanism of MASH, causing metabolic changes that favour the progression of the pathology. MASH-related E2F2 overexpression exacerbates DD-associated progression and targeting DDR when E2F2 levels are high may be a valuable tool to prevent further metabolic dysregulation in this MASH subtype.

FRI-372
MASH-in-a-dish: a multicellular pre-clinical model to identify targetable metabolite crosstalk in MASH

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Background and aims: Affecting more than 25% of the world population, metabolic dysfunction-associated steatotic liver disease (MASLD) is becoming the leading cause of liver failure and liver cancers. Progression of MASLD from benign steatosis to metabolic dysfunction-associated steatohepatitis (MASH) is characterized by sterile inflammation and progressive fibrosis. Metabolites are now recognized as potential signaling molecules. For instance, itaconate, an immunometabolite, can signal via protein cysteine alkylation. Metabolite crosstalk amongst steatotic hepatocytes, Kupffer cells (KCs), and hepatic stellate cells (HSCs) underlies MASH pathogenesis but is challenging to study using *in vivo* models. The present study aims to establish a multicellular co-culture model that (1) mimics clinical MASH phenotypes and (2) allows identification of key metabolite crosstalk in MASH.
Method: We developed "MASH-in-a-dish," a Transwell™ co-culture system of primary mouse hepatocyte organoids (HepOrgs), primary mouse KCs, and primary mouse HSCs. MASH-in-a-dish enabled rapid cell type separation in 1 minute, effectively preserving the cell-type-specific metabolomes. MASH was induced by 4-day treatment with a MASH lipid mix, formulated based on lipidomes of human MASH livers and sera. Different cell type combinations were employed to identify crosstalk metabolites. Clinically relevant MASH readouts were used for validation, including steatosis and hepatocyte ballooning (histology), liver damage marker (aspartate transaminase), inflammation (IL-6, TNFα, C-reactive protein), and fibrosis (type I collagen). Liquid-chromatography-mass-spectrometry-based (LC-MS) metabolomics with $^{13}C_6$-glucose tracing was performed to identify crosstalk metabolites in the MASH condition.
Results: Treatment with MASH lipid mix caused steatosis and ballooning-like changes in 90% and 40% of the HepOrgs, respectively. The MASH lipid mix also significantly induced secretion of inflammatory cytokines by KCs and type I collagen by HSCs. Semi-targeted metabolomics showed that MASH lipids enhanced secretion of several Krebs cycle metabolites, urea cycle metabolites, acetyl-L-carnitine, and itaconate in a co-culture dependent manner. Analysis of intracellular metabolomes in MASH-in-a-dish confirmed KCs as the source of itaconate. $^{13}C_6$-Glucose tracing revealed that the MASH lipid mix decreased ^{13}C labelling in itaconate, suggesting that fatty acids replaced glucose as a carbon source for increased itaconate production in MASH. Crosstalk signaling via itaconate from KCs to HepOrgs was supported by increased levels of itaconate and itaconate-cysteine adduct in the HepOrgs.
Conclusion: MASH-in-a-dish models key clinical features of MASH and identifies itaconate as a lipid-driven crosstalk metabolite between Kupffer cells and hepatocytes. Our findings provide mechanistic insights into increased itaconate in livers of MASH patients.

FRI-373
Calciprotein crystallization assay as calcification biomarker in metabolic-dysfunction associated steatotic liver disease population

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Background and aims: Vascular calcification (VC) is commonly present in patients diagnosed with metabolic-dysfunction associated steatotic liver disease (MASLD). The pathogenesis of VC is multifactorial. One of the pathways is an abnormal metabolism of calciprotein particles (CPP) which is possibly involved in the development of VC in patients with MASLD. Physiological CPP scavenge calcium phosphate salts in the blood circulation. The primary form of CPP is formed around the glycoprotein fetuin A which is produced in the liver. Overload of phosphate/calcium or decrease of fetuin A induces the transition of primary CPP to its crystallized form which drives VC. The novel T50 test measures the transition time to crystalline CPP expressed in minutes. The reference range of T50 ranges from 270 to

470 min. Previous studies have shown that lower T50 values correlate with a greater risk of VC, and cardiovascular and all-cause mortality. In this study, we tested the hypothesis that patients with MASLD with severe liver stiffness suppresses the expression of fetuin A leading to a shorter transition time to crystalline CPP, thus a lower T50.
Method: A retrospective case-control study was conducted including 42 patients at cardiometabolic risk who had been screened for fibrotic MASLD. Two groups were formed based on the liver stiffness measurement (LSM): a group with fibrotic MASLD (high LSM of ≥10 kPa), and a control group without fibrotic MASLD (low LSM of ≤7 kPa). Groups were matched for age, sex, smoking and type 2 diabetes mellitus. The T50 values and fetuin A levels were measured in all patients and statistically analyzed with paired t-test.
Results: The mean LSM for the high and low LSM groups were 14.0 ± 5.3 and 4.9 ± 1.1 kPa, respectively. Additionally, the mean controlled attenuation parameter (CAP) score for the high LSM group was 328.1 ± 42.8 dB/m, and 286.9 ± 58.2 dB/m for the low group. Fetuin A levels were significantly lower in the patients with high LSM (mean = 0.28 ± 0.03 g/L) compared to low LSM (0.32 ± 0.06 g/L; p = 0.041). The mean T50 did not differ between the high (419 ± 67 min) and low LSM groups (376 ± 60 min; p = 0.054).
Conclusion: Fetuin A levels were lower in patients with fibrotic MASLD, but this did not translate into worsening T50 values. The T50 values in patients with MASLD were comparable to those found in the general population. Moreover, the absence of difference in T50 observed in patients with high liver stiffness compared to low liver stiffness argues against a role of abnormal CPP metabolism in the development of VC in patients with MASLD. Therefore, in patient with MASLD the measurement of the T50 does not appear to have added value in the stratification of patients at risk for VC.

FRI-374
Hepatic peroxisome proliferator-activated receptor gamma coactivator-1- alpha impacts the secretion of SerpinA3N in response to obesogenic diets in mice through induction of oxidative stress response in hepatocytes
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Background and aims: The liver has a critical role in metabolism by maintaining homeostatic levels of circulating macronutrients. For instance, when blood glucose is decreasing, the liver will increase glucose output, while excess blood glucose is absorbed and stored in the liver. Chronic excessive caloric intake will eventually overwhelm the ability of the liver to maintain energetic homeostasis leading to Metabolically Associated Steatotic Liver Disease (MASLD), characterized by lipid accumulation in the liver and progressive loss of hepatic function. It is well understood that regulation of metabolic homeostasis is a highly coordinated process involving many organs working together. This high level of coordination is achieved through organ crosstalk via secreted signaling molecules and proteins. What remains poorly understood is how the signals being sent by the liver change in the development of MASLD, and how this change influences the metabolism and health of other organs. We aim to investigate how the secretome of hepatocytes responds to metabolic challenges to better understand the progression of MASLD and the influence of the liver on extrahepatic organs.
Method: Hepatocytes from mice with a 50% reduction of peroxisome proliferator activated-receptor gamma coactivator 1 - alpha (PGC-1alpha), complete loss of PGC-1alpha, fed chow or high fat, high fructose diet for 6 weeks were isolated and the hepatocyte secretome compared between diets and genotypes. Top candidates were explored at the gene and protein level in primary mouse hepatocytes, liver, and plasma. Western blot and ELISA analysis determined hepatic and circulating hepatokine levels. Primary hepatocytes were treated with various chemical and biological inducers of inflammation and oxidative stress and secreted SERPINA3N was measured by western blot.
Results: SERPINA3N, CCL2, antileukoproteinase, and clusterin were identified as strongly influenced by diet and/or PGC-1alpha *in vitro*. Further analysis showed that circulating SERPINA3N was strongly influenced by diet and genotype in a similar manner *in vivo*, while plasma CCL2, antileukoproteinase, and clusterin were not significantly altered. Liver of PGC-1alpha knockout and high fat, high fructose fed mice demonstrate increased oxidative stress markers. Inducing oxidative stress in primary hepatocytes was sufficient to stimulate SERPINA3N expression and secretion.
Conclusion: Our data identified SERPINA3N as a hepatokine that increases in response to an obesogenic diet, an induction impaired by loss of PGC-1a. These data indicate that changes in hepatic SERPINA3N secretion could be an adaptive response to metabolic oxidative stress.

FRI-375
Preclinical characterization of BJT-188, a liver-targeted fatty acid synthase inhibitor for the treatment of MASH
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Background and aims: Fatty acid synthase (FASN) is an enzyme in the de novo lipogenesis (DNL) pathway that converts the metabolites of dietary sugars into the saturated fatty acid palmitate, a precursor of triglycerides and other lipotoxic lipids. The first-generation FASN inhibitor Denifanstat reduces liver steatosis, inflammation, and fibrosis in MASH patients. It is also associated with adverse events, including alopecia, that may limit its clinical utility. Here, we aimed to develop novel targeted FASN inhibitors that retain liver-specific benefits while minimizing exposure to other tissues.
Method: Intrinsic potency was measured using recombinant rat FASN in a fluorescent-based biochemical assay. In vitro DNL inhibition was conducted in primary hepatocytes and other cell types. Initial in vitro safety screen consisted of CYP inhibition and CEREP safety panel of 44 receptors. Predicted clearance was estimated based on metabolic stability in primary hepatocytes. Pharmacokinetic profiling in rats and dogs was used to determine liver exposures, tissue partitioning, and oral bioavailability. Single dose in vivo studies of liver DNL inhibition were conducted in rats.
Results: Lead molecule optimization focused on improving liver-to-plasma partitioning in rodents and enhancing in vitro metabolic stability in multiple species. The resulting candidate, BJT-188, is a potent inhibitor of FASN with an EC_{50} value <100 nM in primary human hepatocytes. Additionally, BJT-188 demonstrated high specificity, showing no inhibition of major CYPs or the 44 human receptors tested, including hERG. In rats, a single oral dose of BJT-188 at 20 mpk resulted in rapid and high exposure to the liver, with minimal levels detected in plasma and other tissues. In a rat PK/PD model, BJT-188 achieved rapid and complete inhibition of hepatic DNL while maintaining low systemic exposures. Lastly, the PK profile of BJT-188 in non-rodent species supports the potential for once-daily dosing in humans.
Conclusion: BJT-188 is a potent and selective FASN inhibitor with high liver-to-plasma partitioning and low potential for alopecia. BJT-188 is currently progressing towards IND enabling studies.

FRI-376
Training non-experts to diagnose steatohepatitis on biopsy slides
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Background and aims: The non-alcoholic fatty liver disease activity score (NAS) is applied to liver biopsies to adequately diagnosis metabolic dysfunction-associated steatohepatitis (MASH). Whilst NAS scores are not routinely reported, they are often required for research purposes and retrospectively applying scores can be costly and time-consuming. We investigated whether a team of trained non-experts, using dedicated computer software, could score biopsy images with a quality comparable to that of an expert pathologist.
Method: Liver biopsy slides were scanned to a digital image viewing software. A national health service (NHS) Consultant Pathologist, with subspecialty interest in liver pathology, trained a group of non-clinical medical annotators to grade slides using the NAS criteria. The medical annotators used a partially adjusted grading system. Slides were viewed using Zeiss Zen 3.10 software on 24 inch monitors at a resolution of 1920 × 1200 and 5x zoom. Hepatocyte ballooning and inflammation were assessed by randomly selecting three sample regions across the biopsy slide and counting the number of ballooned hepatocytes and lobular inflammation nodes within each sample. Medical annotators also had access to a NAS scoring guide prepared specifically for this project. The pathologist sampled 20% of the images and graded them, to assess inter- and intra-observer (medical image annotator) agreement. A linearly weighted Cohen's kappa was applied for agreement calculations.
Results: Ninety-one liver biopsies were obtained from 85 distinct patients. Agreement was best for steatosis percentage, with 0.78 kappa between the team median and the pathologist, and 0.62–0.83 within the team itself. The number of portal tracts scored 0.55 agreement and 0.45 for fibrosis. Inflammation scored the lowest at 0.41 kappa between the team median and pathologist. Consistency of ballooning score was the lowest within the medical annotator team, 0.07–0.26 kappa, but 0.48 between the team median and pathologist. Overall NAS score agreement was 0.42 (0.19–0.51).
Conclusion: Medical annotators were able to apply NAS scores. Agreements scores were moderate to substantial according to kappa scoring for each component and in some cases similar to previous published intra-observer variability scores between pathologists. This method is effective to off-set time and cost for a training dataset.

FRI-381-YI
Oncostatin M contributes to liver steatosis in experimental metabolic dysfunction - associated steatotic liver disease

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Background and aims: Oncostatin M (OSM), a cytokine belonging to the IL-6 family, has been recently proposed as a pro-inflammatory and profibrogenic mediator involved in the progression of experimental and clinical conditions of Metabolic dysfunction – Associated Steatotic Liver Disease (MASLD). The aim of this study is to evaluate whether OSM can contribute to hepatocyte accumulation of triglycerides in MASLD progression.
Method: Morphological, biochemical and molecular biology approaches were used to investigate the role of OSM in: i) mice genetically manipulated to delete the OSM β receptor (OSMβR$^{-/-}$ mice) in hepatocyte and related wild type (WT) control littermates fed for 24 weeks on a Choline-Deficient, AminoAcid-refined (CDAA) lipogenic diet (i.e., to develop a murine model of progressive MASLD); ii) the murine AML12 hepatocyte cell line.
Results: Hepatocyte conditional deletion of OSMβR abrogated OSM/STAT3-related signaling in murine hepatocytes and resulted in a significant reduction of liver steatosis in OSMβR$^{-/-}$ mice vs related WT mice fed on CDAA diet, as for morphological analysis and evaluation of liver triglycerides content. This was accompanied by a number of observations suggesting a correlation of OSM/OSMβR axis and lipid metabolism in hepatocytes, including: i) a reduction of total macrophage infiltration paralleled by a significant increase in TREM2 + macrophages as well as in Osteopontin (OPN) expression observed in OSMβR$^{-/-}$ mice vs WT mice; ii) OSMβR$^{-/-}$ mice, as compared to WT mice, were also characterized by a significantly reduced expression of genes involved in the regulation of lipid metabolism, including CD36, carnitine-palmitoyl transferase 1 (Cpt1) and medium-chain acyl-CoA dehydrogenase (MCAD); iii) recombinant OSM was able to up-regulate the expression of CD36, Cpt1 and MCAD in the AML12 murine hepatocyte cell line.
Conclusion: Results of the present study indicate that the pro-inflammatory and pro-fibrogenic cytokine OSM, by acting on OSMβR expressed by hepatocytes, can also contribute to perpetuate liver steatosis in a murine model of progressive dietary induced MASLD.

FRI-382
The protective effect of dapagliflozin against kidney injuries by tubular mitochondrial preservation in metabolic dysfunction-associated steatohepatitis

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) contributes to kidney injuries. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) provide renal and cardiac protective effects. This study aimed to explore the renal protective effect by dapagliflozin in MASLD-related kidney injuries.
Method: In a controlled study, MASLD and metabolic dysfunction-associated steatohepatitis (MASH) were induced in 8-week-old C57BL/6 male mice using a high-fat diet (HFD) with 5% fructose for six months. Mice were divided into two groups: one receiving dapagliflozin (1 mg/kg/day) and the other a vehicle. Metabolic parameters and renal function were assessed through biochemical assays and transmission electron microscopy for mitochondrial ultrastructure analysis.
Results: There's no significant weight loss between dapagliflozin group and vehicle group. Dapagliflozin-treated MASH mice had improved glucose handling ($p = 0.03$ for fasting glucose; $p = 0.02$ for glucose tolerance) and alleviated insulin resistance ($p < 0.0001$ for HOMA-IR) compared to vehicle group. Dapagliflozin also mitigated renal function deterioration, evidenced by lower serum creatinine ($p = 0.01$) and proteinuria ($p = 0.01$). Renal histological features demonstrated reduced tubular injury scores ($p = 0.01$), glomerulosclerosis ($p = 0.04$), and tubulointerstitial fibrosis ($p < 0.0001$). Transmission electron microscopy showed decreased aberrant tubular mitochondria, and increased cristae length and numbers. Dapagliflozin

reduced reactive oxygen species production ($p = 0.03$) and renal adiponectin levels ($p = 0.04$).
Conclusion: These findings underscore the mechanistic link between the protective effects of dapagliflozin and renal tubular injury in MASH mice.

FRI-383
Comparative anti-fibrotic action of resmetirom, semaglutide, tirzepatide and efruxifermin in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH
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Background and aims: Resmetirom (RES, THR-βR agonist) has recently been FDA-approved for metabolic dysfunction-associated steatohepatitis (MASH). Other drug concepts are in late-stage clinical development for MASH, including semaglutide (SEMA, GLP1R agonist), tirzepatide (TZP, GLP1R-GIPR co-agonist) and efruxifermin (EFX, FGF21 analogue). The present study aimed to compare efficacy of RES, SEMA, TZP and EFX monotherapy on metabolic, biochemically and histopathological outcomes in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis.
Method: Male C57BL/6 mice were fed the GAN diet for 31–34 weeks prior to study start. Only GAN DIO-MASH mice with biopsy-confirmed NAFLD Activity Score (NAS≥5) and fibrosis (stage = F2–3) were included and stratified into treatment groups (n = 18 per group). Mice were administered vehicle (SC/PO, QD), RES (3 mg/kg, PO, QD), SEMA (10/30 nmol/kg, SC, QD), TZP (10 nmol/kg, SC, QD) or EFX (1 mg/kg, SC, QW), for 12 and 16 weeks. Pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included plasma biochemistry and liver histomorphometry expressed as parenchymal (steatosis-adjusted) proportionate area for inflammation (Gal-3) and collagen (PSR, Col1a1).
Results: GAN DIO-MASH mice demonstrated vehicle-corrected weight loss of 15% (EFX), 20% (SEMA) and 25% (TZP), while RES was weight-neutral, after 16 weeks of treatment. All treatment interventions improved hepatomegaly and reduced plasma liver enzymes. Independent of treatment duration, a significant improvement in NAS was achieved with EFX, SEMA and TZP (≥2-point) and RES (≥1-point). Benefits on NAS were supported by quantitative liver histology for steatosis and inflammation. Neither EFX, SEMA, TZP nor RES improved fibrosis stage, albeit all compounds consistently reduced parenchymal collagen proportionate area after 16 weeks of treatment. Notably, EFX, SEMA, TZP and RES effectively reduced fibrogenesis biomarkers (plasma TIMP-1, PIIINP, liver α-SMA) after 12-weeks of treatment.
Conclusion: RES, SEMA, TZP and EFX improved metabolic, biochemical and histopathological endpoints in GAN DIO-MASH mice, highlighting the model clinical translatability. Longer treatment intervention demonstrated histological improvement in fibrosis, highlighting the importance of treatment duration to alleviate fibrosis burden in the GAN DIO-MASH model.

FRI-384
Disease-associated transcriptomic profiles of liver sinusoidal endothelial cells at single nucleus resolution in a non-human primate model of metabolic dysfunction-associated steatohepatitis
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Background and aims: Hepatic endothelial cells (ECs) play an important role in fibrogenesis and EC dysfunction is also critical to the development of portal hypertension, which is an important complication of cirrhosis. Single cell-level characterization of ECs in human livers has been reported for the healthy and cirrhotic states, with a paucity of information on the intervening disease stages. Our long-term diet-fed non-human primate (NHP) model of MASH therefore offers a unique opportunity to examine the EC transcriptome as the disease progresses from steatosis to advanced fibrosis.
Method: Male, middle-aged African Green Monkeys (*Chlorocebus aethiops sabaeus*) were given a high fat, cholesterol and fructose diet for over 90 weeks, with additional fructose enrichment starting at week 36. After 20 and 54 weeks on diet, liver biopsies were collected and single nucleus RNA-sequencing (snRNA-Seq) was performed, yielding 173,669 analyzable nuclei spanning 11 NHPs over 2 time points. Comprehensive blood work performed at more frequent intervals revealed high heterogeneity in this group of animals. We harnessed this heterogeneity to interrogate how specific metabolic co-morbidities affect the EC transcriptome.
Results: 54 weeks of diet-feeding resulted in an average liver picrosirius red staining area of 9.9% in the NHPs, with the staining concentrated in the periportal region. Between 20 weeks and 54 weeks of diet feeding, hepatic ECs showed an upregulation of endocytic vesicle, collagen-containing extracellular matrix, and lipoprotein particle binding genes. The most fibrotic tertile of livers had ECs that showed increased NRF2 transcriptional activity and cytokine-mediated signaling pathway. The NHPs with the highest low density lipoprotein cholesterol levels had ECs with increased expression of basement membrane genes, consistent with sinusoidal capillarization. This result is in agreement with the beneficial effects observed for statins in portal hypertension. To understand why diabetic patients have a blunted hepatic venous pressure gradient response to non-selective beta blockers, we compared the NHP with elevated HbA1c to the rest and found this animal had hepatic ECs with increased SMAD4 transcriptional activity. Notably, a gene that was commonly upregulated in the hyperlipidemic and diabetic animals' hepatic ECs was *CETP*, which is not expressed by mice and rats.
Conclusion: The diet-fed NHP is a MASH model with high translational relevance. A high-throughput drug discovery screen in such a model could elucidate novel therapies to address unmet needs.

FRI-385
High-throughput in vivo pooled screening can identify therapies applicable across the spectrum of metabolic dysfunction-associated steatohepatitis disease severity
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Background and aims: Despite the continuing evolution of complex *in vitro* liver models, many features of liver biology remain difficult to faithfully recapitulate outside of the living mammal, especially in the diseased state. Such features include the intricate canalicular architecture arising from the hepatocytes' unique multiaxial polarization, hepatocyte zonation due to the concentration gradient of oxygen and nutrients, and the infiltration of diverse bone marrow-derived immune cells. To overcome these shortcomings of culture-based screening, we developed a pooled screening platform that enables us to query hundreds of unique interventions in a single live animal.
Method: We delivered a cocktail of hundreds of uniquely barcoded adeno-associated virus (AAV)-based gene therapies to mice fed the Gubra-Amylin (GAN) diet for an average of 60 weeks. The AAV cocktail

dose was titrated to ensure only about 7% of hepatocytes were transduced, thereby avoiding cross-interaction between different interventions. We examined the hepatocyte response to each intervention at the single nucleus level according to mRNA expression of curated gene sets designed to capture multiple aspects of MASH pathogenesis and resolution. Novel interventions with a transcriptomic response that suggested a therapeutic effect were then administered to mice fed the GAN diet for 44–48 weeks at a saturating dose.

Results: After 60 weeks on diet, the livers of the mice showed F2 fibrosis. Overexpression of *Il6* and the dominant-negative mutant of the IL-6 receptor subunit beta both strongly affected the lipid droplet pathway feature, indicating an important role for this cytokine in modulating steatosis. The *Alb* overexpression intervention showed beneficial transcriptomic shifts despite the very high baseline expression levels of the gene and the low multiplicity of infection of the AAV cocktail. Overexpressing *Alb* reduced expression of protumorigenic features while increasing expression of anti-tumorigenic features. This agrees with observations that long term albumin administration improves outcomes in decompensated cirrhosis. Interestingly, *Alb* overexpression resulted in upregulated expression of farsenoid X receptor signaling and *de novo* lipogenesis. Of the candidate AAV therapies tested at the saturating dose in GAN diet-fed mice, 50% showed a reduction from baseline ALT levels within 8 weeks. One intervention showed a reduction in steatosis along with decreased expression of genes indicative of inflammatory cell infiltration and extracellular matrix gene deposition.

Conclusion: The ability to interrogate the expression of diverse disease features means that *in vivo* pooled screening in an animal model of moderate fibrosis could reveal insights into interventions that have implications for simply steatotic liver disease to decompensated cirrhosis.

FRI-386

HK3, a novel oral anti-obesity MASH drug with direct reduction of liver fibrosis

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Background and aims: MASLD has emerged as a global health concern, recognized as the hepatic manifestation of the metabolic syndrome with obesity as the major risk factor. Due to its complexity, a multitarget approach of combined pharmaceuticals may be required. Resmetirom is the only drug that has recently been approved for the treatment of MASH, ehibiting only modest weight reduction. This study aimed to investigate if our allosteric modulator of the GABA-A receptor, HK3, could directly ameliorate fibrosis in different MASH models as well as obesity.

Method: 3D Spheroids of primary human hepatocytes and non-parenchymal cells from MASH patients were treated with insulin and fatty acids, in the presence or absence of HK3 (1, 3, 10 µM) for 1 week. Lipid content, inflammatory cytokines, and fibrosis markers were quantified using specialized assays (AdipoRed, (multiplex) ELISA). Human hepatic stellate cells (LX2) were treated with TGF-β1 (5 ng/ml, 24 h) with HK3 or competitor drugs (semaglutide, lanifibranor and resmetirom, all 10 µM) to assess pro-fibrotic protein levels. Finally, diet-induced obese mice (12 weeks) received HK3 (25 mg/kg, 4 weeks) in addition to high fat diet. Food intake, body weight, body composition and oral glucose tolerance test were measured and serum biomarkers were analyzed.

Results: In the 3D spheroid model, HK3 reduced lipid content, inflammatory cytokine secretion, and pro-collagen level ($p < 0.0001$, $p < 0.05$, $p < 0.05$). HK3 outperformed other MASH drug candidates in reducing fibrotic markers in LX2 cells. In CCl_4-treated mice, HK3 mitigated liver fibrosis progression and reduced inflammatory markers ($p < 0.05$). In addition, HK3 improved liver function markers (ALT, $p < 0.001$; AST $p < 0.0001$), triglyceride ($p < 0.001$) and cholerstol levels ($p < 0.0001$) in the DIO mice, without affecting food intake. HK3 treatment resulted in a significant reduction in body weight (>10%) compared to vehicle-treated animals ($p < 0.0001$), with a marked decrease in fat mass (21%) ($p = 0.001$). Notably, lean mass remained unaffected by HK3 administration. A 28-days GLP-tox study in rats demonstrated the safety of the compound.

Conclusion: This comprehensive study reveals HK3 as a promising candidate for MASH treatment, demonstrating both potent direct anti-fibrotic and anti-obesity effects. Its unique mechanism of action and multi-faceted benefits position HK3 as a potential first-in-class therapy for the concurrent management of MASH and obesity, addressing two critical aspects of metabolic liver disease.

FRI-387

35 kilodalton specific-sized hyaluronan ameliorates high fat diet-induced liver injury in a murine model of moderate

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Background and aims: Obesity is a growing concern in the US and world-wide, associated with an increased risk for several cardiometabolic diseases, including metabolic associated steatotic liver disease (MASLD). Currently, therapeutic interventions to prevent and/or treat MASLD are limited, and research is needed to identify new therapeutic targets. The specific-sized 35 kDa fragment of hyaluronan (HA35), has gut protective and anti-inflammatory properties and a previous pilot clinical study reported it is well tolerated in healthy individuals. Here we tested the hypothesis that HA35 treatment ameliorates high fat diet-induced liver injury.

Method: Five-week-old male C57BL/6J mice were allowed *ad lib* access to control chow or high fat fructose and cholesterol (FFC) diet over a period of 12 weeks. HA35 was administered at 15 mg/kg via oral gavage on the last 6 days of the study as a therapeutic intervention.

Results: Mice on FFC diet-gained more body weight compared to those on chow diet, with final body weights ranging from 30.8–45.6 g. FFC diet caused hepatocyte injury, increased expression of inflammatory cytokine/chemokine mRNA, as well as indicators of liver fibrosis. When mice were stratified based on their final body weight, only mice <40 g were protected by treatment with HA35. In this group, treatment with HA35 also restored tight junction integrity in the colon and increased expression of α -defensins in the small intestine.

Conclusion: Taken together the data suggests that HA35 is an effective therapeutic in ameliorating high fat diet-induced liver inflammation and fibrosis in moderately obese, but not severe, conditions.

FRI-388

Quantitative digital pathology and AI to characterize histological phenotypes of regression in a robust mouse model of human MASH

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Background and aims: Metabolic Dysfunction-Associated Steatohepatitis (MASH) is a liver disease marked by inflammation and damage resulting from excessive fat accumulation, often associated with metabolic co-morbidities including obesity, diabetes, and hypercholesterolemia. If the disease persists, it can progress to cirrhosis. In this study, we focused on investigating the spontaneous regression of fibrosis after the cessation of a MASH-inducing model ("FAT-MASH"; doi:10.1016/j.jhep.2018.03.011) at an early stage of liver fibrosis. We utilized the FibroNest™ Digital Pathology platform

to quantify the phenotypic features of fibrosis and establish its value in quantifying features of disease regression.
Method: In the FAT-MASH mouse model of MASH, animals (n ≥ 6) were fed a Western diet for 6 wks, with sugar water and low-dose weekly CCl4. Mice were euthanized either at peak fibrosis (6 wks) or 2 and 6 wks following cessation of the MASH model to assess spontaneous fibrosis regression and other histologic features. Liver sections were stained with Sirius red and imaged at 40×. The images were analyzed using a single-fiber, high-content image analysis platform to assess collagen deposition (quantity), fiber morphometry (shape and size), and fibrosis architecture (fiber organization and complexity), generating a Phenotypic Fibrosis Score (Ph-FCS), a continuous, quantitative measure of fibrosis severity.
Results: FAT-MASH mice at 6 wks exhibited a significantly higher Ph-FCS compared to the normal diet control group (mean 5.58 vs. 0.91, p = 0.0026). Similar trends were observed in the three sub-phenotypic analysis layers, including collagen quantity, fiber morphometry, and fibrosis architecture. Liver histology revealed predominantly complete, thin bridging septa, along with hepatic fat accumulation. However, a time-dependent reduction in Ph-FCS was observed at 2 and 6 weeks following the discontinuation of disease model (mean 2.74, p = 0.024 and 2.04, p = 0.01, respectively). This reduction was consistent across the 3 sub-phenotypic quantifications, indicating that the fibrosis phenotypic traits, including collagen fiber quantity, shape, and organization were impacted. Histological examination of the liver revealed reduced and thinning of the bridging fibrosis, with nearly complete resolution of hepatic steatosis. These results suggest that spontaneous regression of liver fibrosis and steatosis occurs following the cessation of MASH (at 6 wks).
Conclusion: Fibrosis phenotypic quantification is valuable to assess the features of spontaneous fibrosis regression. The FibroNest™ digital pathology image analysis tool is highly effective in assessing the histological phenotypes of steatosis as well as fibrosis severity and regression in a robust MASH model. These findings may help clarify the mechanisms underlying fibrosis regression in human disease.

FRI-389

Histological phenotypes of regression in advanced liver fibrosis using quantitative digital pathology in a rodent model of cirrhotic human NASH with HCC

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Background and aims: Metabolic Dysfunction-Associated Steatohepatitis (MASH) is characterized by hepatic inflammation and injury associated with accumulation of fat. MASH can progress to cirrhosis and substantially elevate the risk of liver cancer. In this study, we assessed the spontaneous regression of advanced fibrosis following the cessation of a MASH-inducing model ("FAT-MASH"; doi:10.1016/j.jhep.2018.03.011) at a cirrhotic stage of liver fibrosis associated with hepatocellular carcinoma (HCC). The FibroNest™ Digital Pathology platform was utilized to quantify the phenotypic features of fibrosis and determine its effectiveness in measuring disease regression.
Method: In the FAT-MASH mouse model of MASH, mice (n ≥ 5) were fed a Western diet for 40 wks, supplemented with sugar water and low-dose weekly CCl4. The mice were euthanized either at peak fibrosis (40 wks) or at 2, 8, 16, and 24 wks following the cessation of the MASH model to evaluate spontaneous fibrosis regression and other histological features including steatosis. Liver sections were stained with Sirius red and imaged at 40X. The images were analyzed for both non-tumoral and tumoral areas using a single-fiber, high-content image analysis platform to assess collagen deposition (quantity), fiber morphometry (shape and size), and fibrosis architecture (fiber organization and complexity), generating a Phenotypic Fibrosis Score (Ph-FCS), a continuous, quantitative measure of fibrosis severity.
Results: In FAT-MASH mice at peak fibrosis (40 wks), both Ph-FCS and steatosis were significantly increased compared to the normal diet control group (mean 6.21 vs. 2.69, p = 0.0001 and mean 8.68 vs. 0.69, p = 0.00001, respectively). Similar trends were observed across the 3 sub-phenotypic layers, including collagen quantity, fiber morphometry, and fibrosis architecture. Liver histology revealed mostly branching bridging septa, perisinusoidal fibrosis, and hepatic fat accumulation. No time-dependent reduction in Ph-FCS or the 3 sub-phenotypic layers was observed after discontinuing the disease model, although steatosis exhibited a significant decrease over time (mean values at 2, 8, 16, and 24 wks: 3.51, p = 0.012; 1.87, p = 0.034; 1.7, p = 0.001; 2.09, p = 0.006). Concurrently, FAT-MASH mice developed large liver tumors comprising ~45% of overall tissue area in all disease groups. The fibrosis and steatosis patterns in the tumors were similar to those observed in the non-tumoral liver tissues.
Conclusion: These findings indicate that while spontaneous regression of steatosis is achievable, reversing fibrosis in advanced, cirrhotic MASH associated with HCC is more challenging. This degree of fibrosis may represent a "point of no return" where regression is no longer feasible. The FibroNest™ digital pathology image analysis can significantly aid in understanding the mechanisms underlying the irreversibility of fibrosis.

FRI-390

Transcriptomic analysis reveals alterations in mitochondrial energy metabolism and lipogenesis in GIPR/GLP-1R agonists treated metabolic dysfunction-associated steatohepatitis rodents

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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MAFLD) and its progressive form, Metabolic Dysfunction-Associated Steatohepatitis (MASH), present a considerable global health challenge. The lack of regulatory-approved MASH medications emphasizes the critical need for innovative treatments. Various gastric inhibitory polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are undergoing clinical investigations at different stages for MASH, potentially offering new prospects for MASH therapy. Despite prior research reporting reduced liver enzymes and improved MASH histopathology in response to GLP-1RAs, the fundamental molecular mechanism remains unclear.
Method: In this study, RNA profiling was employed to examine the transcriptome profiles of two distinct MASH rodent models: HFD +CCl4 and CDHFD treated with Semaglutide and Tirzepatide.
Results: Semaglutide notably decreased the liver fibrosis score in the CDHFD model and the NAS score in the HFD+CCl4 model. Nevertheless, the histopathological improvement observed with Tirzepatide treatment was not as pronounced. Comparative analysis revealed more than 3000 differentially expressed genes for both peptides. Gene Set Enrichment Analysis (GSEA) identified common lipogenic, fibrotic, and inflammatory pathways consistent with the unique disease characteristics. In addition, mitochondrial energy metabolism and lipogenesis were the most significantly altered signaling pathways, yet with distinctive patterns in the CDHFD mice between two peptides.
Conclusion: The findings suggest the apparent beneficial effect of Semaglutide, primarily through modulations in mitochondrial function and de novo lipogenesis. Although they share a similar mechanism of action, different GIPR/GLP-1RAs may alter energy metabolism via distinctive effector genes, leading to divergence in their therapeutic efficacy against different pathological features.

FRI-391

NEDD4 regulates TGF-beta/SMAD signaling pathway through ubiquinated decorin to ameliorate metabolic dysfunction-associated steatohepatitis

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) poses a significant global public health challenge, with its underlying mechanisms yet to be comprehensively elucidated. NEDD4, as an E3 ubiquitin ligase, is implicated in the regulation of multiple metabolism-associated signaling pathways. However, its role in MASH remains inadequately clarified.
Method: Hepatocellular NEDD4 were knocked down or overexpressed in mice via the AAV8 system respectively, and male C57BL/6J mice (six weeks old) were fed either a western diet (WD), or a methionine-choline deficient (MCD) diet for 10 weeks to induce MASH. 293T and AML12 cells were utilized for in vitro studies.
Results: An integrated analysis of human and murine MASH datasets was conduced and NEDD4 was identified as the differentially expressed E3 ubiquitin ligase in hepatocytes. Notably, NEDD4 protein levels were significantly elevated in both in vivo and in vitro MASH models, with this upregulation predominantly observed in hepatocytes. Lipid accumulation was markedly exacerbated in MASH mice fed an MCD or WD diet for 10 weeks in NEDD4-KD mouse. Conversely, overexpression of NEDD4 in hepatocytes significantly ameliorated hepatic lipid accumulation. RNA-seq analysis revealed an upregulation of the TGF-β pathway in NEDD4 knockdown AML12 cells, with decorin (DCN) exhibiting pronounced transcriptional changes. Additionally, predictions from the Ubibrowser website suggested that DCN is a potential substrate of NEDD4.
Conclusion: Collectively, our findings demonstrate that NEDD4 ameliorates MASH by modulating the TGF-β/SMAD signaling pathway through the ubiquitination of decorin.

FRI-392

Myostatin regulates the muscle-liver axis by inducing hepatocyte senescence via SLC7A11 ubiquitination in metabolic dysfunction-associated steatohepatitis

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Background and aims: Recent studies suggest that skeletal muscle alterations may contribute to the pathogenesis of Metabolic Dysfunction-Associated Steatohepatitis (MASH). Myokines, bioactive peptides released by skeletal muscle, play a pivotal role in regulating peripheral tissues, including the liver. Among them, myostatin (MSTN) has emerged as a critical regulator of muscle mass and metabolism. However, its specific role and underlying mechanisms in MASH development remain unclear.
Method: MASH was induced in mice using high-fat, high-fructose diet (HFHFD) and choline-deficient, amino acid-restricted, high-fat diet (CDA-HFD). Muscle-specific MSTN knockdown was achieved using an adeno-associated virus 8 (AAV8) system. MSTN expression in the serum of MASH patients was assessed via Elisa. The role of MSTN in MASH progression was investigated using recombinant MSTN protein and co-cultures of C2C12 muscle cells and primary mouse hepatocytes. Additionally, RNA sequencing was employed to analyze the impact of MSTN on the hepatocyte transcriptome.
Results: MSTN was found to be overexpressed at both the transcriptional and protein levels in the skeletal muscle tissues of MASH mice. Muscle-specific MSTN suppression significantly inhibited the progression of HFHFD- and CDAHFD-induced MASH. Recombinant MSTN protein exacerbated hepatocyte steatosis, inflammation, and senescence. Transcriptomic analysis identified the cystine transporter SLC7A11 as a key target of MSTN-induced hepatocyte changes. Furthermore, MSTN promoted the degradation of SLC7A11 via the ubiquitination pathway during MASH progression.
Conclusion: Reducing muscular myostatin expression may represent a promising therapeutic strategy for treating MASH.

FRI-397-YI

NMR-based metabolic signature reveals the vicious circle between fasting and feeding in homozygous carriers of the PNPLA3 I148M variant in MASLD

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Background and aims: The *PNPLA3* rs738409 (p.I148M) polymorphism is the most important genetic risk factor for the progression of metabolic steatotic liver disease (MASLD) to steatohepatitis (MASH) and fibrosis. Its expression is regulated by fasting and feeding cycles, which are likely to influence disease outcome. However, the underlying mechanisms remain poorly understood.
Method: We analyzed 353 serum samples from patients with MASLD from two German medical centres using NMR metabolomics. Patients were stratified by *PNPLA3* rs738409 C > G genotype into three subgroups: PNPLA3 CC, PNPLA3 CG and PNPLA3 GG. Metabolites, lipoproteins and glycosylation patterns were assessed based on fasting status.
Results: Homozygous PNPLA3 GG carriers displayed a distinct metabolic profile compared to CG or CC carriers, with notable alterations between fasting and non-fasting states. In the latter case, PNPLA3 148M inhibits adipose triglyceride lipase (ATGL), resulting in impaired triglyceride (TG) export from hepatocytes, as evidenced by reduced VLDL-1 lipoproteins. Following an overnight fast, GG carriers exhibited elevated tricarboxylic acid (TCA) cycle metabolites and ketone bodies, reflecting increased beta-oxidation, likely driven by reduced PNPLA3 expression and unrestricted ATGL activity. Additionally, the ketogenic amino acid lysine, which is critical for mitochondrial carnitine transport, was reduced. TG were enriched in LDL and large HDL particles, and an increased number of intermediate density lipoprotein (IDL) particles emerged as a distinct marker in fasted GG carriers. These metabolic changes were enhanced in individuals with T2DM and/or obesity. Finally, glycan structural variations were found in GG carriers, but were not associated with acute-phase inflammation.
Conclusion: Fasting and feeding cycles significantly exacerbate pathophysiological changes in PNPLA3 GG carriers, with implications for biomarker identification and tailored therapeutic interventions to counteract MASLD progression.

FRI-398

SETDB2 promotes the progression of metabolic dysfunction-associated steatohepatitis by regulating liver macrophages polarization via MAPK signaling pathway

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is an inflammatory stage of metabolic dysfunction-associated steatotic liver disease (MASLD), which is often accompanied by metabolic disorders, such as obesity, type II diabetes, insulin resistance and dyslipidemia. The histone methyltransferase SETDB2 protein is a member of the KMT1 family of lysine methyltransferases, associated with the regulation of chromosome segregation. SETDB2 was reported involving in innate and adaptive immunity, the proinflammatory response, and hepatic lipid metabolism. Our previous study found that SETDB2 was significantly upregulated in liver macrophages of MASH mice models, indicating it might promote the progression of MASH. However, the potential molecular mechanism of SETDB2 regulating the progression of MASH is unclear.
Method: The expression of SETDB2 was detected in liver tissues from MASH and control patients cohorts, respectively. In vivo, myeloid specific Setdb2 knockout mice($Setdb2^{fl/fl}Lyz2^{cre+}$) and control mice ($Setdb2^{fl/fl}$) were feed with WD(Western diet) and MCD(Methionine-choline deficient) diet to construct MASH mice model. H&E and Sirius Red were performed to detect the hepatic steatosis and inflammation. Liver macrophages were isolated, and the proportion of M1 and M2 macrophages was determined by flow cytometry. In addition, to investigate the direct effects of SETDB2 on the polarization of macrophages, mouse bone marrow-derived macrophages (BMDMs) and Raw264.7 cell line were studied in vitro.
Results: Through the detection of liver tissues from clinical MASH and control patients, we found that SETDB2 was upregulated in macropahges of MASH liver. In vivo, myeloid specific Setdb2 knockout($Setdb2^{fl/fl}Lyz2^{cre+}$) allivated hepatic steatosis and inflammation in mice compared with the control mice($Setdb2^{fl/fl}$). In $Setdb2^{fl/fl}Lyz2^{cre+}$ mice, the deficiency of Setdb2 inhibited M1-polarization and promoted M2-polariztion of liver macrophages. Furethermore, the number of M1-type(inflammatory type) macrophages and the proportion of M1 and M2-type macrophages reduced significantly. In vitro, we found that the decrease or increase of SETDB2 protein level directly affected the expression of pMEK and pERK proteins, showing a positive correlation, indicating that SETDB2 regulates macrophage polarization through the MAPK signaling pathway.
Conclusion: The expression of SETDB2 significatntly incresed in macrophages of MASH livers. Also, it may promote the M1 polarization of inflammation-associated macrophages through the MAPK signaling pathway, and then accelerate the inflammatory response in livers, and ultimately promote the progression of MASH. This result may complement the underlying molecular mechanism of MASLD progression, highlight the important role of macrophages in MASLD.

FRI-399-YI

Impaired hepatocyte autophagy and bile dysregulation as a novel histological and genetic signature in metabolic dysfunction-associated steatotic liver disease patients with early fibrosis

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Background and aims: Excessive lipid accumulation into hepatocytes is a hallmark of metabolic dysfunction-associated Steatotic Liver Disease (MASLD), further features are liver inflammation and fibrosis. Recent findings indicate that cholestasis in MASLD patients serves as a significant predictor of poor prognosis, highlighting the putative role of impaired bile secretion in the pathogenesis and progression of the disease. Interestingly, bile acids could interfere with autophagy, a key process for lipid regulation into hepatocytes. Here, we correlate the alteration in bile duct systems with impaired autophagy flow by anatomical and transcriptomic analysis in MASLD patients with early liver fibrosis.
Method: 21 human liver biopsies and clinical data of MASLD patients with early fibrosis were collected. A cholestatic, mixed or hepatocellular pattern was defined based on serological profiles. Tissues were analyzed by immunohistochemistry for autophagy, and biliary cell markers. We performed gene expression analysis on 58 genes involved in lipid metabolism, bile secretion and autophagy. Finally, we correlated the data obtained with clinical data.
Results: Our data demonstrated that in early human fibrosis the impairment of autophagy flux into hepatocytes is linked to cholestasis-related changes in the biliary system, inducing ductular reaction and the expansion of intermediate hepatobiliary cells. Gene expression analysis confirmed alterations in lipid metabolism and homeostasis, mitochondria biogenesis, autophagy and transcription factors involved bile secretion and uptake processes. We observed an increased levels of impaired autophagy marker p62 correlating with the expansion of hepatic progenitor cells and intermediate hepatobiliary cells ($p < 0.05$). Impaired autophagy was also associated with higher mRNA expression of liver X receptor alpha ($p < 0.05$) and farnesoid X receptor ($p < 0.01$), and a greater expression of cholesterol bile efflux pumps, ATP Binding Cassette Subfamily G Member (ABCG) 5 and 8, was observed in patients with cholestatic pattern compared to those with a mixed or hepatocellular pattern ($p < 0.05$). Furthermore, in patients with cholestatic blood profiles, reduced expression of ABCG5 and ABCG8 was associated with increasing ballooning, a feature of MASLD-related liver damage ($p < 0.05$). Also, expression analysis of all selected genes best identifies the patients with cholestatic pattern respect to others ($p < 0.01$).
Conclusion: Our data linked impaired autophagy, bile efflux system dysregulation, and histological changes in MASLD. In early fibrosis, higher ABCG5/8 expression in cholestatic patients may reflect a compensatory bile efflux response to reduce biliary impairment. This could suggest a novel histological and genetic signature of cholestatic MASLD in early disease potentially helpful in identifying patients at risk of disease progression before severe fibrosis occurs.

FRI-400-YI

Impact of ageing on metabolic dysfunction-associated steatotic liver disease in a murine model: insights into progression, biomarkers, and therapeutic stratification

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) ranges from steatosis to steatohepatitis, fibrosis, cirrhosis and hepatocarcinoma. It is more prevalent in older individuals, who frequently present severe manifestations. There are no reliable markers to predict disease progression. This study aims to examine the impact of ageing on MASLD progression in a murine model to provide tools for patient stratification and identification of predictive biomarkers of progression.

Method: Male C75BL/6N mice were divided into 4 groups: 2-month-old mice (young, Y) fed with chow diet (Y-CD), or high fat western diet (Y-WD), and 10-month-old mice (middle-aged, MA) fed with CD (MA-CD) or WD (MA-WD). Weight and blood glucose levels were tracked for 20 weeks. Then, liver tissue was collected for histological staining, gene expression analysis by qPCR and RNAseq. Differentially expressed genes (p-adjusted value <0,05 and |logFC| < 0.585) were identified via Limma differential expression analysis. Gene ontology (GO) analysis was performed with significantly regulated genes to identify regulated biological processes (FDR < 0.05).
Results: Mice on the WD gained more weight than those on the CD, with a greater effect in Y mice. Liver mass increased significantly with WD despite age. MA mice became insulin resistant regardless of diet, while WD also caused insulin resistance in Y mice. Serum ALT, AST, and LDH levels were increased in MA-WD mice as well as total cholesterol, LDL and HDL. NAFLD activity score (NAS) showed that WD had a greater effect on MA mice. A different quantity and distribution pattern of hepatic lipid droplets was observed between Y-WD and MA-WD. WD induced hepatocellular hypertrophy, while ageing promoted inflammation and fibrosis, worsened by WD. GO analysis of MA-CD mice revealed an upregulation of genes associated with circadian rhythm processes compared to Y-CD mice. Notably, WD modulated different biological processes in Y and MA mice: in Y-WD mice, genes related to angiogenesis, extracellular matrix organization, cell migration and adhesion were upregulated; in MA-WD mice, upregulated genes were associated with inflammation while downregulated genes were linked to energy metabolism. Moreover, a group of genes were regulated commonly in Y-WD and MA-WD mice.
Conclusion: These results suggest that disease progression is faster in older animals compared to younger ones, which highlights the importance of considering the age factor when evaluating treatments for the disease. These findings also enhance our understanding of MASLD progression, pointing towards potential biomarkers for better patient stratification and therapeutic targets independent of age.

FRI-401

Assessing perilipin-2 as a liver-specific biomarker: lack of correlation between cardiac damage and its levels in heart failure patients

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Background and aims: Lipid droplets serve as the primary organelles for lipid storage in liver and host a group of proteins known as perilipins (PLINs), including five members: PLIN1 to PLIN5. Perilipin 2 (PLIN2) is linked to lipid deposition in non-adipose tissues, and its increased expression is associated with various metabolic diseases. Several studies report high levels of PLIN2 in metabolic dysfunction-associated steatotic liver disease (MASLD) and atherosclerosis. Recently, PLIN2 has been proposed as a novel, specific and sensitive biomarker for detecting MASLD and/or liver fibrosis.
The aim of this study is to confirm the role of PLIN2 as a specific biomarker of liver damage, excluding its correlation with cardiac damage in patients with cardiovascular disease.
Method: This is a case-control study to assess the association between PLIN2 levels and cardiac damage in patients affected by heart failure (HF) compared to PLIN2 levels in MASLD patients. A total of 50 patients affected by HF, without history of MASLD as determined by non-invasive scoring methods, were enrolled. Patients were divided into two subgroups based on their to history of coronary artery disease (CAD) and degree of systolic dysfunction, expressed as ejection fraction (EF): patients with a previous history of CAD and EF < 50% (CAD n = 33) and patients without history of CAD and EF ≥ 50% (HFpEF n = 17). A total of 20 controls with histological proven MASLD without history of HF were included. Patients underwent physical examination, blood sample and echocardiography at the time of enrollment. PLIN2 monocyte expression was assess by flow cytometry. Data were analyzed by Mann-Whitney U test and expressed as mean ± SEM.
Results: PLIN2 protein level was significantly lower in subjects with HF-noMASLD (3.68 ± 1.13 MFI; p < 0.0001) compared to MASLD patient (19.10 ± 8.48 MFI; p < 0.0001). Moreover, there was no difference in PLIN2 level between patients with CAD or HFpEF (3.68 ± 0.97 and 3.61 ± 1,30 MFI; p = 0.24), highlighting the lack of association between PLIN2 levels and HF.
Conclusion: Preliminary data show that there is no correlation between HF and PLIN2 levels, regardless of ischemic or non-ischemic etiology. This study reinforces the role of PLIN2 as a specific biomarker of liver damage despite the crucial role of monocytes and lipids accumulation in the pathogenesis of CAD.

FRI-402

The Nlrp3 inflammasome affects Kupffer cell phenotype, proliferation and triglyceride accumulation in the liver

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Background and aims: The Nlrp3 Inflammasome is an essential mediator of acute and chronic disease. In the liver, constitutive activation of the Nlrp3 complex in immune cells results in “sterile inflammation,” as damaged hepatocytes and bacterial translocation via the portal blood cause ongoing inflammation via TLR4. Research has shown that the resident sinusoid lining KC are essential responders to mediate inflammation and metabolism in the liver. We here aimed to evaluate the role of Nlrp3 specifically in KC in their role in mediating metabolic related liver disease.
Method: We used primary cell isolation, co-culture and in vivo experiments. For readouts we performed multicolor (intracellular) flow cytometry, IF, mitochondrial respiration assays, and qPCR.
Results: Combining Nlrp3 deficient KCs with Nlrp3 sufficient hepatocytes suggested an impact of the KC on FA uptake in cell culture, which came along a nearly unaltered expression of the Nlrp3 regulator and KC marker Tim4 upon activation, but also the FA transporters MRC1/CD206 and CD36. Unsaturated Oleic acid was taken up readily in the presence of wtKC, while saturated Palmitic acid elicited a diminished gene expression response in N3koKC. The presence of N3koKC significantly decreased mitochondrial respiration in co-cultured hepatocytes, while metabolization of FA between wtKC and N3koKC remained unchanged. 10 weeks of feeding WD to mice with KC specific (Clec4f-ASC$^{fl/fl}$/ C4fA) inflammasome inactivation showed a striking decrease in response, while untreated C4fA mice showed higher numbers of KC with higher CD206 and decreased Tim4 expression. Those CD206/Clec4f positive KC accumulated mostly in the portal field of C4fA/ N3ko mice, and were readily visible WD fed wt mice, both in flow cytometry and IF. As the aforementioned KC profile may be prone to induce obesity, we aged those mice to 40 weeks finding increased liver triglycerides alongside higher KC numbers and increased endothelial marker expression alongside decreased inflammation related markers such as Crig, CCR2 but also Tim4 and CD80.
Conclusion: In summary, we found that the KC cell specific inactivation of Nlrp3 lead to an increase in absolute KC number, alongside CD206^{hi} and ESAM1^{hi} KCs that show decreased expression of Tim4 and Crig. The model results in a phenotypical adaptation of

$CD206^{lo}$ and $ESAM1^{lo}$ KC and numerical adaptation of $CD206^{hi}ESAM^{hi}KC$ similarly resulting in proliferation, inducing a metabolic phenotype inducing local accumulation of triglycerides in the liver. It appears conceivable to us, that $CD206^{hi}ESAM^{hi}$ KC are responsible for the accumulation of fatty acids. As those cells lack a potent response to polysaturated fatty acids in vivo and in vitro, they are conductive to a less inflammatory environment that coincides with higher insulin sensitivity alongside lower IL-12 and hence result in a lesser phenotype compared to wild type controls.

FRI-403-YI

Spatial lipidomics applied to human liver across the spectrum of metabolic dysfunction-associated steatotic liver disease using mass spectrometry imaging

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) results from excessive fat accumulation in the liver while metabolic dysfunction-associated steatohepatitis (MASH) is the progressive, inflammatory form of disease that can lead to fibrosis, cirrhosis, and liver cancer. Patient heterogeneity, variable disease progression and challenges in diagnosis complicate early detection of MASLD. We hypothesized that spatial lipidomics with matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI) offers a powerful approach for identifying lipid biomarkers in liver tissue. This study aims to reveal spatial lipid patterns that could aid in the early diagnosis of MASH and help identify novel therapeutic targets and biomarkers.
Method: Human liver biopsy samples (n = 30, 32–83 years) from the HepaT1ca study (ClinicalTrials.gov NCT03213314) were categorized into groups with low (< 5%), medium (5–33%), and high (>33%) fat content based on histological assessment, with 5 male and 5 female samples per group. MALDI-MSI was applied to liver tissue for untargeted spatial lipid profiling. Data were collected at a spatial resolution of 75 microns using SYNAPT G2-Si qToF mass spectrometer (Waters Corp.). Mimetic tissue spiked with lipid standards served as an inter-batch quality control. Lipid identification was performed using the LipidMaps database, with data processed using MassLynx™ and Lipostar MSI™ software. Statistical analyses, including normalization (by sum) and Pareto scaling, were conducted using MetaboAnalyst. To identify specific lipid markers between groups and sex, partial least squares discriminant analysis (PLS-DA), orthogonal PLS-DA and variable importance in projection (VIP) scores were applied. VIP scores above 1 were considered significant.
Results: PLS-DA revealed clear separation between the three groups by fat level with component 1 accounted for 12% of the variance, and 16.8% by component 2. The high-fat group showed a distinct lipid profile, while profiles of the mid and low-fat groups overlapped. Sex differences were observed in lipid profiles within each group classified by fat level. Lipid markers distinguishing high- from low-fat groups across sexes included triglycerides (e.g., TG 54:10, VIP score = 1.75), diacylglycerols (e.g., DG 36:2, VIP score = 1.74), and phosphatidylcholines (e.g., PC 32:0, VIP score = 1.13). Within the high-fat group, sex-specific differences were observed. Phosphatidylcholines (e.g., PC 36:1, VIP score = 2.2) and lysophosphatidylcholine (e.g., LPC 18:1, VIP score = 1.8) were more abundant in males, while phosphatidylcholines (e.g., PC 34:2, VIP score = 1.0 and PC 38:5, VIP score = 1.1) were more abundant in females.
Conclusion: MSI has the potential to identify sexually dimorphic biomarkers of liver pathology that may improve future diagnostic screening.

FRI-404-YI

Leucine regulates mitochondrial function in an in vitro model of MASLD

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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is becoming a global burden worldwide with a prevalence of 38% in the adult population. Metabolic perturbation disrupts lipid synthesis, esterification, and oxidation processes, leading to lipotoxicity that triggers mitochondrial dysfunction, including reactive oxygen species (ROS) production leading to oxidative stress. On the other hand, branched-chain amino acids (BCAAs: leucine (Leu), isoleucine (Ile), and valine (Val)), are essential nutrients that have become notorious as diagnostic (Fisheŕs ratio) and therapeutic tools during chronic liver diseases. During MASLD, they pass from overconcentrated to low concentrated as liver failure progress and they have shown to influence mitochondrial functionality. This study aims to elucidate the effects of BCAAs on mitochondrial function and lipid metabolism, in vitro model of MASLD.
Method: Primary hepatocytes from male Wistar rats were treated with either palmitic acid (PA: 500 µM) or a mixture of oleic acid/palmitic acid (FFA: 750 µM) in the absence or presence of BCAAs. Mitochondrial function was assessed by determining expression of antioxidant- genes (NRF2, GPX, SOD1 and, SOD2) and proteins (NRF2, MnSOD), ROS production, mitochondrial membrane potential (JC-10 assay), and energy production (Seahorse assay). Lipid accumulation (Bodipy staining) and expression of lipid metabolism-related genes (DGAT, SREBP, PPAR, CPT1, CD36, ACADs) were also assessed. Hepatocyte mitochondria were isolated using multiple centrifugation steps and proteomics analysis was performed.
Results: BCAAs significantly improved cell survival, with Ile and Leu being most effective. FFA significantly increased the presence of lipid droplets, which was reduced by BCAAs. BCAAs, particularly Leu, activated mTOR and its downstream targets. Leu and its metabolite keto-isovaleric acid (KIC) both diminished LD accumulation, partially regulated by mTOR since the mTOR inhibitor Rapamycin decreased this effect. The β-oxidation-related genes CPT1 and ACADs, were slightly increased by Leu and KIC and after mTOR inhibition, suggesting that mTOR acts as a negative regulator of β-oxidation mediated by Leu and KIC. Both Leu and KIC reduced ROS production, but no significant changes were observed in the expression of antioxidant-related genes. Interestingly, antioxidant proteins were upregulated by both leucine and KIC, suggesting post-translational regulation by Leu and its metabolite.
Conclusion: Mitochondrial dysfunction plays a crucial role in the progression of MASLD. BCAAs, particularly leucine and its metabolite KIC, enhance fatty acid oxidation and reduce oxidative stress, with these effects being partly mediated by the mTOR signaling pathway. These findings provide insight into the potential therapeutic role of BCAAs in managing MASLD.

FRI-405

Pharmacological decreases in reductive stress ameliorate lipotoxicity in hepatocytes

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, but the underlying pathophysiology remains unclear. Recent studies have

shown that the severity of MASLD associates with a high plasma beta-hydroxybutyrate-to-acetoacetate ratio, a well-established marker of hepatic mitochondrial reductive stress. Here, we investigated whether palmitate-mediated lipotoxicity can be prevented by small molecules that ameliorate reductive stress, such as mitochondrial uncouplers, electron acceptors, nicotinamide adenine dinucleotide (NAD^+) boosters and citrate-malate shuttle inhibitors. Furthermore, we studied whether these compounds enhance mitochondrial oxidation.

Method: Cellular reductive stress was determined using Promega NAD/NADH-Glo kit. As a model of lipotoxicity, HepG2 cells were incubated in 200–300 uM palmitate for 24 hours, after which cell viability was determined as live-to-dead cell ratio and ATP content using Promega MultiTox-Fluor and CellTiter-Glo 2.0 kits, respectively. Mitochondrial oxidation was determined as oxygen consumption rate (OCR) using Agilent Seahorse XF96. The small molecules that were studied included mitochondrial uncouplers (carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone [FCCP, 0.25–1.0 uM]; 2,4-dinitrophenol [DNP, 0.2–100 uM]; aspirin [0.01–1 uM]), an electron acceptor methylene blue [MB, 2.5–40 uM], NAD^+ boosters (SBI-797812, 0.1–10 uM; JBSNF-000088, 1–50 uM; TES-1025, 0.1–10 uM) and a citrate-malate shuttle inhibitor (CTPI-2, 1–50 uM; decreases reductive stress exclusively in mitochondria). HepaRG cell line was used for validation. All experiments were performed in triplicate. P-values were determined using ANOVA.

Results: The mitochondrial uncouplers FCCP, DNP and aspirin, the electron acceptor MB, the NAD^+ boosters SBI-797812, JBSNF-000088 and TES-1025, and the citrate-malate shuttle inhibitor CTPI-2 decreased cellular reductive stress as determined by $NADH/NAD^+$ by 36.6, 19.1, 26.5, 88.9, 20.3, 15.7, 17.7 and 24.1%, respectively (p ranging from < 0.0001 to < 0.05). The same compounds increased hepatocellular viability under palmitate treatment by 91.8, 13.3, 11.4, 82.2, 13.6, 22.2, 12.3 and 62.4%, respectively (p ranging from <0.0001 to <0.05). Similar improvements were observed using ATP content as a measure of viability. FCCP, DNP, MB and CTPI-2 increased OCR by 23.2, 27.0, 112.0 and 6.8%, respectively (p ranging from < 0.0001 to 0.011). Consistent results were observed using the HepaRG cell line.

Conclusion: Palmitate-induced lipotoxicity in hepatocytes can be ameliorated with small molecules that decrease reductive stress, such as mitochondrial uncouplers, electron acceptors, NAD^+ boosters and citrate-malate shuttle inhibitors. Our results suggest hepatic reductive stress as a potential pharmacological target in MASLD.

FRI-406

A quantitative systems pharmacology model identifies mechanisms attenuated by knockdown of HSD17B13 expression and associated with a reduction in hepatocellular ballooning

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Background and aims: Loss-of-function mutations in *HSD17B13* protect against chronic liver disease, including metabolic dysfunction-associated steatohepatitis (MASH), but mechanisms of action (MoA) underlying this observation are not well understood. ARO-HSD, a hepatocyte-targeted siRNA therapeutic designed to silence HSD17B13 expression, improved markers of liver injury in participants with MASH in a Phase 1/2a clinical trial (NCT04202354). The aim of this study was to utilise quantitative systems pharmacology (QSP) modelling to investigate the MoA by which HSD17B13 modulation impacts clinical biomarkers of MASH.

Method: In the Phase 1/2a trial, ARO-HSD was administered as an open-label treatment on Days 1 and 29 to participants with confirmed/clinically suspected MASH. Liver biopsy was performed pre-dose and on Day 71 to evaluate HSD17B13 expression. Data from the MASH/suspected MASH Phase 1/2a trial cohort were used to calibrate the NAFLDsym QSP model, which was updated to include HSD17B13. A virtual cohort of 135 participants reflective of the Phase 1/2a cohort was generated; this was used to predict changes from baseline in liver fat fraction (Day 71), plasma propeptide of type III collagen (PRO-C3) levels (Week 16) and plasma alanine aminotransferase (ALT; Day 71 and longitudinally to Day 113). Simulations included the following literature-proposed MoA: hepatocellular triglyceride (TG) lipolysis, mitochondrial biogenesis and its downstream effect on lipotoxicity, and neutrophil aggregation. The QSP model was used to predict changes in Non-alcoholic fatty liver disease Activity Score (NAS) following HSD17B13 knockdown.

Results: Consistent with Phase 1/2a data, most (78%) of the virtual cohort demonstrated at least 90% HSD17B13 knockdown and some (22%) had an average of 60% knockdown. No differences in liver fat data between the virtual and clinical cohorts were observed. Simulations invoking TG lipolysis and mitochondrial biogenesis predicted ALT, PRO-C3 and liver fat changes that matched clinical observations. On investigation of each MoA, mitochondrial biogenesis had a major impact on ALT and TG lipolysis had a minor impact on liver fat. Activation of neutrophil aggregation had no effect on the biomarkers of interest. When invoking TG lipolysis and mitochondrial biogenesis, 27% of the virtual cohort were predicted to have ≥ 2 reduction in NAS mostly attributed to an improvement in hepatocyte ballooning.

Conclusion: This QSP study suggests that TG lipolysis and mitochondrial biogenesis may be a key MoA behind HSD17B13 knockdown. The QSP model predicts that HSD17B13 knockdown results in reductions in ALT, as seen in the Phase 1/2a trial, and additionally reduces PRO-C3. The small dataset available for calibration limits the strength of the conclusions that can be drawn. These, and other potential MoA, are being further investigated in the ongoing HORIZON Phase 2b study.

FRI-407

Adding the serotonergic agonist psilocybin to semaglutide as a novel combination therapy to cure MASLD

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Background and aims: Serotonin and glucagon-like peptide 1 (GLP-1) mutually act in the gut and in the brain to control appetite and feeding behavior. Serotonin modulates the nutrient-induced release of GLP-1 by enteroendocrine cells in the ileum. However, the serotonin/GLP-1 axis has not been exploited so far as a pharmacological target for MASLD. This study investigated the potential therapeutic benefit of targeting both pathways simultaneously through a combination of GLP-1 mimetic semaglutide and serotonergic 5-HT2A agonist psilocybin.

Method: To induce MASLD, C57BL/6J mice were fed with a diet rich in fat (60% kcal from fat) and sugar (30% fructose in drinking water), named high fat-high fructose diet (HFHFD), for 17 weeks. From week 6, HFHFD animals (n = 10 per group) received individual or combined treatments with semaglutide (0.04 mg/kg twice weekly, s.c.) and psilocybin at non-psychedelic doses (0.05 mg/kg daily, p.o.). A group of mice (n = 10) fed with standard diet was used as control. Muscle strength was evaluated by the grid test every two weeks.

Intraperitoneal glucose tolerance test (ipGTT) was performed before sacrifice.
Results: Body weight gain was significantly reduced by all treatments, but more effectively in the group treated with the combination (80% in the untreated HFHFD mice, 60% in psilocybin-treated, 32% in semaglutide-treated, 27% in mice treated with the combination, and 20% in healthy controls). Liver steatosis was also significantly reduced by all treatments, as shown by H&E staining. Although all treated mice showed a significant reduction of fasting glucose and HOMA index ($p < 0.05$ vs. untreated HFHFD mice), during the ipGTT only mice treated with the combination showed a significant reduction of the postprandial plasma glucose and insulin concentration (both $p < 0.05$ vs. placebo). Electron microscopy analysis demonstrated that HFHFD produced a severe damage of insulin-producing beta cells which appear proapoptotic and degranulated, typical of severe type 2 diabetes mellitus. At variance, islets of Langerhans of HFHFD mice treated with either psilocybin or semaglutide or both showed healthy and well granulated insulin producing beta cells. Psilocybin alone or in combination caused a significant delay in the deterioration of mice motor performance, compared to HFHFD untreated mice and those treated with semaglutide only. Accordingly, mRNA levels of perilipin 4, which plays a detrimental role in myosteatosis and other related conditions, were significantly reduced in quadriceps of psilocybin-treated mice with respect to untreated ones.
Conclusion: Adding low non-psychedelic doses of psilocybin to semaglutide further ameliorated insulin sensitivity and preserved muscle function in a mouse model of MASLD, paving the route for a possible combination therapy in MASLD patients with obesity, type 2 diabetes mellitus and sarcopenia.

FRI-408-YI
MASLD-associated changes across the gut-liver-brain axis are not ameliorated by a low-fat diet intervention in an aged mouse model

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has increasingly been associated with intestinal microbial dysbiosis, systemic inflammation, cerebral hypoxia, cognitive decline, and increased risk of neurodegenerative disease. MASLD-related changes overlap considerably with age-associated changes, creating an interesting interplay of pathologies which may ultimately drive neurodegeneration. Here, we assessed a low-fat diet (LFD) as a protective intervention against MASLD-associated dysfunction across the gut-liver-brain axis in ageing mice.
Method: 6-week-old male C57BL/6NTac mice were fed control diet (CD) or high-fat high-cholesterol diet (HFD) for 26 weeks to induce MASLD. Half the mice in each group were then placed on the LFD and aged to 18-months. Behavioural tests were performed on all mice. Cortical oxygenation at baseline and in response to systemic hypercapnia (10% CO2) was measured in vivo. Steatosis and fibrosis were assessed by histology. Plasma markers of intestinal dysfunction were measured by enzyme-linked immunosorbent assay, with complementary immunofluorescence ongoing. Cerebrovascular morphology, pericytes, and microglia were characterised by immunofluorescent staining. A qPCR gene panel was used to assess cortical inflammation and mitochondrial function. Cortical metabolites were measured by nuclear magnetic resonance.
Results: Unexpectedly, LFD drove steatosis in CD-LFD mice and fibrosis in some HFD-LFD mice. Both HFD and HFD-LFD mice exhibited anxiety-like behaviours, whilst aged CD-LFD and HFD-LFD mice showed impaired memory. Increased plasma LPS-binding protein indicated intestinal bacterial translocation in CD-LFD and HFD-LFD mice, whilst increased fatty acid-binding protein 2 indicated intestinal epithelial dysfunction in HFD and HFD-LFD mice. HFD, HFD-LFD, and CD-LFD mice exhibited lower baseline cortical oxygenation but preserved cerebrovascular reactivity to systemic hypercapnia. A trend towards reduced vessel volume compared to CD was observed. HFD mice had reduced vascular pericyte coverage. Furthermore, HFD mice had lower cortical nicotinamide and NAD+ compared to CD, indicative of oxidative stress. HFD and HFD-LFD also showed increased microglia density and cell volume, indicating reactive microglia. Interestingly, HFD mice exhibited upregulation of genes associated with inflammation and mitochondrial changes in the cortex, which mirrored the aged groups.
Conclusion: HFD-induced steatosis is associated with intestinal dysfunction, cerebrovascular pathology, and accompanying neuroinflammation. With the additional impact of ageing, these changes may underly the increased risk of neurodegeneration in people with MASLD. The LFD failed to mitigate all MASLD-associated alterations across the gut-liver-brain axis in ageing mice.

FRI-413
Hepatoprotective effects of fatty acid synthase inhibitor TVB-3664 in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background and aims: Denifanstat, an oral fatty acid synthase (FASN) inhibitor, have recently been demonstrated to improve NAFLD Activity Score (NAS) and fibrosis stage in a phase 2b clinical trial (FASCINATE-2) in patients with metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to investigate metabolic, biochemical, histopathological and transcriptomic effects of TVB-3664, a FASN inhibitor analogue, in the translational Gubra Amylin NASH (GAN) diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis.
Methods: Male C57BL/6 mice were fed the GAN diet high in fat, fructose and cholesterol for 39 weeks prior to study start. A liver pre-biopsy was collected 4 weeks before treatment start. Only GAN DIO-MASH mice with biopsy-confirmed NAFLD Activity Score (NAS≥5) and moderate/advanced fibrosis (stage F2-F3) were included and stratified into treatment groups (n = 16–17 per group). Mice were administered once daily oral vehicle or TVB-3664 (10 mg/kg) for 12 weeks. Histopathological pre-to-post individual assessment of NAS and fibrosis stage was performed. Other terminal endpoints included quantitative liver histomorphometry, blood and liver biochemistry in addition to RNA-sequencing-Bioinformatic analysis.
Results: GAN DIO-MASH mice demonstrated vehicle-corrected weight loss of 12% after 12 weeks of TVB-3664 treatment in conjunction with reduced adiposity and preserved lean tissue mass. Furthermore, TVB-3664 treatment improved hepatomegaly, plasma biomarkers (transaminases, plasma cholesterol and triglyceride levels). TVB-3664 treatment promoted a ≥2-point statistically significant improvement in NAS, driven by reduction in steatosis score. Benefits on NAS were supported by quantitative liver histology on steatosis (hepatocytes with lipids)) and marker of inflammation (galectin-3). TVB-3664 treatment did not improve fibrosis stage, albeit reduced histological markers of fibrosis (PSR, Collagen 1a1) in addition to marker (α-SMA) for fibrogenesis. Finally, TVB-3664 induces transcriptomic regulation and reduced gene expression involved in inflammation and extracellular matrix production.
Conclusion: TVB-3664 improved metabolic, biochemical and histological markers of steatosis, inflammation and fibrosis/fibrogenesis. In addition, TVB-3664 improved histopathological NAFLD Activity Score, with longer treatment intervention needed for fibrosis stage

improvement. The therapeutic effects of TVB-3664 highlight the translatability and applicability of the GAN DIO-MASH mouse model in preclinical drug discovery.

FRI-414

Reproducible hepatoprotective effects and clinical translatability of long-term semaglutide treatment in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background and aims: The glucagon-like-peptide (GLP)-1 analogue semaglutide is currently approved for the treatment of type 2 diabetes and obesity. Semaglutide has been reported to promote MASH resolution and improved fibrosis stage in a recent Phase 3 trial (ESSENCE). The present study aimed to evaluate robustness of therapeutic outcomes and clinical backtranslation following long-term treatment with semaglutide in the translational GAN diet-induced obese (DIO) mouse model of biopsy-confirmed MASH and fibrosis.
Methods: Semaglutide was characterized in 3 individual studies. C57BL/6JRj male mice were fed the GAN diet high in fat, fructose, and cholesterol for 34–38 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAFLD Activity Score (NAS) ≥5) and fibrosis (stage ≥F1) were included, randomized and stratified into treatment groups. GAN DIO-MASH mice (n = 14–18 per group) received semaglutide (30 nmol/kg, SC) or vehicle (SC) once daily for 20–24 weeks. Vehicle-dosed chow-fed controls served as healthy controls. Within-subject comparisons (pre- vs. post-treatment) were performed for histopathological NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and liver histomorphometry.
Results: For all studies in GAN DIO-MASH mice, semaglutide consistently reduced body weight and improved hepatomegaly, plasma transaminases and hypercholesterolemia. For all studies, semaglutide promoted a ≥2-point significant improvement in NAS, primarily driven by reduced steatosis scores. Benefits on NAS were supported by quantitative liver histology on steatosis (% lipid-laden hepatocytes) and inflammation (macrophage marker galectin-3). A significant 1-stage improvement in fibrosis was observed when data was pooled across the 3 studies (20% vehicle adjusted), supported by reduced quantitative fibrosis markers (PSR, Col1a1) in addition to α-SMA levels, a marker of hepatic stellated cell activation (fibrogenesis).
Conclusion: Semaglutide consistently improved metabolic and biochemical parameters, as well as histological markers for steatosis, inflammation and fibrosis/fibrogenesis. In addition, semaglutide improved clinical-derived histopathological scoring in the GAN DIO-MASH mouse, resembling findings reported in recent phase 3 trial (ESSENCE). The highly reproducible therapeutic effects of semaglutide highlight the translatability, robustness and applicability of the GAN DIO-MASH mouse model in preclinical drug discovery.

FRI-415

The mGluR5 blockade by MPEP inhibits PKC and triggers AMPK activation reducing hepatic steatosis in vitro

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Background and aims: Metabotropic glutamate receptor type 5 (mGluR5) is involved in lipid metabolism and intracellular signaling, particularly through protein kinase C (PKC) activation. mGluR5 regulates PKC, which in turn can inhibit AMP-activated protein kinase (AMPK) via phosphorylation, impairing its ability to prevent lipid accumulation (Chen et al., 2011; Heathcote et al., 2016). Additionally, mGluR5 hyperactivation in hepatic stellate cells promotes hepatocyte fat accumulation (Choi et al., 2019). In our previous studies, the mGluR5 negative allosteric modulator 2-methyl-6-(phenylethynyl)pyridine (MPEP) reduced lipid deposition in oleate/palmitate-induced steatotic HepG2 cells (Ferrigno et al., 2020), and depleted ATP in hepatocytes (Ferrigno et al., 2018), suggesting potential effects on both PKC and AMPK pathways. To further investigate mGluR5′s role, we used negative allosteric modulators (MPEP, Fenobam), the orthosteric antagonist 2-methyl-4-carboxyphenylglycine (CPG), and the orthosteric agonist 3,5-dihydroxyphenylglycine (DHPG). Phorbol 12-myristate 13-acetate (PMA), a PKC activator, was included to explore the interplay between mGluR5, PKC, and AMPK in steatosis.
Method: steatosis in HepG2 was induced by 2 mM O/P for 24 h. Cells were pre-treated with 0.3–3–30 μM MPEP, 1-25-50 μM Fenobam, or 100-150-200 μM CPG, alone or combined with 0.1-1-10 μM AMPK inhibitor Compound C. To assess mGluR5-PKC interaction, steatotic cells were treated with 0.01-0.1-0.5-1 μM PMA, with or without MPEP or Fenobam. Non-steatotic cells received 100–200-300 μM DHPG, alone or with 30 μM MPEP. Lipid accumulation was assessed using Nile Red dye and quantified by ImageJ; viability was evaluated by MTT. ATP content was measured by luciferin-luciferase assay, and p-AMPK/AMPK levels were analyzed via Western blot.
Results: In O/P-treated steatotic HepG2 cells, MPEP, Fenobam, and CPG reduced lipid accumulation dose-dependently. In non-steatotic cells, DHPG increased lipid accumulation, while MPEP co-treatment neutralized this effect, confirming mGluR5′s role. Only MPEP depleted ATP in HepG2 cells. Since AMPK is activated by ATP depletion, we hypothesized that MPEP's defatting effect involved AMPK; in fact, Western blot showed increased p-AMPK/AMPK levels in steatotic cells treated with MPEP. Co-treatment with Compound C reduced MPEP's effect, supporting this mechanism. Also PMA reversed MPEP's lipid-lowering effect, confirming PKC's role in lipid modulation. Thus, MPEP modulates lipid metabolism via ATP depletion-driven AMPK activation and inhibition of PKC-mediated suppression.
Conclusion: mGluR5 negative allosteric modulators and antagonists reduce fatty acid accumulation in an in vitro steatosis model via selective receptor inhibition. MPEP uniquely modulates both PKC and AMPK, the former with a receptor-independent mechanism.

FRI-416

Patatin-like phosphatase domain-containing 3 (PNPLA3) genotype and dietary fat modify the liver adiposity

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Background and aims: Patatin-like phosphatase domain-containing 3 (*PNPLA3*) GG genotype and bad quality of dietary fat are causal for metabolic dysfunction-associated steatotic liver disease (MASLD). We studied the impact of dietary fat quality modification on liver adiposity in men homozygotes of *PNPLA*3.
Method: Ninety-nine randomly assigned men (age: 67.8 ± 4.2 years, body mass index: 27.2 ± 2.5 kg/m^2), homozygous for *PNPLA3* rs738409 variant (I148M), participated in a 12-week diet intervention. The quality of dietary fat was planned according to the National and Nordic nutrition recommendations in the recommended diet (RD) arm, and according to the average fat intake in Finland in the average diet (AD) arm. Liver imaging was performed by ultrasound with 2D-shear wave elastography (2D-SWE) and magnetic resonance imaging (MRI) in combination with magnetic resonance spectroscopy (MRS).
Results: MRI-based liver fat decreased in the RD arm (CC: from 3.8 ± 3.2% to 3.2 ± 3.3% and GG: from 3.9 ± 3.3% to 3.5 ± 3.1%, *p time* = 0.032) and increased in the AD arm (CC: from 4.1 ± 3.6% to 4.8 ± 3.9% and GG: from 4.7 ± 3.7% to 6.7 ± 5.3%, *p time* = 0.015). Liver elasticity decreased in the AD arm with the *PNPLA3* CC genotype and increased with the GG genotype (from 6.1 ± 1.5 kPa to 6.5 ± 1.4 kPa and from 6.2 ± 1.4 kPa to 5.8 ± 1.0 kPa, respectively, time and genotype interaction *p* = 0.013). MRS-quantified liver saturated fat content increased with AD (lipid methylene CC from 5899 ± 6534 a.u. to 8252 ± 8714 a.u. and GG from 6621 ± 3689 a.u. to 9663 ± 6168 a.u., *p time* = 0.010). Liver triglyceride concentration did not change in either arm with the CC genotype but increased in the AD arm with the GG genotype (for time *p* = 0.082 and for time and genotype interaction *p* = 0.027).
Conclusion: The *PNPLA3* genotype modifies the response of dietary fat quality modification to both the content and composition of liver fat.

FRI-417-YI
The HSD17B13 rs72613567:A variant is associated with reduced hepatic glycolipid content in non-obese individuals
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Background and aims: The HSD17B13 rs72613567:A variant displays strong, reproducible protective effects against MASLD. HSD17B13 is a lipid droplet-associated protein predominantly expressed in hepatocytes. However, the effects of the rs72613567:A variant in the liver tissue of normal-weight individuals have not been investigated. We aimed to examine potential changes in lipid metabolism associated with rs72613567.
Method: Human liver tissue was acquired during routine liver resection with informed consent. Taqman SNP Genotyping was performed on 504 cryopreserved liver tissues without a history of chemotherapy or significant fibrosis (>F2). 6 cases with minor homozygosity for rs72613567:A were chosen for further analyses. All liver tissues analyzed were major homozygous (WT) for the previously described MASLD-related genetic variants (PNPLA3 rs738409, TM6SF2 rs58542926, MTARC1 rs2642438). Carrier and non-carrier groups of rs72613567:A were matched for age, sex, BMI, steatosis, and fibrosis grade. Mass spectrometry-based lipid analyses of selected liver tissues (n = 12) were performed and analyzed with Lipid R (Version 2.20.0). Differential lipid analysis was performed, and results were visualized using lipid set enrichment analysis. Additionally, Liquid Chromatography-Mass spectrometry-based proteomics was performed on 22 human liver tissues comprising samples from the lipidomic analysis and FragPipe visualized proteomic data.
Results: The allele frequency of rs72613567:A was 24% among patients undergoing liver resections. After matching there were no significant differences in mean age (control: 63.5 vs. HSD17B13: 63.3), mean BMI (23.2 vs. 25.6), mean steatosis (11.7% vs. 6.67%), and fibrosis grade. Carriers of rs72613567:A exhibited significantly reduced HSD17B13 protein expression in liver tissue (p = 0.008). Lipidomic analysis revealed enrichment of phospholipids (phosphatidylcholine [PC], phosphatidylinositol [PI], sphingomyelin [SM]) in carriers of rs72613567:A, while glycolipids (diacylglycerol [DAG] and triacylglycerol [TAG]) were significantly reduced.
Conclusion: This study provides the first lipidomic analysis of human liver tissue in non-obese individuals with the HSD17B13 rs72613567:A variant. We conclude that carriers of the HSD17B13 rs72613567:A variant have a phospholipid surplus (PC, PI, SM) in the liver. In addition to previous findings, hepatic glycolipids (DAG and TAG) were reduced in carriers of rs72613567:A.

FRI-418
Plasma proteomics identifies pathways to target in metabolic dysfunction-associated steatotic liver disease
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) involves a variety of complex mechanisms such as inflammation, oxidative stress, and metabolic dysregulation. Plasma proteomics offers an opportunity to explore disease-specific pathways. This study evaluates the plasma proteome in MASLD patients compared to controls.
Method: Proteomics data from the UK Biobank were linked to MASLD diagnosis determined using liver MRI scans and a proton density fat fraction (PDFF) value of > = 5%. Differential OLINK protein expression analysis was performed to identify proteins of interest. Pathway enrichment analysis was conducted using EnrichR, with pathways annotated using Reactome 2022 and WikiPathways 2024 databases.
Results: Among 40,189 participants with OLINK plasma protein data, 9,692 were diagnosed with MASLD and 29,303 as controls. Differential protein expression analysis revealed: Downregulated pathways: Reactome analysis identified disruptions in glycosaminoglycan metabolism, extracellular matrix organization, and dermatan sulfate biosynthesis, indicative of altered structural and metabolic functions. IGFBP-2 (Insulin-like Growth Factor Binding Protein 2) was found to be downregulated, suggesting its potential involvement in sarcopenia amid metabolic dysregulation in MASLD. WikiPathways further highlighted impairments in lipid metabolism and PI3K-Akt signaling pathways. Upregulated pathways: Reactome findings showed enrichment in immune system processes, including interleukin-10 signaling and neutrophil degranulation. WikiPathways highlighted proinflammatory and oxidative stress-related pathways, such as cytokine receptor interactions and NRF2 activation, suggesting a role for immune-inflammatory responses in MASLD pathophysiology.
Conclusion: This study provides an exploratory analysis of the plasma proteome in MASLD, identifying potentially dysregulated biological pathways. While the findings suggest disruptions in extracellular matrix remodeling, lipid metabolism, and immune-inflammatory processes, further validation in independent cohorts is essential to confirm these results and select drugs that target these pathways.

FRI-419-YI

Therapeutic potential of targeting processing-bodies in metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma

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Background and aims: Processing-Bodies (P-bodies) are small cytoplasmic compartments composed of untranslated mRNAs and proteins involved RNA decay (i.e., decapping enzymes, deadenylases, exonucleases). P-bodies control the expression of a wide range of genes associated with inflammatory, metabolic, and cancer-related processes. Accordingly, alterations of P-bodies assembly or P-bodies components contribute to the development of a wide range of diseases, including cancers. Although previous works have reported that some P-bodies-related proteins (e.g., TTP, CNOT6L) are involved in metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatocellular carcinoma (HCC), the role of P-bodies remains largely unexplored. Herein, we aim at characterizing the role of P-bodies in MASLD and HCC.
Method: The expression of specific P-bodies markers (EDC4, DCP1A, DDX6, TTP) was investigated in liver tissues from patients or mouse models of MASLD, HCC. The impact of different stress (oxidative stress, lipotoxicity) and anti-cancerous drugs (sorafenib) on P-bodies assembly was investigated by immunofluorescence staining of P-bodies proteins (EDC4) in hepatic cancer cells and primary hepatocytes. Loss of function analyses (siRNA) were performed in a panel of hepatic cancer cell lines to assess the impact of P-bodies proteins deficiency (EDC4) on cancer cells proliferation, survival and sensitivity to stress. In vivo experiments were carried out to decipher the impact of TTP or EDC4 silencing (i.e., AAV8 encoding shRNAs) in MASLD development, in mice fed a CSAA (choline supplemented L amino acid defined) or a CDAHFD (choline deficient L amino acid defined, high-fat diet).
Results: The expression of TTP is downregulated in HCC as compared to adjacent hepatic tissues. Although EDC4 is heterogeneously expressed in HCC, the high expression of EDC4 correlates with a poor clinical outcome. Interestingly, an increase of P-bodies number was observed in sorafenib/hydrogen peroxide-treated cells, thus suggesting that P-bodies assembly is part of a stress response. Moreover, EDC4 is upregulated in sorafenib-resistant HCC patients as compared to responders. EDC4 silencing reduces P-bodies number and hinders hepatic cancer cells proliferation and viability, thus suggesting a tumor promoting function. Preliminary findings suggest that EDC4 silencing in vivo markedly reduces hepatic steatosis in mice fed a CSAA or a CDAHFD.
Conclusion: Our study suggest that P-bodies assembly contribute to the development of MASLD and HCC and may represent a resistance mechanism against harmful conditions and sorafenib. Targeting P-bodies may therefore represent an efficient therapeutic approach for the management of MASLD and HCC.

FRI-420

Low frequency, mild gradient intermittent hypoxia still induces liver fibrogenesis in mice fed a high-fed diet

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Background and aims: Fibrogenesis in metabolic dysfunction-associated steatohepatitis (MASH) may progress when complicated by obstructive sleep apnea (OSA). High-frequency intermittent hypoxia (IH) exposure, mimicking human OSA (e.g., nadir oxygen concentration of 5%, with rapid cycles of 60 times/hour), is commonly used to study OSA pathogenesis in animal models. However, IH is not always harmful and may exert health-protective effects under milder conditions. This study investigated whether low-frequency, mild-gradient IH exposure could aggravate liver injury and fibrosis in a mouse model of fatty liver.
Method: Control (n = 16; room air 8, IH 8) and high-fat diet (HFD) mice (n = 16; room air 8, IH 8) were exposed to low-frequency, long-duration IH (12 minutes/cycle) for 12 hours/day over four weeks. The groups were compared for laboratory data, liver fibrosis levels via Sirius red staining, hydroxyproline assay, quantification of liver 8-OHdG, and serum nitric oxide (nitrite/nitrate) levels as markers of oxidative stress. Cytokine arrays were used to identify specific cytokines induced under fatty liver and IH conditions. Real-time RT-PCR and immunohistochemistry determined gene expression levels.
Results: ALT/AST and lipid levels were not significantly higher in the HFD + IH group compared to the HFD + room air (RA) group. However, the serum albumin/globulin (A/G) ratio, liver fibrosis levels, liver 8-OHdG, and nitrite/nitrate as oxidative stress markers were elevated in the HFD + IH group, indicating that even low-frequency, mild-gradient IH exposure accelerated fibrogenesis in fatty liver. Conversely, systemic insulin resistance levels were decreased in the HFD + IH group, suggesting mild IH had bidirectional effects. Intercellular adhesion molecule (ICAM-1) and osteopontin (OPN) were upregulated under HFD + IH conditions.
Conclusion: Low-frequency, mild-gradient IH accelerated fibrogenesis in HFD mice by inducing oxidative stress without significant increases in liver injury, independent of insulin resistance. ICAM-1 and OPN may be involved in this pathogenesis.

FRI-421

Differential fatty acid metabolism in the liver and adipose tissue in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease. The hallmark of MASLD is hepatic steatosis, which can progress in some patients to metabolic dysfunction-associated steatohepatitis (MASH). Fatty acids (FAs) are mainly stored in adipose tissue and mobilized through lipolysis to the liver. They can also be synthesized in the liver via *de novo* lipogenesis. The liver esterifies FAs into lipoproteins for circulation, but when its capacity is exceeded, excess FAs accumulate, causing steatosis. To assess inter-tissue crosstalk in FA metabolism in those with MASLD, we compared FA profiles in the liver, serum, and visceral and subcutaneous adipose tissue samples from severely obese patients with either normal liver, simple steatosis or MASH. This comprehensive approach provided a unique opportunity to explore depot-specific alterations in FA profiles in those with MASH, which has not been previously studied.

Method: Samples were collected from the liver, subcutaneous, and visceral adipose tissue during laparoscopic bariatric surgery together with preoperative serum samples from 183 severely obese patients (122 women, mean age 46.9 ± 9.7 years, and body mass index 43.5 ± 5.7 kg/m^2). Liver histology was assessed by one pathologist according to the standard criteria. FA composition in different tissue depots was analyzed with gas-liquid chromatography. The enzyme activities were estimated using the product-to-precursor-ratios of individual FAs.
Results: In general, the differences observed in the liver based on the histology were more distinct than those in adipose tissue. Proportion of all polyunsaturated FAs were significantly lower in liver in patients with MASH compared to those with normal liver (all adjusted $p < 0.01$). In contrast, dihomo-gamma-linoleic acid, adrenic acid and arachidonic acid proportions were higher in subcutaneous and visceral adipose tissue in patients with MASH compared to those with normal liver (all adjusted $p < 0.001$). Interestingly, monounsaturated and saturated FAs exhibited opposite trends between liver and adipose tissue. Estimated delta-5-desaturase activity was lower (adjusted $p = 0.02$) and elongase activity was higher (adjusted $p = 0.006$) in liver in those with simple steatosis compared to those with normal liver. In visceral adipose tissue, the elongase activity was lower in patients with MASH compared to those with normal liver (adjusted $p = 0.04$).
Conclusion: The lower proportion of arachidonic acid in the liver suggests its increased utilization in eicosanoid production or decreased synthesis due to a reduced linoleic acid proportion or diminished delta-5-desaturase activity. These findings highlight distinct differences in FA metabolism between the liver and adipose tissue in patients with MASLD, emphasizing tissue-specific regulatory mechanisms.

FRI-422-YI
Taurine reprograms hepatocyte metabolism and its plasma levels are inversely associated with the progression of MASLD
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Background and aims: Liver diseases, particularly those related to metabolic disorders like Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), pose a significant global health challenge. Identifying reliable biomarkers for early diagnosis and understanding metabolic changes is essential for effective management. Taurine, a semi-essential micronutrient synthesized in the liver, declines with aging. Hepatocytes, the primary cells for fat accumulation and metabolism in the liver, interact with immune cells, influencing the progression of MASLD. This study investigates taurine as a potential biomarker for MASLD and explores its regulatory role in hepatic metabolism-related to this condition.
Method: The study examined polar metabolomics in EDTA-plasma from age-matched healthy subjects (n = 5) and MASLD patients at stages F0-F2 (n = 10) and F3-F4 (n = 10). Primary mouse hepatocytes were treated with 1 mM taurine for 24 hours, followed by 0.3 mM free fatty acids (FFA) (1:1, palmitic and oleic acid) for another 24 hours. Neutrophils were isolated using negative selection microbeads, while bone marrow-derived macrophages were obtained with anti-F4/80 microbeads. Cellular bioenergetics were assessed using 10 mM glucose, 2 mM pyruvate, and 1 mM glutamine, with fuel preference evaluated via the XF Seahorse analyzer.
Results: Levels of taurine decreased 2-fold in MASLD patients at stages F0-F2 ($p < 0.05$), and further decreased by 2.5-fold from F0-F2 to F3-F4 ($p < 0.05$). This decline in taurine levels correlates with the progression of chronic liver disease severity toward fibrosis and cirrhosis, as confirmed in a validation cohort that showed a 50% reduction in taurine between healthy individuals (n = 29) and those with compensated cirrhosis (n = 43, $p < 0.0001$). Since taurine is primarily synthesized in the liver, we aim to examine its role and mechanism in steatotic hepatocytes. Our findings indicate that taurine reduces fatty acid uptake and lipogenesis by downregulating CD36, FATP2, and FATP5, maintaining its effects even with FFA treatment. Taurine supplementation halved lipid accumulation ($p < 0.001$) without increasing fatty acid oxidation, suggesting its benefits arise from reduced FFA uptake and lipogenesis. FFA-exposed steatotic hepatocytes preferred glucose over fatty acids for ATP production, but taurine decreased glucose-dependent oxidative phosphorylation by 2-fold ($p < 0.001$). Additionally, taurine reduced the attraction of neutrophils and bone marrow-derived macrophages (BMDMs) to steatotic hepatocytes by 1.5-fold and 2-fold, respectively ($p < 0.001$), indicating its potential to mitigate liver inflammation.
Conclusion: Taurine functions as an early biomarker for liver disease, with significant decreases in plasma levels observed across various disease stages. Additionally, taurine supplementation reduces fatty acid uptake and lipid accumulation while also modulating inflammatory response, highlighting its potential therapeutic benefits in managing MASLD.

FRI-423
Targeting activated fibroblasts in metabolic-associated steatotic liver disease with Nintedanib
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a significant health challenge, with activated fibroblasts playing a crucial role in its progression. Targeting and eliminating these fibroblasts could be key in managing MASLD. This study aimed to evaluate the potential of nintedanib, an established treatment for idiopathic pulmonary fibrosis (IPF), in alleviating MASLD through its effects on activated fibroblasts.
Method: Fibroblasts isolated from the livers of MASLD patients were treated with nintedanib and compared to sorafenib for efficacy. Hepatic stellate cell line LX2 was activated with TGF-β1 and treated with varying concentrations of nintedanib. Bulk RNA sequencing was used to examine RNA changes in response to treatment. To assess the role of PDGFR suppression, siPDGFR was transfected into LX2 cells. In vivo, a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) mouse model was employed to study nintedanib's effects using FACS analysis, Sirius red staining, H&E staining, IHC, and single-cell sequencing.
Results: In vitro, nintedanib significantly reduced the viability of activated fibroblasts compared to sorafenib. Western blotting revealed decreased levels of phosphorylated-AKT and phosphorylated-ERK in nintedanib-treated fibroblasts, indicating reduced inflammation and fibrosis. Bulk RNA sequencing reveled that PDGFR, the target of nintedanib, decreased in dose-dependent manner with nintedanib treatment. Additionally, fibrosis markers such as FN1 and Col1a1 were also found to decrease in a dose-dependent manner. After transfecting LX2 cells with siPDGFR and inducing activation with TGF-β1, a reduction in fibrosis marker FN1, FAP and α-SMA was observed. Additionally, phosphorylated-AKT levels was also found to decreased. In the CDAHFD mouse model, nintedanib treatment selectively eliminated FAP+PD-L1+ activated

fibroblasts at low concentrations, suggesting its potential as a therapeutic option for MASLD.
Conclusion: Nintedanib effectively reduces activated fibroblasts in both in vitro and in vivo MASLD models. By targeting PDGFR, nintedanib suppresses fibrosis markers and selectively eliminates key fibroblast populations. These results support nintedanib as a promising therapeutic option for MASLD by addressing the fibroblast-driven progression of liver fibrosis.

FRI-424
Differential activation and clonal expansion of T cells by PNPLA3 I148 M genetic variant is associated with the progression of metabolic dysfunction-associated steatotic liver disease
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Background and aims: Increasing evidence highlights the pivotal role of T cells in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD). The *PNPLA3 I148M* variant has been linked to hepatic inflammation and fibrosis, but its role in T cell infiltration, activation, and clonal expansion within the liver remains unclear.
Method: A total of 70 patients with MASLD were prospectively enrolled. Genomic DNA was extracted from buccal swabs or liver biopsy samples, and SNP genotyping was performed to determine the rs738409 SNP genotype at codon 148 of PNPLA3 using the XENOHELIX PNPLA3 genotyping kit. Immunohistochemistry was conducted using CD3 and CD68 antibodies to quantify T cell and macrophage infiltration, respectively. Cell counts were assessed in three periportal regions, normalized to a unit area (20,000 μm²), and averaged. Additionally, total RNA extracted from biopsy specimens was used for quantitative RT-PCR to assess the expression of specific markers associated with T cell activation and clonal expansion.
Results: Among the 70 MASLD patients, 34 carried the GG genotype, while 21 and 15 carried the GC and CC genotypes, respectively. GG genotype carriers exhibited significantly higher CD3+ and CD68+ cell counts in the periportal region compared to GC/CC carriers ($P < 0.05$). Increased CD3+ and CD68+ cell number was positively correlated with advanced fibrosis stages and higher NAS scores (5–8 vs. 0–4, $P < 0.05$). In sensitivity analysis comprising fibrosis stage 0–2, GG genotype still exhibited higher CD3+ and CD68+ cell counts compared to GC/CC carriers ($P < 0.05$). Interestingly, the transcriptional profile of these clonally immune cells differed based on genotype. MASLD livers with GG genotype showed stronger expression of markers of chronic Ag stimulation (KLRG1, CD160, CD244, TIGIT, TOX, and PDCD1) than those with GC and CC genotypes.
Conclusion: This study demonstrates a significant correlation between the PNPLA3 I148M variant and increased T cell infiltration, activation, and clonal expansion within the MASLD liver. Further study is on-going regarding TCR sequencing and in-vitro co-culture experiments. Funding: This research was supported by the Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (RS-2024-00438542).

FRI-425
Thrombospondin-2 reflects improved metabolism and attenuated liver fibrogenesis in severely obese patients undergoing an intensive weight-loss therapy
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Background and aims: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is common in the severely obese population, with a global prevalence of up to 30%. Lifestyle interventions aimed at weight loss are the cornerstone of MASLD management. However, non-invasive assessment of response to intervention is not yet established. Here, we investigated a novel fibrogenesis marker, thrombospondin-2 (TSP2), in association with intensive weight loss and with special attention to markers of liver inflammation, metabolism and fibrosis after lifestyle intervention in a severely obese population.
Method: The Kiel intervention cohort consists of 160 patients with severe obesity (BMI≥40) who underwent a multimodal, intensive interdisciplinary weight loss program at the UKSH in Kiel (Germany) for six months, which includes guideline-based recommendations. Clinical and biochemical parameters were assessed at baseline, after a 10-week very low-calorie diet (VLCD) and after a further 16-week normo-caloric diet (NCD). Serum TSP2 was measured using a validated ELISA and compared with metabolic markers and liver stiffness measurement (LSM) by transient elastography.
Results: TSP2 levels decreased significantly after weight loss therapy ($-14.8 \pm 18.6\%$, $p < 10^{-5}$), which correlated significantly with the decrease in BMI ($-17.1 \pm 5.9\%$, $p < 10^{-5}$; $r = 0.19$, $p = 0.04$). BMI and fat mass continuously decreased in both arms (VLCD & NCD), while TSP2 and liver stiffness along with other metabolic markers decreased significantly after VLCD and maintained at low levels after NCD. TSP-2 correlated with anthropometric values, liver enzymes, fat mass, visceral fat and liver stiffness at baseline and during the intervention. TSP2 levels were higher in men ($p = 7.1 \times 10^{-3}$) and in patients with pre- and manifest diabetes ($p = 9.3 \times 10^{-4}$) and also correlating with the HOMA index for insulin resistance, triglycerides and HDL-Cholesterol levels. Based on baseline liver stiffness, subjects were classified as normal-mild (<7.5 kPa, n = 65), elevated (7.5–13 kPa, n = 38), and cirrhotic (>13 kPa, n = 14). Interestingly, TSP2 was significantly reduced in all groups during VLCD.
Conclusion: Circulating TSP2 levels showed significant changes in individuals with severe obesity who achieved weight loss through diet and may be a useful tool to assess metabolic improvements and liver fibrosis in patients undergoing lifestyle and therapeutic interventions. Ongoing further analyses will investigate its possible connection with body composition, metabolic status and inflammatory activity.

FRI-429

Generation of patient-derived liver organoids from needle biopsies for precision disease modeling of metabolic-associated steatotic liver disease

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Background and aims: Metabolic-associated steatotic liver disease (MASLD) is a complex disease with a high degree of population and individual variability. Therefore, it is important to develop human-based preclinical models that recapitulate patient heterogeneity to fine new and personalized therapeutic strategies. Here, we aim to generate patient-derived liver biopsy organoids (b-Orgs) from MASLD patients for precision disease modelling.
Method: A portion of a liver tru-cut biopsy from patients with different stages of MASLD (n = 53) was seeded in Matrigel to generate b-Orgs. b-Orgs were characterised by immunofluorescence, functional analysis and bulk RNA sequencing. b-Orgs were stimulated with lipotoxic media to model MASLD and the response was assessed by lipidomic and RNASeq analysis and imaging. Hyperpolarised magnetic resonance (HPMR) was used for real-time metabolic assessment of b-Orgs.
Results: Our methodology allowed the successful generation of b-Orgs with a high efficiency (87%), ranging from 100% for early stages (MASLD F0) to 83% for advanced stages (MASH F3/F4). b-Orgs showed an enriched hepatocyte-like phenotype as assessed by immunofluorescence, bulk transcriptomics and functional studies. b-Orgs expressed high levels of albumin and HNF4A, but also EpCAM, SOX9, and KRT7. In addition, b-Orgs produced albumin and alpha-1-antitrypsin and contained functional bile canaliculi as stained with MRP2. b-Orgs retain disease stage characteristics, b-Orgs from advanced MASLD patients showed a tendency to lose the hepatocyte-like identity, with increased ductular reaction and epithelial-to-mesenchymal transition markers. When stimulated with a lipotoxic media, b-Orgs showed morphological changes, increased lipid accumulation and upregulated inflammatory markers. Finally, metabolic imaging of b-Orgs was assessed by HPMR after injection of hyperpolarised [1-13C]-pyruvate (PA) and downstream metabolites were examined. Real-time monitoring of PA metabolism revealed the conversion of PA to lactate via LDH in MASLD b-Orgs, indicating the potential of b-Orgs and HPMR for real-time assessment of metabolic response.
Conclusion: Overall, we have successfully developed a methodology to generate patient-derived b-Orgs from different stages of MASLD. b-Orgs allow modelling MASLD while incorporating patient characteristics and disease stage features, highlighting their potential as a tool for personalised medicine studies.

FRI-430

Hepatic estrogen receptor alpha drives liver metabolic adaptation during pregnancy

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Background and aims: Pregnancy is a unique physiological state marked by extensive metabolic adaptations, particularly in the liver, to meet the increased energy and nutrient demands of both the mother and the developing fetus. The liver dynamically adjusts glucose, lipid, and protein metabolism in response to hormonal signals, with estrogen receptor alpha (ERa) playing a key regulatory role. In the liver of female mice, ERa not only supports metabolic demands but also integrates reproductive and metabolic processes to maintain homeostasis. Disruptions in hepatic ERα regulatory network can contribute to pregnancy-related liver disorders, such as intrahepatic cholestasis of pregnancy (ICP) and acute fatty liver of pregnancy (AFLP). ICP is characterized by impaired bile acid transport and accumulation, while AFLP results from defective fatty acid oxidation, potentially leading to liver failure. Despite its pivotal role in metabolic homeostasis, the mechanisms by which hepatic ERa drives metabolic adaptations during pregnancy and its potential contribution to pregnancy-related liver diseases remain poorly understood. Unraveling how ERa coordinates liver metabolism during pregnancy could offer new insights into therapeutic strategies to prevent or mitigate these conditions. This study aims to explore the role of hepatic ERa in metabolic adaptation during pregnancy and its potential involvement in the pathogenesis of pregnancy-related liver disorders.
Method: To evaluate the relevance of hepatic ERa in metabolic adaptation during pregnancy, we compared liver-specific ERa-knockout (LERKO) and control (CTRL) female mice at gestational days 6.5, 14.5, and 17.5. Virgin females at the proestrus phase (when circulating 17β-estradiol levels are highest) were used as the reference group.
Results: Pregnancy induced significant changes in the hepatic transcriptome, with the most pronounced alterations occurring at mid-pregnancy compared to virgin controls. Each gestational timepoint exhibited distinct transcriptomic patterns, especially enriched in genes involved in lipid, bile acid, and steroid metabolism, as well as hepatokine signaling. Although pregnancy rates were comparable between LERKO and control females, LERKO mice displayed altered

gene expression patterns, indicating that hepatic ERa is essential to fully optimize liver metabolic adaptations during pregnancy.
Conclusion: Hepatic ERa is crucial for orchestrating metabolic adaptations across different stages of pregnancy, likely supporting the energy demands of the developing fetus. These findings suggest that dysregulated hepatic ERa signaling may contribute to an increased risk of pregnancy-related liver disorders, including ICP, AFLP, and metabolic dysfunction-associated steatotic liver disease (MASLD). Targeting ERa could offer a novel approach to preventing or mitigating these conditions.

FRI-431
A novel GLP-1/GDF15 dual-agonist reduces hepatic inflammation and fibrosis in murine models of chemical-induced liver fibrosis and metabolic associated steatohepatitis (MASH)
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Background and aims: QL1005, a glucagon-like-protein-1/growth differentiation factor 15 (GLP-1/GDF15) dual-agonist, shows significant effects in reducing body weight and metabolic disorders in human and animal models with low-toxicity. This study aimed to explore the effects of QL1005 against hepatic fibrosis.
Method: The chemical-induced liver fibrosis model was established in male mice by intraperitoneal injections of 10% CCl4 for 7 weeks. The MASH model was created by feeding mice a Western diet supplemented with fructose (WDF) for 26 weeks. During the last 3 or 6 weeks, mice received daily subcutaneous injections of QL1005, GLP-1 (QL1005 with inactive GDF15), GDF15 (QL1005 with inactive GLP-1), or Vehicle at a dose of 30 nmol/kg. At the end of the experiments, plasma and liver samples were collected for analysis.
Results: During both hepatic injury and resolution phases (24 and 72 hours after last injection, respectively), QL1005 and GLP-1 significantly reduced ALT and AST levels compared to Vehicle, while GDF15 showed no effect. QL1005 uniquely lowered TNF-α and MCP-1 levels in both phases. No significant anti-fibrotic effects were observed during the injury phase for QL1005 or the mono-agonists. In the resolution phase, QL1005 reduced tissue injury and fibrosis, as shown by Sirius Red staining, with a 38.2% decrease in α-SMA-positive regions and downregulation of α-SMA, type 1, and type 3 collagen mRNA levels. RNAseq analysis revealed decreased expression of genes related to fibrosis, inflammation, apoptosis, and oxidative stress. In the MASH model, treatment with all three agonists significantly reduced weight gain and liver size. Liver enzymes, fasting blood glucose, triglycerides, and cholesterol levels were also notably improved, with QL1005 showing the greatest effect. QL1005 significantly reduced the hepatic expression of a-SMA and COL1a1 as confirmed by immunohistochemistry and pro-inflammatory cytokines including IL-6, TNFα and IL-1, as confirmed by qPCR. In HSC of scRNA-seq analysis, KEGG enrichment analysis revealed that QL1005 may influence apoptosis、oxidative phosphorylation、fatty acid metabolism and interferon-α response pathways. In QL1005-treated mice, macrophage counts were significantly reduced, accompanied by downregulation of TGF-β and p53-related pathways.
Conclusion: GLP-1/GDF15 dual-agonist showed a synergistic effect in reducing hepatic inflammation and fibrosis was observed in chemical-induced fibrosis and MASH models, highlighting its potential as a therapeutic candidate for treating liver fibrosis.

FRI-432
Role of TOX3 in regulating the progression of metabolic dysfunction-associated steatotic liver disease
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most common cause of chronic liver disease globally, affecting over 30% of adults. Thymocyte selection-associated high mobility group box factor 3 (TOX3) is a member of an evolutionarily conserved DNA-binding protein family. Our previous study found that TOX3 could promote the progression of hepatocellular carcinoma (HCC) through the PPAR signaling pathway. However, the role and mechanism of TOX3 in MASLD have not yet been elucidated.
Method: The expression of TOX3 was detected in patients with chronic liver diseases and several murine models of MASLD induced by methionine-choline deficiency (MCD) diet, western diet (WD) and carbon tetrachloride (CCl_4) injection. The role of TOX3 was evaluated in heterozygous Tox3 gene knockout (*Tox3*$^{+/-}$) mice and hepatocyte-specific Tox3 knockout (*Tox3*^{Hep}) mice in vivo. Direct effects of TOX3 on hepatocytes (AML12 and THLE-2) and hepatic stellate cells (HSCs) (LX-2) were studied in vitro. Single-cell sequencing was used to explore the molecular mechanism of TOX3 regulation of MASLD progression.
Results: In this study, we found that TOX3 was highly expressed in fibrotic/cirrhotic tissues from patients with multiple etiologies and in mice treated with MCD diet, WD or CCl_4 injection. PSMP deficiency resulted in a marked amelioration of hepatic injury and steatosis in mouse models of MASLD. At the same time, the secretion of various proinflammatory cytokines in the serum and tissue of *Tox3*$^{+/-}$ and *Tox3*^{Hep} mice was also significantly reduced. *In vitro*, we found that the overexpression of TOX3 could directly promote the activation and survival of human LX-2 cells, while knockdown of TOX3 inhibits the activation and survival of LX-2 cells.
Conclusion: Taken together, TOX3 promotes hepatic injury and steatosis by activating the HSCs. The results are expected to clarify the role and mechanism of TOX3 in the liver immune microenvironment for the first time and indicate that TOX3 may be a potential therapeutic target for the treatment of MASLD.

FRI-433
Beneficial effects of milk-derived extracellular vesicles on liver fibrosis progression by restoring intestinal barrier integrity
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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD) has emerged as the most prevalent chronic liver disease, leading to metabolic dysfunction associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma (HCC). However, no treatment for MASH-related fibrosis is available for clinical use. Extracellular vehicles (EVs) are bilayer membrane vesicles released from various cells into the extracellular space, participating in multiple life processes. Recent studies have indicated that bovine milk-derived EVs (B-mEVs) suppress inflammation, have anti-tumor effects, and protect the intestinal barrier in an in vivo model. Whether EVs from bovine milk exert a beneficial effect against MASH is worth investigating. We explored the effect of B-mEVs on MASH-related liver fibrosis by modulating the gut barrier function.
Method: MASH-related liver fibrosis was induced in female C57BL/6J mice by feeding them a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) for eight weeks. B-mEVs (1.2 mg/kg) were orally administered every two days for four weeks. Seven-week-old female C57BL/6J mice were randomly divided into four groups and treated for 12 weeks as follows, n = 5 for each; i) normal chow with vehicle; ii) normal chow with B-mEVs; iii) CDAHFD diet with vehicle; iv) CDAHFD diet with B-mEVs. The mice were then sacrificed for histological analyses to assess the effect of B-mEVs on steatohepatitis

and fibrosis. Intestinal barrier integrity was also evaluated by the intestinal permeability using FITC-dextran and immunohistochemistry of tight junction proteins (TJPs). The effect of B-mEVs on the Caco-2 cell line barrier function was similarly evaluated in vitro using the permeability assay.
Results: B-mEVs significantly suppressed macrophage expansion, proinflammatory responses, and liver fibrosis in CDAHFD-fed mice by blocking hepatic translocation of lipopolysaccharide (LPS) and activating toll-like receptor (TLR) 4 signaling. Moreover, B-mEVs improved intestinal permeability by restoring TJPs like ZO-1, Occludin, and Claudin-2. B-mEVs also directly suppressed LPS-induced barrier dysfunction and TJP depletion in Caco-2 cells.
Conclusion: B-mEVs reduced MASH-related fibrosis by inhibiting lipid accumulation and macrophage expansion and suppressing LPS/TLR4/NF-κB-mediated inflammatory responses by restoring intestinal barrier function.

FRI-434
Investigating the pharmacological potential of a new investigational drug- AD64 for treating metabolic dysfunction-associated steatohepatitis induced by a hepatopathogenic diet in rats
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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disorder marked by inflammation, fibrosis, and metabolic irregularities. Globally, metabolic dysfunction-associated liver disease (MASLD) affects approximately 32.4% of the population, with MASH impacting 3%–5%. This study investigates the therapeutic efficacy of AD64, a xanthine derivative, in a rat model of MASH induced by a high-fat/high-fructose (HF/HFr) diet.
Method: MASH was induced in Wistar rats (n = 6/group) through a 12-week diet consisting of 60% kcal from fat and supplemented with fructose. Rats were subsequently treated with AD64 at doses of 41.3, 82.6, or 124 mg/kg body weight for 12 weeks. Key outcomes included liver histopathology, body weight, serum liver enzymes (ALT, AST), abdominal ultrasonography (USG), lipid profiles, hydroxyproline content, and oxidative stress markers.
Results: MASH development in HF/HFr-fed rats was characterized by increased liver steatosis, inflammation, and hepatocyte ballooning. AD64 treatment resulted in significant improvements, with all dose groups achieving a ≥3-point reduction in NAS scores. At the highest dose, body weight decreased by 30%, AST levels by 40%, and ALT levels by 35%. USG findings indicated a reversal of stage III steatosis to near-normal levels. Lipid profile improvements included a 67% reduction in triglycerides. AD64 also reduced hydroxyproline content, indicating antifibrotic activity, and enhanced glutathione levels while suppressing reactive oxygen species, mitigating oxidative stress. A linear dose-response relationship was observed, further supporting AD64's efficacy.
Conclusion: AD64 demonstrated significant efficacy in alleviating MASH by improving liver histopathology, enzyme levels, ultrasonographic findings, lipid profiles, and oxidative stress markers while reducing inflammation and fibrosis progression. These findings position AD64 as a promising therapeutic agent for MASH, likely mediated through adenosinergic receptor modulation and PDE inhibition.

FRI-435
Increased nuclear localization of small heterodimer partner despite incresed serum BA profile in patients with metabolic dysfunction-associated steatohepatitis
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Background and aims: Elevated serum bile acid (BA) levels have been documented in individuals with metabolic-dysfunction steatohepatitis (MASH), yet the underlying pathogenesis remains elusive. The nuclear factor small heterodimer partner (SHP) serves as a critical regulator in maintaining BA homeostasis. In this study, we investigated the associations of hepatic subcellular distribution of SHP and BA dysregulation in MASH patients.
Method: Hepatic tissues and serum samples were collected from MASH patients and healthy participants. Subcellular distribution of hepatic SHP protein was investigated by immunofluorescence staining. Serum BA levels were measured by liquid chromatography–mass spectrometry (LC-MS/MS) and tissue mRNA of BA-related genes were determined through quantitative reverse transcription-PCR (RT-PCR). Results were correlated to hepatic SHP subcellular distribution.
Results: We enrolled 68 patients with biopsy-proven MASH and 10 healthy participants. Patients with MASH exhibited elevated serum primary and conjugated BAs while having similar serum secondary BAs compared to healthy participants. Patients with MASH also demonstrated a markedly increased hepatic cytochrome P450 family 7 subfamily A member 1 (CYP7A1) mRNA and genes related to BA conjugation and transporters. Immunofluorescent staining revealed a marked increase in hepatocellular SHP nuclear ratio in patients with MASH (nuclear ratio of SHP in patients with MASH vs. control participants: 50.36% vs. 1.55%, $p < 0.001$), which is correlated with serum hepatitis markers, tissue NF-κB signaling intensity, and degree of hepatic steatosis, but not with serum BAs or BA-related genes.
Conclusion: Increased SHP nuclear localization represents a distinct characteristic of MASH liver that is linked to hepatic inflammation and steatosis. In patients with MASH, SHP may have deficiency in its canonical role to suppress BA synthesis.

FRI-436
Inhibition of hepatic bile salt uptake using the anti-HDV drug Bulevirtide attenuates inflammation in mouse models for colitis and diet-induced steatohepatitis
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Background and aims: Although activation of the bile salt receptor Takeda G protein-coupled receptor 5 (TGR5) leads to reduced pro-inflammatory cytokine production in macrophages and attenuated

inflammation in mice, synthetic agonists of TGR5 did not reach clinical application. Instead, we aimed to exploit systemic bile salt signaling by using Bulevirtide, a clinically applied inhibitor of the main hepatic uptake transporter of bile salts-Na^+ Taurocholate Co-transporting Polypeptide (NTCP). We investigated if NTCP inhibition could attenuate intestinal and hepatic inflammation and the role of TGR5 and the nuclear receptor FXR in bile salt-immunosuppressive effects.

Method: Mice that lack the Organic Anion Transporting Polypeptide (OATP)1a/1b gene cluster were used to mimic human (NTCP-centered) hepatic bile salt dynamics. Acute inflammation and colitis were induced using lipopolysaccharide (LPS) and dextran sodium sulfate (DSS), respectively, and metabolic dysfunction-associated steatohepatitis (MASH) was induced by a high-fat-high-cholesterol diet and fructose water. Mice were treated with vehicle or Bulevirtide once (LPS), 5-days (DSS) or 6 weeks (MASH). Additionally, bone marrow-derived macrophages (BMDM) from wild-type (WT), $TGR5^{-/-}$, and $FXR^{-/-}$ mice were stimulated with LPS and treated with taurochenodeoxycholic acid (TCDCA) *in vitro*.

Results: Bulevirtide increased plasma bile salt levels ~10-fold in all mouse models. In LPS-treated mice, Bulevirtide reduced plasma levels of the inflammatory cytokine TNFα and increased the anti-inflammatory cytokine IL10 increased, both 2-fold. In the colitis model, Bulevirtide prevented body weight loss, attenuated intestinal damage, and reduced intestinal gene expression of inflammatory cytokines TNFα, IL1β and IFNγ 2–3 fold. In the MASH model, Bulevirtide lowered liver weight, tended to reduce histological signs of steatosis and lobular inflammation, lowered abundance of $CD45^+$ $CD11b^+$ monocytes in plasma and liver and caused a shift towards a less inflammatory ($Ly6C^{high}TREML4^{low}$) and more regulatory ($Ly6C^{low}TREML4^{high}$) profile. In LPS-stimulated WT BMDM, TCDCA administration reduced TNFα and IL1β secretion. This effect was preserved in $TGR5^{-/-}$ and $FXR^{-/-}$ BMDM.

Conclusion: NTCP inhibition reduces intestinal inflammation and steatohepatitis, suggesting novel clinical applications of Bulevirtide and NTCP targeting small molecules. Interestingly, the effects of bile salts on BMDM *in vitro* were independent of TGR5 and FXR, suggesting the involvement of additional bile salt receptors underlying the beneficial effects of NTCP inhibition.

FRI-437

Liver sinusoidal endothelial cells affect lipid metabolism in hepatocytes and form lipid droplets under steatotic conditions

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Background and aims: Increasing evidence emphasizes the regulatory effect of liver sinusoidal endothelial cells (LSECs) in metabolic dysfunction-associated steatotic liver disease (MASLD). Dysfunctional LSECs aggravate MASLD progression, already from the stage of early stage of isolated steatosis. We aimed to characterize the role of LSECs in regulating lipid metabolism in hepatocytes under steatotic conditions by deploying a co-culture of lipid-laden human hepatocytes (HepG2) and immortalized LSECs (HLEC), using human aortic endothelial cells (HAECs) as control.

Method: HepG2 cells were cultured in 12-well-plates, HLECs and HAECs were in separate transwell inserts. HepG2 were treated with a mixture of fatty acids (250 µM oleic acid and 125 µM palmitate acid, OA/PA) or BSA for 24 hours, with or without the transwells of HLECs/HAECs above, creating a setting to study paracrine effects and mimicking the space of Disse. The intracellular lipid droplets in both hepatocytes and endothelial cells were stained and measured, and mRNA expression was studied.

Results: Upon OA/PA loading, co-culturing with HLECs resulted in smaller lipid droplets in HepG2 cells and 68% reduced intracellular triglyceride content. In HepG2 treated with OA/PA, lipogenic mRNA expression was inhibited upon co-incubation with HLECs but not with HAECs, including those encoding fatty acid synthase (*Fasn*), acetyl-CoA carboxylase alpha (*Acaca*), and sterol regulatory element-binding protein 1 (*Srebp1*). The mRNA expression of the genes encoding carnitine palmitoyl transferase 1A (*Cpt1a*) involved in fatty acid oxidation as well as the lipid transporter CD36 was down-regulated upon co-culture with HLECs but not with HAECs. Of interest, *Cd36* mRNA expression was upregulated in HLECs but was reduced in HAECs when co-cultured with HepG2 cells. In line, co-culturing with HepG2 cells resulted in more lipid droplets in the HLECs.

Conclusion: Co-culturing of hepatocytes with LSECs resulted in a less severe steatotic phenotype of the former cells, a feature that's absent in the presence of HAECs. These data strongly suggest that LSECs have a protective effects on hepatocytes via a paracrine factor. Future research aims to explore this paracrine LSEC-hepatocyte axis.

FRI-438

Identification of differences in therapeutic mechanisms between Resmetirom and Semaglutide on metabolic dysfunction-associated steatohepatitis treatment in western diet-fed melanocortin 4 receptor knockout mice

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with metabolic abnormalities such as obesity and insulin resistance, and MASLD develops into metabolic dysfunction-associated steatohepatitis (MASH). Recently, Resmetirom, a thyroid hormone receptor (THR)-beta agonist, was approved for first MASH therapeutic drug. There are some reports of Resmetirom using diet-induced obese (DIO) mice. However, DIO mice models show only mild liver fibrosis and do not fully reflect human MASH pathology. Melanocortin 4 receptor (MC4R) expressed in hypothalamus regulates appetite and energy expenditure and MC4R KO mice gain appetite and body weight. Western diet (WD)-fed MC4R KO mice show multiple aspects of pathophysiology of MASH patients such as liver injury, steatosis, and fibrosis. Therefore, WD-fed MC4R KO mice are an attractive MASH model with significant fibrosis as compared with DIO mice model. For treatment of MASH, recently, it was reported that Gulcagon-like peptide-1 (GLP-1) analogue, Semaglutide, also has ameliorative effects on MASH. In this study, we confirmed and compared anti-MASH effects of Resmetirom and Semaglutide respectively using this mouse.

Method: To induce disease conditions, MC4R KO mice were fed with WD for 6 weeks before treatment. Resmetirom (5 mg/kg) was orally administered and Semaglutide (0.1 mg/kg) was subcutaneously injected daily for 7 weeks. Energy expenditure was analyzed after 6 weeks treatment. On the 7 weeks of treatment, body composition was measured using Magnetic Resonance Imaging. Then, mice were anesthetized and then blood was collected, and the liver was harvested. Plasma and liver were used for biochemical and pathological analyses.

Results: WD-fed MC4R KO mice showed increase in liver weight, plasma AST and ALT. Both Resmetirom and Semagluride treatments significantly improved these parameters. LDL-cholesterol in plasma was also increased in this model, however only Resmetirom lowered the level of LDL-cholesterol in accordance with the mechanism of THR-beta. Although Resmetirom and Semagluride ameliorated liver

fibrosis and fat mass, Semaglutide significantly suppressed lean mass. Moreover, regarding energy expenditure, Resmetirom enhanced oxygen consumption but Semaglutide reduced energy expenditure. The results of gene expressions and pathological analysis are also explained in this conference.
Conclusion: These results revealed that the different mechanisms of anti-MASH effects between Resmetirom and Semaglutide. Similar to clinical evidence, Semaglutide treatment might have a problem on muscle mass reduction by food intake suppression. This study provides the first evaluation to compare Resmetirom and Semaglutide simultaneously on MASH phenotypes and revealed their mechanism of action using WD-fed MC4R KO mice.

FRI-439

Shallow-deep neural networks reveal extracellular vesicles as robust biomarkers for liver steatosis stages S0 vs. S1-S3 in metabolic dysfunction-associated steatotic liver disease patients

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Background and aims: Extracellular vesicles (EV) have emerged as promising biomarkers in liver diseases. This study explores their utility in distinguishing the steatosis (S1-S3) stages in metabolic dysfunction-associated steatotic liver disease (MASLD) from non-steatosis (S0). Additionally, we evaluated the performance of a shallow-deep neural network (sDNN) architecture in leveraging EV data, showcasing its potential in handling limited sample volumes effectively.
Method: We included 74 MASLD patients with ultrasound-confirmed steatosis and at least one cardiometabolic risk factor after excluding other causes of steatosis. We performed transient elastography via the "iLivTouch" FT100 device by Wuxi Hisky Medical Technologies Co., Ltd. (Hisky Med), China by which we acquired Ultrasound Attenuation Parameter (UAP) values. Patients were categorized into S0, S1, S2 and S3 steatosis stages based on the UAP (dB/dl) thresholds, <S0 244 dB/dl, ≥S1 244 dB/dl, ≥S2 269 dB/dl, ≥S3 296 dB/dl. Plasma samples were collected and further processed for the isolation and characterization of EVs with differential centrifugation and Nanoparticle Tracking Analysis, respectively. We used data exclusively from EV characterization, with steatosis stages categorized as S0 versus S1-S3. The dataset was partitioned into training and testing subsets with 80/20%. Model performance was assessed via three-fold cross-validation (3CV), employing a custom-designed DNN architecture with shallow-deep layers to balance interpretability, feature representation and avoid over-fitting. Metrics included specificity, sensitivity, receiver operating characteristic (AUROC) area, and F1 score, averaged across CV folds.
Results: The sDNN achieved outstanding test performance: specificity of 0.6, sensitivity of 0.9, AUROC of 0.75, and an F1 score of 0.86. Cross-validation results demonstrated robustness, with mean specificity of 0.65 ± 0.16, sensitivity of 0.82 ± 0.20, AUROC of 0.73 ± 0.06, and F1 score of 0.80 ± 0.10. Notably, even with the minimal dataset size of 74 patients (59/15), the architecture effectively captured the discriminative power of EV, underscoring their relevance as biomarkers.
Conclusion: This study highlights extracellular vesicles as viable non-invasive biomarkers for staging liver steatosis. The shallow-deep architecture demonstrated excellent performance despite the limited data size, paving the way for scalable and interpretable artificial intelligent applications in biomarker-driven diagnostics.

FRI-440

The role of extracellular ATP (ATPe) in the progression of metabolic dysfunction – associated steatotic liver disease (MASLD)

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Background and aims: Extracellular ATP (eATP) is a damage-associated molecule that triggers the inflammatory response, leading to immune cell infiltration and cytokine release. ENTPD1/CD39 is an ectonucleotidase which is responsible for metabolizing ATP, decreasing circulating ATP levels, allowing a regulation of inflammation. In addition, P2RX7 is also an ATP receptor which triggers de NLRP3 inflammasome pathway, increasing the release of IL-1B. The aim of this study was to determine the role of eATP and the pathways in which it is involved in the progression of MASLD.
Method: Thirty-six male C57BL/6J mice were fed a High Fat High Carbohydrate and Cholesterol (HFHCC) diet (5TJT Test Diet) (n = 29) or chow (n = 7) for 52 weeks and thirty male C5BL/6J mice were fed a CDACHFD diet (Teklad Rodent Maintenance 2014) (n = 20) or chow (n = 10) diet for 8 weeks. *Entpd1* gene and Entpd1 and P2rx7 protein expression were assessed by PCR and IHC assays. Moreover, one-hundred three biopsy proven MASLD patients were included and classified according to SAF and NAS Score as bland steatosis (n = 42) or MASH (N = 61). Patients with at least 1 point in each parameter of SAF score and NAS Score > 4 were classified as MASH. Serum CD39 levels were measured by ELISA.
Results: In mice fed a HFHCC diet for 52 weeks 5 times higher levels of Entpd1 were observed compared to controls ($p < 0.0001$). Moreover, in mice fed with a CDAC-HFD diet, an increase of Entpd1 levels were observed (fold change of 1 ± 0.37 vs 4.3 ± 2.08; $p < 0.0001$). Entpd1 protein expression is observed around the central vein in the control group, while there is no expression around the

portal vein. However, in both HFHCC and CDACHFD diet mice, the expression presented a shift towards the portal vein, showing a heightened expression in the portal vein region and a decline in the central vein region. Regarding P2rx7 expression, there is an elevated number of positive cells per area in mice fed HFHCC diet *vs.* controls, indicating an increased expression of P2RX7 in this group (272.4 ± 79.82 *vs.* 391.8 ± 121.8; p = 0.0035). Patients with MASH (1368 ± 1094 pg/ml) had increased ENTPD1 levels compared to patients with bland steatosis (925 ± 474 pg/ml) (p = 0.006). Based on inflammation, an increase in ENTPD1 serum levels were observed as inflammation increased [none (n = 19), 879 ± 484 pg/ml; mild (n = 56), 1164 ± 757 pg/ml; moderate (n = 28), 1444 ± 1312 pg/ml; p = 0.112]. In addition, a correlation between ENTPD1 levels and SAF Score's activity was found (p = 0.03). ENTPD1 levels did not show significant differences in fibrosis [F0 (n = 22), 947 ± 563 pg/ml; F1 (n = 22), 1404 ± 1536 pg/ml; F2 (n = 17), 1263 ± 656 pg/ml; F3 (n = 33), 1227 ± 749 pg/ml; F4 (n = 9), 960 ± 490 pg/ml; p = 0.491].
Conclusion: Entpd1 mRNA and protein levels and P2rx7 protein levels were increased along with the progression of the disease, suggesting that eATP related pathways play an important role in the progression of MASLD, mainly in the transition steatosis to steatohepatitis.

FRI-445
Deep learning analysis reveals the impact of steatosis size and density on the progression of non-alcohol-related liver disease in severe obesity
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Background and aims: Over the last few decades, the worldwide prevalence of obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has grown significantly. Metabolic Dysfunction-Associated Steatohepatitis (MASH) represents the progressive form of MASLD, and suffering from it can result in a higher risk of premature death. It has been shown that steatosis has an important role in the pathogenesis of the disease. This study aims to determine the effect of steatosis percentage, size and density on the presence of MASH-associated comorbidities and liver damage, influencing the severity and progression of MASH in people with severe obesity.
Method: A cohort of 354 patients with severe obesity undergoing bariatric surgery at Hospital Universitari Sant Joan de Reus were recruited and classified based on liver biopsies into non-MASH (134), uncertain (132) and MASH (88). Blood samples were collected pre-surgery, and liver biopsies were processed for histological analysis using Haematoxylin & Eosin and Masson's Trichrome staining. Biochemical parameters were assessed using an automatic analyzer, and clinical variables were obtained from medical history. A deep learning-based method quantified steatosis in digitalized liver slides.
Results: Comparing the deep learning-based approach with pathologists' assessments, we found that pathologists tended to overestimate the severity of steatosis. Our analysis revealed that not only does the percentage of steatosis increase, but lipid droplet size and density also rise as the disease progresses. In our study of variables impacting steatosis development, we observed a link between age and increased steatosis. Factors such as male sex, structured diet schedules, hypertension, type 2 diabetes, and metabolic syndrome were also shown to play a significant role in the pathogenesis of the disease. Additionally, liver damage enzymes increased with the progression of steatosis.
Conclusion: Significant differences were found between groups regarding steatosis percentage, size, and density. Moreover, sex, age, and metabolic disorders significantly influenced the prevalence of steatosis. Altered levels of liver enzymes were also observed with the progression of the disease. Our findings highlight the complex interplay between metabolic dysfunction, hepatic steatosis, and the progression of MASLD to MASH in individuals with severe obesity.

FRI-446
Metabolomic profiling reveals early biomarkers of gestational diabetes mellitus with MASLD as a mediator
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Background and aims: This study aims to identify early metabolomic biomarkers of gestational diabetes mellitus (GDM) and evaluate their association with hepatic steatosis.
Method: We compared maternal serum metabolomic profiles between women who developed GDM (n = 118) and matched controls (n = 118) during the first (10~14 gestational weeks) and second (24~28 gestational weeks) trimesters using ultra-performance liquid chromatography coupled with mass spectrometry. Mediation analysis was performed to evaluate the mediating role of metabolic dysfunction-associated steatotic liver disease (MASLD) in the relationship between metabolites and subsequent development of GDM. A refined prediction model was developed to predict GDM using established clinical factors and selected metabolites.
Results: Significant alterations in circulating metabolites, including amino acids, bile acids, and phospholipids, were observed in the GDM group compared to controls during early pregnancy. Mediation analysis revealed that several metabolites, including glycocholic acid (proportion mediated (PM) = 31.9%), butanoyl carnitine (PM = 25.7%), and uric acid (PM = 22.4%), had significant indirect effects on GDM incidence mediated by hepatic steatosis. The refined prediction model composed of clinical factors and selected metabolites in the first trimester demonstrated higher performance in predicting GDM development than the established prediction model composed solely of clinical factors (AUC, 0.85 vs. 0.63, p < 0.001).
Conclusion: Women who developed GDM exhibited altered metabolomic profiles from early pregnancy, which showed a significant correlation with GDM, with MASLD as a mediator. Selected metabolomic biomarkers may serve as predictive markers and potential targets for early risk assessment and intervention in GDM.

FRI-447
Preclinical studies of a novel hydrolysis-based prodrug for treating metabolic dysfunction associated steatohepatitis
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Background and aims: Approval of resmetirom for treating Metabolic dysfunction associated steatohepatitis validated thyroid hormone receptor beta (THR-b) as an effective therapeutic target. VK-2809, another THR-b-targeting drug, showed significant reductions in cholesterol, liver fat and fibrosis in a phase II study. It is a prodrug relying on cytochromes P450 (CYP) for bioactivation to its active metabolite (MB07344) in the liver. We designed and synthesized novel prodrugs based on MB07344 but using fast hydrolysis by esterases for bioactivation and avoiding CYP related issues.
Method: Our prodrugs were tested in a HepG2 assay for *in vitro* activity and evaluated in rats and dogs for pharmacokinetics (PK) and distribution. CG-025016 was selected for efficacy testing in a hypercholesterolemia rat model, fed with either a normal diet (11% kcal fat, lean control) or a 60% high-fat diet (HFD) for 2 weeks prior to dosing. Serum cholesterol levels (total cholesterol, TC and LDL-cholesterol, LDL-C) were measured at baseline and 24 h post-dose.
Results: CG-025013 and CG-025016 showed EC50 of 39.3 and 44.5 nM, respectively, in HepG2 vs 662 nM for VK-2809. For oral PK

study in rats, both CG-025013 and CG-025016 at 1 mg/kg dose were barely detectable (Cmax <1 nM) in the plasma, liver, and heart. In contrast, VK-2809 at same dose was found at a much higher concentration with Cmax around ~100 nM in the same tissues. For the active metabolite, the Cmax was much higher in the liver for CG-025013 and CG-025016: 5,000 and 3,335 nM, respectively, vs 464 nM for VK-2809. Area under the curve (AUC) values were similarly differentiated. Similar results were observed in dogs. Rats on HFD treated with 1.5 mg/kg CG-025016 led to significantly greater declines in plasma TC (87.1%) and LDL-C (69.5%), compared to declines in plasma TC (21.3%) and LDL-C (16.6%) with resmetiron treatment at same dose. At 0.3 mg/kg, CG-025016 resulted in slightly higher reductions compared with VK-2809 at same dose in plasma TC (55.0% vs 45.9%, respectively) and LDL-C (52.0% vs 47.4%, respectively). The dose-dependent reductions were also observed for CG-025016. CG-025016 was safe and well tolerated in 7-day rat safety study.

Conclusion: Our prodrugs showed a ~15-fold *in vitro* activity increase over VK-2809 in HepG2 assay. *In vivo* PK studies showed that they were barely detectable while the active metabolite was preferentially concentrated in the liver compared to VK-2809. The ratio of the active metabolite AUC between liver and heart was 116 (CG-025013), 158 (CG-025016) vs 63 (VK-2809). These findings suggest that our novel prodrugs based on esterase hydrolysis can indeed enrich the active metabolite more efficiently in the liver, resulting in higher potency while reducing the exposure outside the liver. *In vivo* efficacy in rats was also observed. Overall, CG-025016 is a highly potent THR-b agonist with an excellent PK and safety profile, making it a promising clinical candidate to address the limitations of current treatment options.

FRI-448

Genipin 1-β-D-gentiobioside alleviates MASH by inhibiting hepatocyte PP2A enzymatic activity

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Background and aims: Genipin 1-β-D-gentiobioside (GG) is one of the important natural components from the herb Gardenia jasminoides. The aim of this study is to explore the potential therapeutic targets of GG against metabolic-associated steatohepatitis (MASH) and elucidate its potential pharmacological mechanism.

Method: In this study, two MASH mouse models induced by high trans-fatty acid and high-sugar diet (HFHC) and methionine/choline deficient diet (MCD) and the rat model induced by high-fat diet (HFD) were used to investigate the anti-MASH effect of GG. Concurrently, we used an FFAs (Free Fatty Acids)-induced THLE2 cell model for in vitro observations. The potential GG-binding proteins were screened by HuProt protein chip and pull-down mass spectrometry. Surface Plasmon Resonance (SPR), Drug Affinity Responsive Target Stability (DARTS), and Cell-based Thermal Shift Assay (CETSA) techniques were used to verify the interaction between GG and the target protein. Phosphorylated protein chip technology was used to screen the downstream substrates of the binding protein. Ultimately, both in vivo and in vitro models of liver-specific gene editing were used to ascertain the mechanism of effect of GG against MASH.

Results: We demonstrated that GG significantly reduced hepatic lipid accumulation, inflammation, and early liver fibrosis in the MASH models. GG could substantially reverse lipid deposition under metabolic stress in FFAs-induced cells models. Importantly, the combined analysis results suggested that Protein phosphatase 2 (PP2A) was the direct binding proteins of GG, which was strongly verified by SPR (KD = 7.99E-06 mol/L). Interestingly, we further observed in liver tissues and hepatocytes that GG did not alter PP2A expression but significantly inhibited PP2A enzyme activity that was significantly elevated under metabolic stress. The phosphoprotein screening results showed that ACC1, the key enzyme regulating de novo lipid synthesis, was the most likely downstream substrate of PP2A, and CO-IP experiments confirmed that the two could interact. With the decrease of PP2A enzyme activity after GG intervention, the phosphate level of ACC1 was significantly increased. Hepatocyte-specific gene deletion of PP2A in vitro and in vivo blunted the therapeutic effect of GG in the MASH model.

Conclusion: Our study clearly showed that GG could inhibit de novo lipogenesis and improve MASH liver lipid deposition by targeting hepatocyte PP2A and then up-regulating ACC1 phosphorylation, which provided evidence for the clinical practice of natural active ingredients in MASH field.

FRI-449

Caffeine ameliorates metabolic-associated steatohepatitis by rescuing hepatic Dusp9

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Background and aims: Caffeine (CAFF) is abundant in black coffee and is known for its antioxidant properties. As one of the most widely consumed beverages globally, coffee has been the focus of increasing clinical and basic research, particularly regarding its benefits in alleviating metabolic dysfunction-associated steatotic liver disease (MASLD). However, the therapeutic effects of CAFF on metabolic-associated steatohepatitis (MASH) and the underlying mechanisms remain unclear. The objective of this research is to investigate the targets of CAFF against MASH and to clarify the mechanisms involved.

Method: Utilizing a high trans-fatty acid and high-sugar diet to induce MASH in mice, along with high-fat combined carbon tetrachloride injections to establish MASH models, we observed the effects of CAFF on pharmacodynamic indicators. Concurrently, we used an FFAs (Free Fatty Acids)-induced THLE2 cell model for in vitro observations. Subsequently, we conducted combined transcriptomic analysis of the liver samples from the mice with GEO (Gene Expression Omnibus) database to screen potential targets of CAFF. Following this, we validated the potential binding targets using SPR (Surface Plasmon Resonance), DARTS (Drug Affinity Responsive Target Stability), and CETSA (Cell-based Thermal Shift Assay). Finally, we utilized liver-specific gene-edited mouse models and gene-edited cell models to observe whether CAFF intervention leads to changes in MASH phenotype and pharmacological mechanisms.

Results: In this study, we demonstrated that CAFF significantly reduced hepatic lipid accumulation, inflammation, and early-stage liver fibrosis in MASH mice induced by HFHC diets and HFD combined with CCl_4 injections. Through sequencing analysis and drug target screening validation, we identified dual-specificity phosphatase 9 (Dusp9) as a key therapeutic target directly bound by CAFF (KD = 1.860E-4 mol/L), which was diminished by HFHC but restored with CAFF treatment. Furthermore, CAFF inactivated the ASK1-p38/JNK, a downstream signaling pathway of Dusp9, which regulates inflammation and apoptosis. In vivo and in vitro

knockdown of Dusp9 exacerbated glycolipid metabolism disorders and unexpectedly diminished the systemic therapeutic effects of CAFF in the MASH model.
Conclusion: Our study highlights the multi-faceted benefits of CAFF in treating MASH by rescuing hepatic Dusp9 expression, thereby reversing glycolipid metabolism disorders, liver inflammation, and fibrosis. These findings provide foundational evidence supporting the clinical and daily use of CAFF and black coffee in MASH patients.

FRI-450
ALG-055009, a potent and selective thyroid hormone receptor beta agonist for the treatment of metabolic dysfunction-associated steatohepatitis, induces pro-metabolic and anti-fibrotic gene expression in the liver of diet-induced obese mice
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) encompasses a heterogenous series of disorders ranging from fatty liver to more severe metabolic dysfunction-associated steatohepatitis (MASH). Thyroid hormone receptor beta (THRbeta) is a clinically validated target for the treatment of MASH, with THRbeta agonists able to selectively reduce fat deposits in the liver and potentially prevent the downstream consequences of MASLD (inflammation, fibrosis, hepatocellular carcinoma). ALG-055009 is a THRbeta agonist that has demonstrated significant reductions in liver fat (placebo-adjusted median relative reductions up to 46.2%) and atherogenic lipids in patients with presumed MASH and stage 1–3 liver fibrosis. Here, we present the effects of ALG-055009 in a diet-induced obese (DIO) mouse efficacy model and primary human liver cells.
Method: C57BL/6J mice were fed with a high fat diet (HFD) for 14 weeks, followed by drug treatment for 4 weeks. ALG-055009 treatment groups included two QD doses of 0.5 and 1.5 mg/kg/day, and four BID doses ranging from 0.075 to 0.35 mg/kg/dose. Pharmacodynamic endpoints included serum lipids and liver gene expression monitored by RT-qPCR. Primary liver cells were used to study in vitro gene expression changes associated with ALG-055009.
Results: We previously reported significant, dose-dependent reductions in serum lipid levels in parallel with significant increases in *Dio1* liver gene expression in DIO mice after treatment with ALG-055009. Newly generated data further elucidate the compound's mechanism of action. ALG-055009 significantly upregulated *Fgf21* expression in the liver of DIO mice (2.8- to 10.3-fold), while significantly downregulating liver *Dio3* expression (0.4- to 0.1-fold). Concurrently, liver expression of pro-fibrotic gene markers, *Enpp2* and *Lgals1*, significantly decreased (0.7- to 0.4-fold and 0.6- to 0.2-fold, respectively) in response to ALG-055009 treatment in a dose-dependent manner.
Conclusion: Preclinical and clinical data demonstrate that ALG-055009 is positioned as a potential best-in-class THRbeta agonist for the treatment of MASH. Here, we offer new evidence for the compound's mechanism of action. The resulting increased Fgf21 expression, another emerging therapeutic target for MASH, suggests improved lipid metabolism and insulin sensitivity from treatment with ALG-055009. Dio1 encodes a selenoenzyme that supports the production of active thyroid hormone (TH) and the clearance of inactive TH, while Dio3 inactivates TH. We hypothesize that by decreasing Dio3 together with upregulation of Dio1, ALG-055009 may increase local availability and activity of TH, leading to reduced hepatosteatosis and curbed MASH progression. Additionally, treatment with ALG-055009 downregulated the expression of known pro-fibrotic/cancer prognostic gene markers in the liver.

FRI-451
Comparative analysis of NAD+ boosters reveals the role of liver-nerve axis in metabolic health
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Background and aims: Nicotinamide adenine dinucleotide (NAD+) is an essential metabolite for cellular redox reactions and a substrate for several classes of non-redox enzymes, regulating metabolism, DNA repair and nerve degeneration. NAD+ levels decline in a range of metabolic diseases and upon aging. Enhancing NAD+ improves metabolic health. Despite considerable interest in boosting NAD+ levels for health, the mechanistic understanding of its metabolic benefits remains incomplete, particularly in relation to its consumption by enzymes such as poly(ADP-ribose) polymerases (PARPs) and the NAD+ hydrolase, SARM1. In a diet-induced mouse model of metabolic dysfunction-associated steatohepatitis (MASH), we compared the metabolic benefits of inhibiting PARP and SARM1 to the benchmark treatment of supplementing the NAD+ precursor nicotinamide riboside (NR).
Method: C57BL/6J mice were fed a western-style diet (WD) or chow at thermoneutrality (30°C) for 23 weeks with therapeutic treatment of NR (500 mg/kg/day), SARM1i (60 mg/kg/day), or olaparib (50 mg/kg/day) during the final 14 weeks. Body weight, composition, energy expenditure, and plasma factors were measured using EcoMRI, Promethion, and Luminex. Hepatic fibrosis and inflammation were analyzed histologically. Gene expression and metabolites was measured by RNA sequencing and mass spectrometry.
Results: SARM1 inhibition increased energy expenditure and reduced liver inflammation similarly to NR, but more effectively decreased liver steatosis and obesity, mitigated liver damage, and improved insulin sensitivity. In contrast, PARP inhibition showed less improvement compared to NR and SARM1 inhibition. Bulk liver transcriptome changes reflected these physiological improvements, with both NR and SARM1 inhibition strongly reversing pathological gene expression patterns. Liver metabolomics revealed that while NAD+ levels were similarly elevated across different treatments, glycolysis and TCA cycle metabolites were differentially enhanced by NR and SARM1 inhibition, correlating with their distinct effects on insulin sensitivity.
Conclusion: These findings suggest that increasing NAD+ levels through SARM1 inhibition alone can lead to comparable or greater metabolic benefits than NR, highlighting the importance of preserving nerve health for these effects. Furthermore, NR supplementation in vitro protects against nerve degeneration. Thus, preserving nerve health, including the function of the hepatic sympathetic nervous system, which is impaired in MASH, is central to the metabolic benefits of NAD+ elevation. SARM1 inhibition, therefore, offers a very targeted therapeutic approach for managing metabolic diseases.

FRI-452
Bispecific small interfering RNA targeting YAP1/WWTR1 reduces low-density lipoprotein-cholesterol via proprotein convertase subtilisin/kexin type 9 transcriptional regulation in metabolic dysfunction-associated steatotic liver diseases
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the leading cause of chronic liver

disease worldwide. MASLD affects not only liver-related mortality but also cardiovascular disease (CVD). It is known that YAP (Yes-associated protein, encoded by *YAP1*) and TAZ (transcriptional coactivator with PDZ-binding motif, encoded by *WWTR1*) contribute to MASLD via various transcriptional factors. However, the therapeutic potential of YAP/TAZ inhibition for MASLD-associated metabolic disorders and CVD remains unclear due to the lack of approved agents. We established bispecific small interfering RNA (bsiRNA) targeting *YAP1* and *WWTR1*, causing selective RNA interference. This study aimed to explore the therapeutic potential of *YAP1*/*WWTR1* silencing on MASLD-related dyslipidemia and clarify the mode of action in mice.

Method: Negative control siRNA (siNC), siRNA targeting *Yap1* (siY) or *Wwtr1* (siW), and bsiRNA targeting *Yap1*/*Wwtr1* (bsiYW) were chemically modified and encapsulated in lipid nanoparticles (LNP). Each formulation and vehicle were administered to mice fed a choline-deficient L-amino-acid-defined high-fat diet (CDAHFD). RNA sequencing (RNA-seq) and assay for transposase-accessible chromatin sequencing (ATAC-seq) were performed. Each formulation was also administered to mice fed with or without CDAHFD and ob/ob mice fed with or without the Gubra-Amylin (GAN) diet. Gene expressions and biochemistry were evaluated. In vitro studies involved transfecting AML12 cells with siNC, siY, siW, or bsiYW, followed by gene expression analysis. Expression levels of *YAP1*/*WWTR1* and their responsive genes were explored in publicly available datasets of bulk RNA-seq from MASLD patients (GSE167523).

Results: RNA-seq revealed 122 differentially expressed genes (DEGs) in the livers of bsiYW-administered mice fed a CDAHFD, compared to siNC, with *Pcsk9* identified as one of the most significant DEGs. ATAC-seq also revealed decreased chromatin accessibility of Exon1 in *Pcsk9* promoter region. Reduction of *Pcsk9* was observed in the liver of mice administered bsiYW but not siY or siW alone. Similarly, bsiYW, but not siY or siW alone, decreased *Pcsk9* in AML12 cells. The reduction of *Pcsk9* in the liver was associated with decreased plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) and low-density lipoprotein cholesterol (LDL-C) levels in mice fed with or without a CDAHFD and ob/ob mice fed with or without a GAN diet. Furthermore, a significant correlation between *YAP1* or *WWTR1* and *PCSK9* was observed, similar to other YAP/TAZ-responsive genes, *CCN1* and *CCN2*, in the MASLD cohort.

Conclusion: Dual silencing of *Yap1*/*Wwtr1* lowers plasma LDL-C levels by decreasing *Pcsk9* transcription in mice. bsiYW is a potential therapeutic agent for preventing and treating MASLD-related CVD. Blood PCSK9 levels could serve as proof of mechanism for YAP/TAZ inhibition in the liver and as a biomarker to identify responsive patients.

FRI-453

Proteomics reveals the effect of liraglutide in enhancing fatty acid metabolism and reducing fibrosis in metabolic dysfunction-associated steatotic liver disease

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Background and aims: Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved by the FDA for the treatment of obesity and type 2 diabetes, has demonstrated significant potential in improving metabolic dysfunction-associated steatotic liver disease (MASLD). As the most common chronic liver disease worldwide, MASLD is a leading cause of liver-related morbidity and mortality, with its prevalence driven by the rising rates of obesity and type 2 diabetes. Despite liraglutide's promising therapeutic effects, its precise molecular mechanisms in MASLD remain unclear. In this study, we used a high-fat diet (HFD)-induced MASLD mouse model to explore liraglutide's regulatory effects on the hepatic proteome, aiming to identify key pathways and molecules involved in its amelioration of MASLD.

Method: C57BL/6J mice were fed a HFD for three months to develop a MASLD model, with a control group maintained on a normal diet (ND). Liraglutide was administered via injection for one week in the treatment group (HFDL). Liver samples were sectioned and stained with Oil Red O to evaluate lipid accumulation. Serum biochemical parameters, including alanine aminotransferase (ALT) and total cholesterol (TC), were measured. Equal amounts of liver tissue were collected for protein extraction. After trypsin digestion, the resulting peptides were analyzed using nano-LC-MS/MS to characterize the liver proteome.

Results: Liver morphology, tissue staining, and serum indicators confirmed the MASLD mouse model's success and showed liraglutide significantly improved liver pathology. The proteomic analysis yielded significant insights into the molecular mechanisms underlying liraglutide's effects on MASLD. A total of 4,636 proteins were identified across 3 groups, with 1,799 proteins retained for quantitative analysis after filtering for accuracy. Principal component analysis (PCA) demonstrated that liraglutide partially normalized the proteome disrupted by HFD. Differentially expressed proteins (DEPs) analysis identified 161 DEPs in the HFDL group compared to the HFD group. Gene Ontology (GO) and KEGG pathway analysis indicated that liraglutide significantly regulated fatty acid degradation. Additionally, extracellular matrix-receptor interactions were notably affected. Protein-protein interaction (PPI) analysis highlighted Acaa2 and Lamc1 as key regulatory molecules, and their gene and protein expression levels were confirmed by qPCR and Western blot, validating the proteomic findings.

Conclusion: Our study demonstrated that liraglutide significantly improves MASLD by regulating specific fatty acid metabolism and extracellular matrix interactions. Acaa2 and Lamc1 were identified and validated as potential regulatory molecules. These findings provide valuable insights into liraglutide's therapeutic mechanisms and highlight its potential for treatment. These findings contribute to advancing the clinical potential of liraglutide in treating MASLD.

FRI-454

BTB and CNC homology 1 aggravates metabolic dysfunction-associated steatohepatitis by activating calreticulin

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease, and metabolic dysfunction-associated steatohepatitis (MASH) is the more severe form of MASLD. BTB and CNC homology 1 (BACH1) is associated with the progression of MASLD, but its role in the MASH process remains unclear. We aimed to explore the role of BACH1 in the MASH process.

Method: The BACH1 expression was analyzed in MASH patient livers, MASH mouse livers, and macrophages. Liver specimens confirmed pathologically as MASH were collected at the Third Affiliated Hospital of Sun Yat-sen University. 6-week-old male C57BL/6 mice were fed a choline-deficient, l-amino acid-defined, high-fat diet (CDAHFD) for 9 weeks to construct a MASH mouse model. Liver tissue sections were used for H&E staining, Oil Red O staining, and immunofluorescence staining. BACH1-plasmid or small interfering RNA targeting BACH1 was used to upregulate or downregulate BACH1 expression in macrophages. Real-time quantitative polymerase chain reaction,

Western blot, Enzyme linked immunosorbent assay, and flow cytometry were also performed.
Results: The expression of BACH1 in the livers of MASH patients and MASH mice was higher than that in the control group. Importantly, BACH1 was mainly localized in liver macrophages, and the expression of BACH1 was increased in M1 macrophages. Besides, the levels of Bach1 were positively correlated with alanine transaminase content, aspartate aminotransferase content, and nonalcoholic fatty liver disease (NAFLD) activity score. Calreticulin (CALR) was identified as the target of BACH1, and there was a binding site between BACH1 and CALR. Upregulation of BACH1 promoted the expression of CALR, while knockdown of BACH1 inhibited the expression of CALR. Upregulation of BACH1 in macrophages promoted the increased expression of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α). Upregulation of BACH1 also increased the proportion of CD86-positive cells. Moreover, knockdown of BACH1 resulted in decreased expression of IL-1β and TNF-α in macrophages, as well as a reduction in the proportion of CD86-positive cells.
Conclusion: BACH1 is upregulated during MASH. BACH1 activates CALR to promote the polarization of M1 macrophages, thereby aggravating MASH.

MASLD – Therapy

TOP-444

Lifestyle intervention with a mediterranean diet and structured exercise promotes improved liver steatosis, steatohepatitis, and fibrosis, and allows for patient stratification. EHmet+DIA study

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Background and aims: The Mediterranean diet and physical activity promote the regression of metabolic-associated steatotic liver disease (MASLD). We aimed to evaluate liver outcomes using magnetic resonance-imaging (MRI) after a lifestyle program.
Method: 96 patients with histologically confirmed MASLD were subjected to a hypocaloric Mediterranean diet and randomized to engage in structured and supervised physical activity or follow clinical practice guideline recommendations (EASL 2021) for 12 weeks, with an additional 12 weeks of follow-up. We defined response as follows: a) Steatosis if ≥30% fat infiltration by PDFF; b) Steatohepatitis if normalization of ALT or a decrease of 17 U/L along with a reduction >30% PDFF; c) Fibrosis: improvement ≥ one fibrosis stage assessed by MR elastography using published cut-off points: significant fibrosis, 3.14 kPa; advanced fibrosis, 3.53 kPa; and cirrhosis, 4.45 kPa (J Hepatol 2023); complete response: >30% PDFF reduction and regression of at least one fibrosis stage with resolution of steatohepatitis.
Results: Regression of at least one stage of fibrosis was achieved in 11/30 (36.7%) patients with fibrosis >F2. Resolution of steatohepatitis occurred in 39/89 (43.8%) and improvement of steatosis in 24/66 (36.4%). Fibrosis regression was 9/22 (40%) in patients with advanced fibrosis (F3-F4) vs 4/22 (18.18%) in F1-F2; p = 0.057. Resolution of MASH was 13/30 (43.3%) vs 24/56 (42.85%); p = 0.966, steatosis 12/23 (52.17%) vs 11/40 (27.5%); p = 0.05, and complete response 6/19 (31.5%) vs 2/43 (4.6%), p = 0.008. In univariate analysis, nut consumption was significantly higher in patients with resolution of steatohepatitis (6.8 ± 4.87 vs. 4.14 ± 4.69; p < 0.008). Improvement in steatosis was associated with increased physical activity in MET/min/week (2,499 ± 1086 vs. 1257 ± 807; p < 0.007) and lower wine consumption (0.66 ± 1.92 vs. 3.56 ± 5.52; p < 0.011). Fibrosis regression was associated with higher coffee consumption (19.4 ± 12.4 vs 29.2 ± 10.9; p < 0.049). In multivariate analysis, independent predictive variables of response were: Fibrosis regression was associated with increased coffee consumption [1.172; 95% CI: 1.002–1.370; p < 0.046]. Resolution of steatohepatitis was independently associated with age [1.195 (1.027–1.390); p < 0.021] and nut consumption [1.616 (95% CI: 1.103–2.366)]. Improvement in steatosis was associated with increased METs/min/week of physical activity: 1.001; 95% CI: 1.000–1.003; p = 0.05.
Conclusion: Intervention with the Mediterranean diet and structured physical exercise promotes the resolution of steatohepatitis, fibrosis regression, and steatosis improvement. The response is significantly higher in individuals with advanced fibrosis. It would be highly recommended to increase coffee and nut consumption, avoid alcohol consumption, and increase physical activity to improve MRI-assessed features.

TOP-457-YI

Statin, but not aspirin use, is inversely associated with steatotic liver disease and liver fibrosis: results from two large population based studies

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Background and aims: Liver disease is a growing public health concern, mainly due to the increasing prevalence of steatotic liver disease (SLD). As therapeutics targeting steatosis and fibrosis are limited, drugs used in cardiovascular disease are increasingly being explored for their potential hepatoprotective effects. Here we investigate associations of statin and aspirin with liver disease in the general population.
Method: Data were used from two population-based cohorts: the Rotterdam Study (RS; the Netherlands) and the NHANES (2017–2020 cycle; United States). Participants aged ≥40 years with reliable liver stiffness measurements (LSM) and data on statin and aspirin use were included. Those with excessive alcohol consumption (≥50/60 g/day F/M), viral hepatitis, or heart failure were excluded. Fibrosis was defined as LSM ≥8.0 kPa, and SLD by ultrasound or CAP ≥280 dB/m. Logistic regression models were used to evaluate associations between statin, aspirin and liver outcomes. Models were adjusted

for age, sex, ethnicity, triglycerides, cholesterol, waist circumference, diabetes, hypertension and the number of metabolic risk factors. Interaction and multicollinearity were explored via interaction terms and variance inflation factors. Non-linearity was assessed in the pooled cohort by restricted cubic splines for the duration of statin use.
Results: 11.197 participants were included. 6.055 participants were included from the RS (median age 64 years [56–71], 44% male) and 5.142 from the NHANES (median age 60 years [50–69], 50% male). SLD prevalence was 33% in the RS and 48% in the NHANES and fibrosis was present in 4.7% in the RS and 11% in NHANES. In the RS, 22% used statin and 15% aspirin, compared to 30% and 29% in the NHANES. Statin was associated with SLD in the RS (aOR 0.47; 95%CI: 0.38–0.58) and fibrosis in the RS (aOR 0.57; 95%CI 0.38–0.86) and NHANES (aOR 0.60; 95%CI 0.47–0.78). Non-linear effects were observed for SLD (p = 0.033) and fibrosis (p = 0.002). Risk reduction during the first three years of statin use was 20% for steatosis and 40% for fibrosis. Thereafter, this effect stabilized in statin users for up to 20 years. Aspirin was not significantly associated with steatosis (RS: aOR 1.05; 95% CI 0.87–1.28; NHANES: aOR 1.19; 95% CI 0.95–1.49) nor fibrosis (RS: aOR 0.94; 95% CI 0.65–1.36; NHANES: aOR 0.94; 95% CI 0.69–1.26. There was no significant interaction or multicollinearity between statin and aspirin. The significant inverse association of statin therapy with SLD and fibrosis was consistently observed among subgroups with metabolic dysfunction.
Conclusion: Statin, but not aspirin, was independently inversely associated with SLD and fibrosis in a population-based settings. Risk reduction increased up to three years of treatment and remained stable thereafter. These result warrant further evaluation of statin therapy for liver disease in a randomized, controlled setting.

TOP-458

qFibrosis enables earlier detection of fibrosis response in Efruxifermin-treated patients with F2-F3 MASH in 96-week HARMONY study

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Background and aims: Efruxifermin (EFX) has been observed to improve fibrosis without worsening MASH, by conventional histopathology, with a doubling of response rates between week 24 and week 96 for the 50 mg EFX group, with a slight increase observed for the 28 mg EFX group. The placebo-adjusted effect sizes for fibrosis improvement without worsening of MASH grew from 21% to 52% between week 24 and week 96 for 50 mg EFX and from 20% to 22% for 28 mg EFX. This post-hoc analysis investigates changes in fibrosis using AI-based qFibrosis that can detect subtle intra-stage changes by using collagen morphometry for precise quantification on a continuous scale.
Method: Subjects with unstained biopsies at baseline (BL), week 24 (W24), and week 96 (W96) (n = 82) were available for qFibrosis analysis using SHG/TPEF imaging. The qFibrosis score incorporated a correction to account for a significant reduction in hepatic fat observed with EFX treatment, as well as offering a detailed assessment of fibrosis dynamics across the following defined hepatic zones: portal, peri-portal (zone 1), peri-sinusoidal (zone 2), central, and peri-central (zone 3).
Results: In this analysis, for the 28 mg EFX group, CRN staging identified most responders at W24 (n = 9), with 2 new responders captured at W96. In contrast, qFibrosis captures statistically significant ≥1 stage fibrosis improvement at W24 (60–70%) which converges with the 1-stage fibrosis improvement by CRN staging at W96 (70–80%), demonstrating the capability of qFibrosis to capture earlier W24 fibrosis regression, which may not be sufficient to be captured as a 1-stage improvement by conventional histopathology. The earlier capture of W24 responders by qFibrosis is evident in the statistically significant regression of fibrosis in Zones 1 and 2 in EFX arms compared to placebo, which was sustained in EFX arms at W96. The quantitative regression in Zones 1 and 2 was observed in subjects whether or not improvements in fibrosis had been seen by conventional histopathology staging, highlighting the consistency and sensitivity of qFibrosis in capturing subtle but significant fibrosis reductions for EFX-treated subjects.
Conclusion: Analysis of fibrosis response at W24 with qFibrosis resulted in a higher proportion of early responders that later become fibrosis responders by conventional histopathology at W96, compared with conventional histopathology at W24. This finding supports the potential utility of using qFibrosis zonal analysis provided by digital pathology to identify potential early improvements in zonal fibrosis patterns for interventional trials in subjects with F2 and F3 MASH to support drug development.

SATURDAY 10 MAY

SAT-405

Efficacy of lower carbohydrate diets for reducing liver fat and improving metabolic dysfunction: a systematic review and meta-analysis

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Background and aims: Weight loss through dietary and lifestyle changes is advised in the clinical management of metabolic dysfunction-associated steatotic liver disease (MASLD) for reducing liver fat and improving other markers of metabolic health. However, the recommended 5–10% weight loss can be difficult for many patients to achieve, and questions remain about optimal dietary interventions for MASLD treatment. Therefore, the aim of this work was to evaluate the relative efficacy of lower carbohydrate diets (LCD) for reducing liver fat (intrahepatocellular triglyceride, IHTG) and improving parameters of metabolic dysfunction in MASLD.
Method: In accordance with PRISMA guidelines and prospectively registered at Prospero (CRD42021223085), the MEDLINE, Scopus, Cochrane Library and EMBASE electronic databases were systematically searched from inception through May 31, 2024, for randomized or crossover intervention trials assessing the effects of LCD on IHTG (assessed by MRS, MRI or ultrasound) versus lower fat (LFD) types in adults aged 18 or older. Secondary outcomes included liver stiffness, body weight, fasting glucose, insulin, and HOMA-IR. The R software environment (v4.3.0) was used to conduct meta-analyses using the inverse variance method and random effects models. Heterogeneity between studies was evaluated with Cochran's Q-test and the I-squared index. Comparison between subgroups was done using a plural, fixed effects, model.
Results: From 10,537 records screened, 321 were eligible for full-text review, 26 studies were included in the qualitative synthesis, and 20 studies (n = 786 participants) could be meta-analysed for IHTG. Examining effect sizes as weighted mean difference (WMD) from baseline to intervention endpoint showed that, although both LCD and LFD significantly reduced IHTG (WMD [95% confidence intervals]: LCD: −2.76% [−3.93,−1.58] versus LFD: −1.54% [−2.52,−0.56]; p

= 0.12), there were no significant differences between groups in the plural model. Similarly, for body weight (19 studies, n = 708; p = 0.27), fasting glucose (15 studies, n = 609; p = 0.48), fasting insulin (13 studies, n = 623; p = 0.91), HOMA-IR (11 studies, n = 564; p = 0.33), there were no significant differences between the reductions observed in both LCD and LFD. No improvements in liver stiffness (6 studies, n = 458) were observed in either group (LCD: −0.56 kPA [−1.20, −0.12]; LFD: −0.12 kPA [−0.32, −0.08]). On the other hand, much more pronounced reductions were observed in hypocaloric trials for both IHTG (HYPO: −3.82% [−5.01,−2.63] versus ISO: −0.67% [−1.17, −0.18]; p < 0.01) and body weight (HYPO: −5.23 kg [−7.21, −3.26] versus ISO: −1.71 kg [−3.44, 0.02]; p < 0.009).
Conclusion: In conclusion these data show dietary interventions decreasing either carbohydrate or fat intakes were similarly effective for lowering IHTG and body weight and improving markers of insulin sensitivity in MASLD.

SAT-406
Role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in mortality reduction among patients with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) cirrhosis: a global retrospective analysis
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Background and aims: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are approved for managing type 2 diabetes mellitus (T2DM) and promoting weight loss. These agents have demonstrated efficacy in reducing hepatic fat content and the production of inflammatory cytokines, thereby alleviating liver inflammation and fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). However, their effects on MASLD complicated by cirrhosis remain inadequately understood.
This study aims to compare mortality and incidence of hepatocellular carcinoma in patients who were and were not prescribed GLP-1 RAs after diagnosis of MASLD cirrhosis. Secondary outcomes include decompensating events, sepsis, obesity-associated malignancies, inpatient admissions, and liver transplants.
Method: A retrospective analysis was conducted using the multi-institutional research network TriNetX that compiled data from 2004–2024. Patients with cirrhosis who have never been prescribed a GLP-1 RA (nonusers) were compared to patients with cirrhosis who were prescribed a GLP-1 RA (users) after diagnosis. Patients with decompensated cirrhosis and cirrhosis from other aetiologies were excluded. The patients were propensity matched to control for confounding factors. Multivariable-adjusted Cox proportional hazards models were used to compare the outcomes between GLP-1 RA nonusers and users.
Results: 40,646 patients were included in the analysis, of which 4,328 patients were prescribed a GLP-1 RA after diagnosis of cirrhosis. After propensity score matching, 3,846 patients were included from both groups. Five years after initiation of GLP-1 RA, there was a decrease in mortality (Hazard Ratio [HR] 0.37; 95% Confidence Interval [CI], 0.27 to 0.50) and incidence of hepatocellular carcinoma (HCC) (Hazard Ratio [HR] 0.57; 95% Confidence Interval [CI], 0.36 to 0.89) among users. Additionally, compared with the nonuser group, the user group had a lower incidence of sepsis (HR 0.52; 95% CI, 0.36 to 0.76), obesity-associated malignancies (HR 0.64; 95% CI, 0.54 to 0.76), major adverse cardiovascular events (MACE) (HR 0.84; 95% CI, 0.72 to 0.98), incidence of liver transplants (HR 0.45; 95% CI, 24 to 0.82), and inpatient admissions (HR 0.54, 95% CI 0.47 to 0.62).
Conclusion: In patients with obesity and MASLD cirrhosis, GLP-1 RAs were associated with a lower risk of HCC, sepsis, obesity-associated malignancy, hospital admission, MACE, liver transplantantation, and death. Future prospective studies may be beneficial in understanding more clearly the role of GLP-1 RAs in MASLD cirrhosis.

SAT-407-YI
Assessing early changes and responses to resmetirom therapy using real world single center data
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Background and aims: Metabolic-dysfunction associated steatotic liver disease (MASLD) affects an estimated 30% of the world's population, and metabolic-dysfunction associated steatohepatitis (MASH) is the leading cause of cirrhosis worldwide. In March 2024, resmetirom received conditional United States Food and Drug Administration approval as the first medication for MASH and is currently under evaluation with the European Medicines Agency for approval in the European Union. However, real-world use is limited; some early guidance suggests assessing at 12 months for treatment response. We aimed to assess whether treatment response can be evaluated at an earlier (3-month) timepoint.
Method: Single-center data from a New York City-based academic institution were collected on patients with F2 or F3 fibrosis, identified by non-invasive tests, who were initiated on resmetirom therapy between March 2024 and November 2024. Liver enzymes, lipids, hemoglobin A1c (HbgA1c) and Fibrosis-4 were collected at months 1, 3, and 6. Liver stiffness measurement (LSM) by transient elastography was reassessed at 3 months. Baseline and 3-month values were compared using two-sided Wilcoxon matched-pairs signed-rank test.
Results: Our center initiated 36 patients on resmetirom, with 3-month follow up available for 19 patients: 16 on 80 mg daily and 3 on 100 mg daily. Pre-treatment mean LSM was 10.9 kPa and controlled attenuation parameter (CAP) was 292 dB/m. Follow up LSM was performed at a mean of 99.4 (IQR 11) days after initiation of therapy. The 3-month mean LSM significantly decreased to 8.2 kPa (−2.7 kPa, p = 0.02) and CAP trended towards improvement (mean 271 dB/m, −21.2 dB/m, p = 0.06). 10 (52%) participants had ≥25% reduction in LSM from baseline, and 1 (5%) had ≥25% increase from baseline. There was a trend towards reduction in low-density lipoprotein at 3 months (79.2 mg/dL to 70.6 mg/dL, p = 0.09) and in triglycerides (133 mg/dL to 116 mg/dL p = 0.42). No significant changes were seen in body mass index (BMI) (31.1 kg/m^2 to 30.9 kg/m^2); HgbA1c% (6.0% to 6.1%); aspartate aminotransferase (39.6 U/L to 38.9 U/L); or alanine amino-transferase (58.2 U/L to 57.7 U/L). Patients on concomitant glucagon-like peptide-1 receptor agonists (GLP-1 RA) (n = 11) did not have a significant difference in percent LSM change compared to those not on GLP-1 RAs (n = 8). Six-month data will also be reported.
Conclusion: In the first 19 patients to reach three months of treatment on resmetirom, LSM reduced from pre-treatment levels, independent of liver enzymes, weight/BMI change, diabetes control or GLP-1 RA use. These data suggest that response to therapy may be assessable at the 3-month timepoint, helping to guide future management in high-risk patients. Limitations include a small cohort and the lack of a control population. Our follow-up data will assess whether these changes persist to one year and identify potential predictors of early response.

SAT-408
Effectiveness of bariatric surgery versus glucagon-like peptide-1 receptor agonists for prevention of adverse cardiovascular outcomes among patients with metabolic dysfunction-associated steatotic liver disease, diabetes, and obesity
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Background and aims: Cardiovascular disease (CVD) is the leading cause of death in individuals with metabolic dysfunction-associated fatty liver disease (MAFLD). Risk factors for CVD and MAFLD overlap and are linked to metabolic syndrome. Weight loss and reduced cardiovascular events have been observed in type 2 diabetes (T2DM) patients treated with GLP-1 receptor agonists (GLP-1RAs). Bariatric surgery (BS) also significantly lowers cardiovascular risks and improves metabolic health. However, limited evidence compares the impact of BS and GLP-1RAs on mortality and major adverse cardiovascular events (MACEs). This study assessed the incidence of major CVD in patients with MAFLD, T2DM, and obesity, without prior CVD, treated with BS versus GLP-1RAs at a population level.
Method: This population-based, retrospective cohort study utilized the TriNetX database to analyze adult patients (>18 years) with MAFLD, T2DM, and obesity, excluding other chronic liver diseases and prior CVD history. A 1:1 propensity score matching (PSM) adjusted for demographics, BMI, comorbidities, lab parameters, and medications. Bariatric surgery (BS) included Roux-en-Y gastric bypass and sleeve gastrectomy. The GLP-1RA cohort was defined by the first-ever use date, with a 6-month lag for both groups to reduce protopathic bias. The primary outcome was CVD incidence, a composite of heart failure (HF), MACE, or cerebrovascular disease. The secondary outcome was all-cause mortality. Sensitivity analyses ensured result robustness, and hazard ratios (HRs) compared BS outcomes with controls.
Results: A total of 167,895 individuals with MASLD, T2DM, and obesity were identified. Of those, 6898 patients had a history of BS, whereas 49,767 newly received GLP-1RAs. After PSM, each cohort included 6,430 patients, with BS patients being younger (49.1 vs. 54.6 years) and having a higher mean BMI (45.1 vs. 41.2). Both groups were predominantly female and white, with a mean follow-up of 4.6 years (up to 10 years). At 1 year, BS significantly reduced the incidence of HF (HR 0.67), MACE (HR 0.75), and cerebrovascular disease (HR 0.59). Adjusted analyses showed lower risks for MACE (HR 0.87), HF (HR 0.67), and cerebrovascular disease (HR 0.70) in the BS group compared to GLP-1RAs. Mortality rates were similar at 1 year (HR 0.92; 95% CI, 0.77–1.02), but BS showed a lower all-cause mortality risk (HR 0.34) and composite CVD outcomes over longer follow-ups (3, 5, and 7 years). Sensitivity analyses confirmed the consistency of these findings.
Conclusion: BS demonstrated a stronger and sustained reduction in cardiovascular events and all-cause mortality compared with GLP-1RAs among patients with MASLD, T2DM, and obesity. These findings suggest that BS may serve as a more effective intervention for reducing adverse outcomes in this high-risk population. Given the increasing adoption of GLP-1RAs, further long-term, comparative studies are warranted to guide evidence-based treatment decisions and optimize patient outcomes.

SAT-413

Cardiovascular disease risk, liver outcomes, and statin use among adults with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). Statins reduce cardiovascular events and are considered safe for patients with liver disease. However, limited population-level data exist regarding their impact on adverse CVD events and liver-related outcomes in patients with MASLD. This study aimed to assess the association of statin use with major adverse cardiovascular events (MACE), liver disease progression, and all-cause mortality in this population.
Method: This was a population-based cohort study with consecutive patients diagnosed with MASLD using TriNetx. The cohort included adults (>18 years) without other chronic liver disease etiologies. Statin users were identified based on first-ever statin prescriptions, with a 6-month exposure lag to minimize protopathic bias. Propensity score matching (PSM) (1:1) balanced baseline covariates between cohorts. Primary outcomes included new-onset heart failure (HF), MACE, composite cerebrovascular disease, and liver disease progression (decompensation, hepatocellular carcinoma [HCC]), and secondary outcomes assessed all-cause mortality. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards models. Sensitivity analyses assessed robustness by excluding patients with events within two years post-index.
Results: We identified 176,983 patients with MASLD. Among these, 51,481 received statins, and 125,502 did not, with a median follow-up time of 5.1 years. PSM resulted in well-matched groups (42,227 each). Statin use was associated with significantly lower risks of MACE (HR 0.29, 95% CI: 0.25–0.33), HF (HR 0.94, 95% CI: 0.91–0.98), cerebrovascular diseases (HR 0.87, 95% CI: 0.83–0.91), liver-related outcomes (HR 0.77, 95% CI: 0.71–0.84), and all-cause mortality (HR 0.85, 95% CI: 0.81–0.89). Interaction analysis revealed a greater benefit for women in reducing MACE (HR 0.66) than men (HR 1.09). Sensitivity analyses confirmed consistent findings. Statin use was also associated with lowering the risk of cardiovascular outcomes, such as MACE (HR, 0.29), HF (HR, 0.94), and cerebrovascular diseases (HR, 0.87). All-cause mortality (HR, 0.85) was significantly lower in statin users. However, there was a significant interaction with sex with a decreased risk of MACE for women (HR 0.66 vs. HR 1.09). The sensitivity analysis results were consistent, and all statistically significant associations remained unchanged.
Conclusion: Statin use in patients with MASLD significantly reduces the risk of adverse cardiovascular events, liver disease progression, and mortality, underscoring its role as a cornerstone therapy in high-risk populations. These findings highlight the dual benefits of statins in cardiometabolic and liver disease management while emphasizing the need for personalized strategies to mitigate metabolic side effects.

SAT-414-YI

Can non-diabetic patients with metabolic dysfunction associated steatotic liver disease benefit from glucagon-like peptide-1 analogs? A multicenter cohort study

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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD) has evolved into the most common cause of chronic liver disease affecting more than a third of the global population and is a leading cause of liver-related mortality. Treatment of MASLD relies on weight management and control of insulin resistance, and the most effective treatment to achieve these outcomes is either bariatric surgery or use of glucagon-like peptide-1 (GLP-1) analogs. While GLP-1 analogs are increasingly used for diabetes mellitus and weight loss; the evidence to support their use in MASLD is limited. We aim to investigate the effectiveness of GLP-1 analogs in patients with MASLD without diabetes mellitus in reducing the risk of cirrhosis with decompensation, hepatocellular carcinoma and 4-year mortality.
Method: We performed retrospective cohort study utilizing a large research network (TriNetX) comprising data of over 115 million patients. Study period was January 2016 to December 2021. Patients ³18 years with steatotic liver disease along and at least one of the cardiometabolic factors were identified. Patients with diabetes mellitus (or HBA1C ³6.5%) cirrhosis and other etiologies of chronic liver disease, and alcoholic liver disease, history of bariatric surgery were excluded. Patients were followed up to four years. Primary outcome were development of decompensated cirrhosis, hepatocellular carcinoma (HCC) and overall survival (OS) in patients treated with GLP-1 analogs compared to patients not treated with GLP-1 analogs. Propensity score (1:1) matching was performed to control for confounding variables.
Results: 271,125 (49.66%) out of 545,911 patients with MASLD did not have diabetes mellitus and 16,464 (6.07%) of them were treated with GLP-1 analogs. Females (65.74% vs. 52.17%), obese (85.02% vs. 38.01%) and patients with cardiovascular morbidity and obstructive sleep apnea (46.65% vs. 18.55%) were more like to receive a GLP-1 analog, while Hispanics (11.81% vs. 14.86%) were less likely to receive GLP-1 analogs. In an age-, gender-, race-, and comorbidity matched cohort of MASLD patients, the rate of developing decompensated cirrhosis (0.94% vs. 2.64%, hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.39–0.56) and all-cause mortality (0.67% vs. 3.66%, HR 0.24, 95% CI 0.19–0.29) was lower in patients who received GLP-1 analogs compared to those who did not receive GLP-1 analogs. However, there was no difference in HCC incidence (HR 0.67, 95% CI 0.32–1.38) between the two groups.
Conclusion: Our study using real-world evidence shows that while half of patients with MASLD may not have diabetes mellitus, this cohort of patients can benefit from GLP-1 analogs with lower risk of decompensated cirrhosis and overall mortality. Prospective studies on the use of GLP-1 analogs targeting MASLD patients without diabetes are needed to provide policymakers with concrete evidence to approve these novel therapeutics for this patient population.

SAT-415

Are glucagon-like peptide-1 analogs better answer for obese patients with metabolic dysfunction associated steatotic liver disease than bariatric surgery? Real-world evidence

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Background and aims: Bariatric surgery is an established treatment for morbid obesity and there has been growing interest in and use of glucagon-like peptide-1 (GLP-1) analogs for the same indication with promising results. However, GLP-1 analogs have not been routinely prescribed or widely accepted for primary use in metabolic dysfunction-associated steatotic liver disease (MASLD). Moreover, there is limited data comparing GLP-1 analogs and bariatric surgery for the treatment of MASLD. We aim to explore the trends in the use of GLP-1 analogs and bariatric surgery and compare the effectiveness of the two treatment options in reducing the risk of developing cirrhosis with decompensation, hepatocellular carcinoma, and 4-year mortality.
Method: We performed a retrospective cohort study utilizing a large research network (TriNetX) comprising data from over 115 million patients. The study period was January 2016 to December 2021. Patients ≥18 years with steatotic liver disease and at least one of the cardiometabolic factors were identified. Patients with cirrhosis and other etiologies of chronic liver disease were excluded. Patients were followed up to four years. Primary outcomes were the development of decompensated cirrhosis and all-cause mortality in patients treated with GLP-1 analogs (semaglutide, tirzepatide, dulaglutide, exenatide, lixisenatide) compared to patients treated with bariatric surgery (gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch, vertical band gastroplasty). Propensity score (1:1) matching was performed to control confounding variables.
Results: Out of 545,931 patients with MASLD, 73,339 (13.44%, median 733 days) patients were treated with GLP1 analog, 38,541 (7.06%, median 690 days) sodium-glucose cotransporter 2 (SGLT 2) inhibitors and 29,917 (5.48%, median 832 days) received other weight loss medications (naltrexone, topiramate or phentermine). 33,738 (6.18%) underwent bariatric surgery. The median follow-up was 46.43 months. Patients treated with GLP-1 analogs were older (53.89 vs. 47.70) and had more comorbidities but sleep apnea (54.97% vs. 43.85%) was more common in patients treated with bariatric surgery. After propensity score matching for confounding variables, the rate of decompensation (1.56% vs. 3.87%, risk ratio [RR] 0.43, 95% confidence interval [CI] 0.39–0.48) and all-cause mortality (1.67% vs. 2.97%, RR 0.56, 95% CI 0.51–0.62) were lower in patients treated with GLP-1 analogs compared with patients who had bariatric surgery.
Conclusion: GLP-1 analogs are increasingly being used in patients with MASLD. GLP-1 analogs and bariatric surgery reduce the risk of decompensated cirrhosis in obese patients with MASLD. Our results indicate that patients with MASLD treated with GLP-1 analogs have a lower risk of decompensated cirrhosis and better overall survival than patients treated with bariatric surgery despite being older and having more comorbidities.

SAT-416

The impact of SGLT-2i and GLP-1RA on liver-related events in patients with metabolic dysfunction-associated steatotic liver disease: a systematic review and network meta-analysis

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a major global health issue. Potential benefits of glucose-lowering agents in preventing liver-related events in MASLD patients with type 2 diabetes (T2D) have been reported, but the comparative efficacy of these glucose-lowering agents remains inconclusive, especially for long-term liver-related events. This study aimed to systematically review and compare the efficacy of glucose-lowering agents on liver-related events in patients with MASLD and T2D using a network meta-analysis (NMA).
Method: Data from observational studies were collected through PubMed, EMBASE, Cochrane Library and Web of Science from inception to October 2024. We evaluated the efficacy of glucose-lowering agents, including glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium–glucose cotransporter 2 inhibitors (SGLT-2is),

dipeptidyl peptidase-4 inhibitors (DPP-4is), sulfonylureas, and thiazolidinediones, on liver-related events (defined by cirrhosis, hepatic decompensation, liver failure, liver transplantation, hepatocellular carcinoma, or liver-related death) using a frequentist NMA approach, with results expressed as estimated pooled hazard ratios (HRs) and 95% confidence intervals (CIs). Treatment ranking in the frequentist NMA were presented as a P-score.

Results: A total of 12 eligible studies with 656,629 patients with MASLD and T2D were included. Among five glucose-lowering agents, SGLT2is and GLP-1RAs are the most effective classes for preventing liver-related events, with P-score 0.8845 and 0.8677, respectively. while other glucose-lowering agents had P-scores below 0.5. In addition, GLP-1RAs were shown to have comparable effects to SGLT2is for liver-related events (pooled HR 1.01; 95%CI 0.87–1.18). SGLT2is were significantly associated with a decreased risk of liver-related events compared with DPP4is (pooled HR 0.69; 95%CI 0.54–0.87), thiazolidinediones (pooled HR 0.58; 95%CI 0.45–0.74), and sulfonylureas (pooled HR 0.56; 95%CI 0.42–0.76). Consistent risk reduction was observed in GLP-1RAs users when compared with DPP4is (pooled HR 0.69; 95%CI 0.56–0.85), thiazolidinediones (pooled HR 0.59; 95%CI 0.45–0.77), and sulfonylureas (pooled HR 0.57; 95%CI 0.43–0.75).

Conclusion: Both SGLT2is and GLP1RAs are promising glucose-lowering agents for preventing liver-related events in patients with MASLD and T2D. These findings may help guide therapeutic strategies for managing patients with MASLD and T2D.

SAT-417-YI

Sex disparities in response to low-carb, high-fat diet in MASLD

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Background and aims: Dietary approaches affect women and men differently, in relation to both quality of life (QOL) and clinical outcomes. To improve adherence, it is essential to identify who benefits most in both aspects. This study compares QOL and clinical outcomes between the Low Carbohydrate High Fat (LCHF) diet and the high-carbohydrate, low-fat (HCLF) diets, with a focus on potential gender differences.

Method: These results are from a six-month randomized controlled trial in people with type 2 diabetes. Participants were randomized in a 2:1 ratio to follow either a LCHF diet or a HCLF diet. Both diets were based on non-processed, isocaloric and healthy foods. Liver biopsies, standard clinical assessments, and the Diabetes-39 QOL questionnaire were conducted at baseline and after six months. We used one question from the questionnaire to evaluate overall QOL, called "Please mark the box that represents your overall assessment of your quality of life," the score was from 1–7, with 1 being lowest quality. Liver biopsies were scored according to the NAS CRN scoring system. Subgroup analyses were performed to evaluate sex-specific differences in clinical and QOL response to the dietary interventions.

Results: We included 165 participants, 96 (58%) were women and 69 (42%) were men, median age was 56 (IQR, 50–63) years, mean BMI was 33 ± 7 kg/m^2, mean HbA1c was 56 ± 10 mmol/mol, 141 had MASLD with a median NAS score of 3 (IQR, 2–4) and a median overall QOL score of 5 (IQR, 4–6). QOL improved in both groups with 0.60 (95% CI: 0.05 to 1.16) on the LCHF diet and with 0.80 (95% CI: 0.00 to 1.60) on the HCLF diet (p = 0.692). The impact on QOL did not differ between sexes (p = 0.338). However, looking at the clinical impact between men and women, we saw significant differences. Women on the LCHF diet improved liver steatosis with −2.79 (95% CI: −4.16 to −1.42) compared to −0.74 (95% CI: −2,07 to 0.59) on the HCLF diet (p-value = 0.02), and lobular inflammation with −1.45 (95% CI: −2.52 to −0.38) compared to 0.19 (95% CI: −1.11 to 1.48) on the HCLF diet (p = 0.059). Men did not improve within-group or between-group in liver steatosis or lobular inflammation (steatosis: p-value = 0.764, inflammation: p-value = 0.901). Both sexes improved their HbA1c and weight more on the LCHF diet compared to the HCLF diet (Mean difference in change; women, HbA1c: −5.21 mmol/mol (95% CI: −8.74 to −1.68), weight: −4.76 kg (95% CI: −6.71 to −2.81), men: −7.84 mmol/mol (95% CI: −13.42 to −2.27), weight: −2.33 kg (95% CI: −4.47 to −0.20).

Conclusion: The LCHF diet significantly reduced liver steatosis and inflammation in women, whereas men did not experience similar benefits, despite comparable reductions in weight and HbA1c levels. Notably, neither diet had a negative impact on QOL.

SAT-418-YI

Indication of resmetirom in patients with metabolic dysfunction associated steatohepatitis in the real-world setting - data from the german SLD-registry

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Background and aims: The THR-β agonist resmetirom is the first and only treatment approved for metabolic dysfunction-associated steatohepatitis (MASH) in the US so far. The indication for prescribing resmetirom is MASH and moderate to advanced fibrosis consistent with F2/F3 ("at-risk MASH"). This definition is biopsy driven, although biopsy is only available in selected patients and not necessary in accordance with the US prescribing information. We therefore analyzed how many patients would qualify for resmetirom in the real-world scenario of the German Steatotic Liver Disease (SLD)-Registry.

Method: Indication for resmetirom was assessed by three different approaches: (i) biopsy proven MASH with F2/3 fibrosis and NAS-score ≥ 4; (ii) FibroScan-AST (FAST)-score > 0.67 and vibration controlled transient elastography (VCTE) < 15 kPa; (iii) US expert recommendation with VCTE 10–15 kPa and platelets ≥ 140 109/L (Noureddin et al., Clin Gastroenterol Hepatol 2024).

Results: 1113 patients were recruited across 8 academic and 12 non-academic centers. NAS grading and fibrosis staging were available for 180 cases (16%) with 179/180 conducted at academic centers. Of these, 61 (34%) qualified for resmetirom based on approach (i). FAST score and VCTE, but not histology were available for 638 cases (57%), of which 612 (98%) were from academic and 26 (2%) from non-academic centers. Based on approach (ii), 41 (6.4%) individuals qualified for resmetirom. VCTE was performed in 744 patients (67%) with 624 (84%) at academic and 120 (16%) at non-academic centers. Using approach (iii), 129 (17.3%) individuals qualified for resmetirom. Overall, 201 (31%) patients met the criteria for resmetirom if either VCTE values between 10–15 kPa and platelets ≥ 140 109/L or FAST

score > 0.67 were present. A direct comparison of biopsy results and FAST scores was available for 170 patients, although a substantial amount of time often elapsed between the two assessments. Of these, resmetirom was not indicated by FAST score in 150 cases, however, 47 (31%) would have qualified based on biopsy results.
Conclusion: The selection of eligible patients for resmetirom treatment depends on the method used to identify "at-risk MASH." The availability of diagnostic approaches differs between academic and non-academic centers. Non-invasive assessment may miss patients who would qualify for resmetirom according to biopsy.

SAT-419-YI
A postbiotics and metabiotics reduces the hepatic steatosis indices and aminotransferase activity in MASLD patients: a randomized clinical trial (DELI_MASLD study)
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Background and aims: The background for current study was previously reported by our team in pilot study (EASL 2024; Milan, Italy; SAT-213) findings that postbiotic supplementation for 3 months can reduce hepatic fat content in NAFLD patients as measured by MRI-PDFF. The aim of the current study was to conduct a placebo controlled randomized clinical trial (RCT) to assess the short-term efficacy and safety of the same formulation on the main serum parameters which characterized hepatic fat accumulation and transaminases activity in patients with MASLD according to new EASL–EASD–EASO criteria.
Method: A total of 52 patients met the criteria for inclusion. The study included 3 periods. A screening period of up to 1 week was used to assess eligibility for the inclusion/exclusion criteria. The treatment and follow-up periods were 3 months each. The participants received a twice-daily oral dose of postbiotics/metabiotics containing cell lysate and DNA fragments of the probiotic strain *L. rhamnosus DV - NRRLB-68023* at the assigned dose of 100 mg or placebo in capsules. The primary main outcomes were the change of biochemical steatosis indices: fatty liver index (FLI), hepatic steatosis index (HSI) and triglyceride to glucose (TyG) index. Secondary outcomes were the changes in serum lipid content, transaminase activity, markers of chronic inflammation (Il-6, hs-CRP) and anthropomorphic variables. Trial registration: NCT06352697.
Results: Postbiotic/metabiotics supplementation for 3 months was associated with significant reductions in FLI (78.23 ± 14.47 to 71.95 ± 21.62; p = 0.016) and HSI (45.48 ± 5.05 to 42.75 ± 4.98; p = 0.001). For TyG index decreasing trend was observed (4.92 ± 0.39 to 4.84 ± 0.34; p = 0.081). In secondary outcomes analysis, from abovementioned endpoints, only transaminase activity (ALT - 43.15 ± 29.2 to 27.75 ± 18.22 IU/L; p = 0.001 and AST - 31.34 ± 17.98 to 23.88 ± 8.11 IU/L; p = 0.006) and anthropometric parameters changes significantly after 3 months of probiotic lysate administration. In the placebo group, in both outcomes analysis only HSI significantly decrease at the end of treatment period (43.50 ± 4.59 to 42.43 ± 4.79; p = 0.015). After intervention discontinuation, at follow-up visits (6 months), the endpoints increased compared to those at the end of the treatment visits. However, the parameters did not achieve the baseline level.
Conclusion: The present RCT demonstrated the beneficial effects of postbiotic/ metabiotics supplementation on the biochemical steatosis indices, anthropometric parameters and transaminases activity in MASLD patients. However, larger studies are needed to confirm these findings.

SAT-420
Natural explant with dihydromiricetin in metabolic associated steatotic liver disease (MASLD): a double-blind, placebo controlled, randomized clinical trial
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Background and aims: MASLD has a prevalence of 25–30% globally representing the most common current cause of cirrhosis and liver transplantation in Western countries. However, effective treatment options for MASLD are limited. The aim of this prospective, double-blind, placebo controlled trial was to assess the efficacy of a dietary supplement containing dihydromyricetin (Hepatrat®) in patients with MASLD.
Method: Adult patients with MASLD seen at our liver clinics were included. All patients should have had elevated ALT and/or GGT and radiologically diagnosed hepatic steatosis, but no other cause of liver injury. Enrolled patients were randomized to receive Hepatrat® (dietary supplement in tablet form containing dihydromyricetin from Ampelopsis grossedentata extract, along with essential nutrients such as vitamins C and E, and choline) or placebo for 12 months (NCT05052515). Patients were assessed every 3 months and the primary end-point of the study was biochemical responses at 12 months.
Results: In total, 55 patients were randomized to active treatment (Group A, n = 28) or placebo (Group B, n = 27), but 9 patients (Group A/B = 2/7) withdrawn early for personal reasons. Baseline characteristics were not different between patients of Group A vs B except for gender distribution. Patients of Group A vs B did not differ in the normalization rates of ALT or GGT alone, but they achieved higher 12-month rates of combined ALT and GGT normalization (ITT analysis:32% vs 4%, p = 0.012, PP analysis:35% vs 5%, p = 0.028). Patients with normal both ALT and GGT compared to those with elevated ALT and/or GGT at 12 months did not differ in baseline age, gender, BMI, diabetes, platelets, liver stiffness or CAP values. Median weight was numerically reduced at 12 months (−1.2 kg, p = 0.103). Weight reduction at 12 months did not differ between patients of Group A vs B (p = 0.571), while it was greater in patients with than without normalization of ALT+GGT (−5.0 vs −1.0 kg, p = 0.035). In multivariable analysis, Group A was the main factor associated with normalization of ALT+GGT at 12 months (OR:11.76, 95%CI:1.15–120.41, p = 0.038) independently of weight reduction (p = 0.059).
Conclusion: The 12-month use of Hepatrat® seems to result in increased rates of normalization of both ALT and GGT in patients with MASLD regardless of their baseline characteristics. Therefore, the use of Hepatrat® in MASLD needs further evaluation.

SAT-421
The reversal of MASH cirrhosis. Pooled analysis from RCTs
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Background and aims: Metabolic-associated steatohepatitis (MASH) is a progressive liver disease characterized by liver fibrosis and inflammation, posing significant risks for liver-related complications and mortality. This meta-analysis synthesises data relating only to MASH Cirrhosis to examine the effect of regression using the placebo arm from randomised controlled trials.
Method: A comprehensive strategy was done on Embase and Medline (Ovid) for MASH randomized controlled trials (RCT) from inception to Dec. 26, 2023, with placebo treatment arms. Primary outcomes were defined as at least one point reduction in fibrosis as per the National Institutes of Health Nonalcoholic Steatohepatitis Clinical Research Network (NIH NASH CERN) criteria, and/or two point reduction via Non-alcoholic fatty liver disease (NAFLD) activity score without worsening fibrosis, or resolution of NASH.
Results: Among MASH patients, a ≥1 stage improvement in fibrosis per NASH CRN criteria was observed in 17.23% (95% CI: 10.18–27.67%), with Ishak fibrosis stage improvement reported in 23.88% (95% CI: 15.34–35.20%). Fibrosis improvement without worsening of MASH occurred in 17.19% (95% CI: 11.54–24.83%), while histological resolution was rare at 3.82% (95% CI: 1.14–12.08%). Liver-related complications were notable. Variceal bleeding was observed in 0.19% (95% CI: 0.01–5.18%), ascites in 1.23% (95% CI: 0.27–5.41%), hepatic encephalopathy in 1.22% (95% CI: 0.55–2.69%), and spontaneous bacterial peritonitis (SBP) in 1.61% (95% CI: 0.40–6.22%). Patients with Model for End-Stage Liver Disease (MELD) scores ≥15 demonstrated an elevated risk of adverse outcomes, with a pooled proportion of 4.64% (95% CI: 2.43–8.67%). Liver-related mortality was recorded at 0.68% (95% CI: 0.13–3.38%).
Conclusion: MASH may have spontaneous regression without pharmacotherapy, with histological resolution. This study demonstrates the first pooled evidence of placebo arm related MASH progression. Further characterisation of natural MASH regression and effect of placebo on histological response may aid in further pharmacological profiling and designing of targeted demographic clinical trials.

SAT-422

Effect of hepatic impairment on the pharmacokinetics of Miricorilant: results from a phase 1, open-label, adaptive-design study

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Background and aims: Miricorilant is a nonsteroidal selective glucocorticoid receptor modulator (SGRM) that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the mineralocorticorticoid receptor. Miricorilant is currently being evaluated in the phase 2 MONARCH trial (NCT06108219) for the treatment of noncirrhotic (F1-3) metabolic dysfunction-associated steatohepatitis (MASH). In a previous phase 1b trial, patients (pts) with presumed MASH treated with twice-weekly miricorilant 100 mg had reduction in liver fat content as well as improvements in hepatic, lipid, and glycemic markers (Alkhouri et al. *Hepatology* 2024). As the primary route of elimination for miricorilant is hepatic (Custodio et al. EASL 2024), our objective here was to evaluate the effect of hepatic impairment on the pharmacokinetic (PK) profile of miricorilant.
Method: In this phase 1, open-label, adaptive-design study (NCT05553470), adult pts with moderate (Child-Pugh Class B; including pts with MASH) or severe (Child-Pugh Class C) hepatic impairment were matched with healthy control volunteers based on gender, age (±10 years), and weight (±20%). All participants received a single oral dose of miricorilant 600 mg under fed conditions. Plasma concentrations of miricorilant were determined with a validated LC-MS/MS bioanalytical method at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours post-dose. Safety and tolerability were monitored throughout the study.
Results: The study enrolled pts with moderate hepatic impairment (n = 10, including 4 pts with MASH), severe hepatic impairment (n = 9), and healthy volunteers (n = 10). The observed effect of moderate and severe hepatic impairment on miricorilant PK was small. Following a single dose of miricorilant, the geometric mean ratios (90% CI) of miricorilant AUC_{inf} and C_{max} were 133% (97.9–179.9%) and 82% (65.7–101.5%), respectively, in pts with moderate hepatic impairment compared to healthy matched volunteers. The geometric mean ratios (90% CI) of miricorilant AUC_{inf} and C_{max} were 136% (91.4–202.6%) and 30% (24.2–37.5%), respectively, in pts with severe hepatic impairment compared to healthy matched volunteers. The half-life of miricorilant in pts with moderate and severe hepatic impairment was 36.0 and 76.7 hours, respectively, as compared with a half-life of 25.5 hours in healthy matched volunteers. No grade ≥3 treatment-emergent AEs or laboratory abnormalities were observed, and no new safety concerns were identified.
Conclusion: Miricorilant 600 mg was generally well tolerated in pts with moderate and severe hepatic impairment and in matched healthy volunteers. Hepatic impairment had minimal impact on the systemic plasma exposures (as measured by AUC) of miricorilant. These findings support future inclusion of pts with compensated cirrhotic (F4) MASH in the miricorilant clinical development program.

SAT-423

Survodutide, a glucagon/GLP-1 receptor dual agonist, in people with MASH with moderate-to-advanced liver fibrosis (stage F2-F3): rationale and design of an event-driven, multinational, randomised, placebo-controlled, phase 3 trial (LIVERAGE™)

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Background and aims: Dual agonism of the glucagon (GCGR) and glucagon-like peptide-1 (GLP-1R) receptors may be effective for treating metabolic dysfunction-associated steatohepatitis (MASH). Survodutide, a GCGR/GLP-1R dual agonist with a receptor ratio of ~1:8 in vitro, markedly improved both steatohepatitis and liver fibrosis in a 48-week phase 2 trial in people with MASH and fibrosis stages F1-F3. We describe here the design of an ongoing phase 3 trial of survodutide for treatment of non-cirrhotic MASH (LIVERAGE™).
Method: In this 2-part trial in ~1800 participants in ~40 countries (NCT06632444), the main eligibility criteria include age ≥18 years, a biopsy-proven diagnosis of MASH and F2-F3 fibrosis (by MASH Clinical Research Network [CRN] stage), screened through the following parameters: aspartate aminotransferase (AST) >20 U/L, liver stiffness by FibroScan vibration-controlled transient elastography (VCTE) ≥7.5 kPa, FibroScan-AST (FAST) score >0.36, and liver fat

fraction ≥8% by magnetic resonance imaging-proton density fat fraction. Exclusion criteria include AST and/or alanine aminotransferase ≥5x upper limit of normal [ULN], platelets <140,000/mm^3, albumin <3.5 g/dL, international normalised ratio of prothrombin time >1.3, bilirubin ≥1.5x ULN, acute or other chronic liver disease, cirrhosis, portal hypertension, decompensated liver disease, hepatocellular carcinoma, Model for End-stage Liver Disease (MELD) score ≥12, or liver transplant. Participants are randomised 2:1 to double-blind, once-weekly, subcutaneous injections of survodutide uptitrated to 6.0 mg or placebo. In part 1, the two primary endpoints will be assessed in the first 700 participants at week 52: 1) resolution of MASH without worsening of liver fibrosis by MASH CRN stage and 2) ≥1-point improvement in fibrosis stage with no worsening of MASH. Key secondary endpoints are % change from baseline in body weight, absolute change from baseline in glycated haemoglobin (in participants with type 2 diabetes), Enhanced Liver Fibrosis score and liver stiffness by VCTE, and achievement of no progression of fibrosis. In part 2, the primary endpoint evaluated in all participants is a composite outcome of time to first event of progression to cirrhosis, all-cause mortality, liver transplant, hepatic decompensation event (s), worsening of MELD score to ≥15, or progression to clinically significant portal hypertension. Safety evaluation is based on treatment-emergent adverse events and laboratory tests.
Results: Recruitment of participants began in October 2024. Follow-up is estimated to end in 2031.
Conclusion: The phase 3 LIVERAGE™ trial will elucidate the long-term effects of survodutide on steatohepatitis, fibrosis, liver outcomes, and all-cause mortality in people with fibrotic MASH without cirrhosis, as well as its tolerability and safety.

SAT-424

Baseline characteristics in well-compensated NASH cirrhosis patients diagnosed with or without a liver biopsy in MAESTRO-NASH-OUTCOMES, a clinical outcome phase 3 study assessing the effect of resmetirom in well compensated NASH cirrhosis

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Background and aims: MAESTRO-NASH Outcomes (NCT05500222) is a multi-national, multicenter, double-blind, randomized, placebo-controlled study in well-compensated NASH cirrhosis. Patients were randomized 3:1 in a blinded manner to receive resmetirom 80 mg or matching placebo given orally once daily in the morning for the duration of the study (until the required number of Composite Clinical Outcome events are achieved). Composite Clinical Outcome events are defined as any of the following: mortality, liver transplant, and significant hepatic events, including potential hepatic decompensation events (ascites, hepatic encephalopathy, or gastroesophageal variceal haemorrhage), and confirmed increase of Model for End-stage Liver Disease (MELD) score from <12 to ≥15. The study comprises an up to 60-day screening period and an approximately 3-year treatment period. Baseline factors in patients who were diagnosed with NASH cirrhosis on liver biopsy were compared with those diagnosed with NASH cirrhosis who did not receive a liver biopsy.
Method: The study enrolls NASH cirrhosis patients with confirmed F4 fibrosis on biopsy with 3 metabolic risk factors, meeting other non-invasive testing and eligibility requirements, or NASH cirrhosis diagnosed non-invasively requiring at least 2 non- invasive testing requirements for screening: FibroScan VCTE ≥15 kPa and/or if FibroScan VCTE <15 kPa; at least two other non- invasive tests (MRE ≥4.2, platelets <140 K, ELF ≥10.25, FIB-4 ≥3). Other screening tests include blood tests, MRE, MRI-PDFF and assessments for HCC and ascites, with MELD <12 (except for Gilbert).
Results: A total of 845 patients are enrolled, including 392 with NASH cirrhosis with biopsy-confirmed F4 fibrosis, and 453 with NASH cirrhosis diagnosed non-invasively. Baseline factors were generally similar between patients diagnosed as NASH cirrhosis on liver biopsy or diagnosed as NASH cirrhosis without a liver biopsy: mean age 63 years; 32–35% males; mean BMI of 35 kg/m^2, 70–79% with hypertension, 65–77% with T2DM. Approximately one third of patients had more advanced disease based on MRE ≥ 6, ELF ≥ 11.3, MRI-PDFF < 5%. A higher percentage of NASH cirrhosis patients diagnosed without a liver biopsy had baseline characteristics suggestive of more advanced portal hypertension (Platelets <140 K, higher MRE, ELF and FibroScan VCTE), 67% and 83% meeting Baveno VII criteria for probable or possible clinically significant portal hypertension (CSPH) in the biopsy and no biopsy groups, respectively.
Conclusion: These data support the accuracy of using non-invasive testing to accurately diagnose well-compensated NASH cirrhosis.

SAT-425

Evaluating the efficacy of a carnitine orotate and biphenyl dimethyl dicarboxylate complex in the pathogenetic treatment of metabolic-associated fatty liver disease: midterm data

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Background and aims: Nowadays the prevalence of metabolic-associated fatty liver disease (MAFLD) is increasing rapidly, whereas clinicians all over the world still have serious limitations in the treatment of MAFLD. Several investigations showed the effectiveness of drugs based on carnitine orotate and biphenyl dimethyl dicarboxylate (COC and BDD) in the complex therapy of patients with MAFLD. The main purpose of this study was to evaluate the effectiveness of the carnitine orotate and BDD complex in the pathogenetic therapy of BDD.
Method: A prospective cohort study of MAFLD patients has been ongoing in Kazakhstan since February 2023. From February 2023 to July 2024, 121 participants aged 18–75, taking COC and BDD, were included in the study in Almaty and the surrounding region. Participants were observed for 48 weeks, with 24 weeks of COC and BDD treatment. The analysis included 78 participants who completed the treatment by September 2024. Anthropometric data (BMI, waist circumference), steatosis and fibrosis levels (measured by transient elastography [FibroScan] with Controlled Attenuation Parameter), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, triglycerides, and FIB-4 (a non-invasive fibrosis marker) were assessed at baseline and at week 24. Statistical analysis was performed using Jamovi 2.4.8.
Results: After 24 weeks of treatment, significant reductions were observed in ALT (32.4 [19–51.5] U/l to 20.1 [14.9–28.4] U/l, $p < 0.001$), triglycerides (1.4 [1.1–2.2] to 1.3 [1.0–2.0] mmol/L, $p = 0.007$), steatosis (304 [268–325] to 283 [246–312] dB/m, $p < 0.001$), and fibrosis (6.5 [5.3–8.3] to 6 [4.7–7.2] kPa, $p = 0.022$). ALT showed a slight increase over time (from 23.3 [17.9–38.6] U/l at baseline to 23.5 [19.1–28.4] U/l at week 24, $p = 0.021$), but remained within the

reference range. The median BMI decreased from 30.4 to 29.8 kg/m² (p = 0.214), with no significant changes in waist circumference (p = 0.943), indicating that weight loss did not significantly impact steatosis, fibrosis, or ALT levels. The frequency of severe fibrosis (F3) decreased from 8.1% to 1.4%, while F2 decreased from 27% to 21.4% (p = 0.022). The frequencies of F1 and F0 increased, indicating improvements in fibrosis. Severe steatosis (S3) decreased from 52.7% to 45.7%, and mild steatosis (S1) increased from 17.6% to 21.4%, with new cases of S0 (10%) appearing at week 24 (p = 0.001). No significant changes were found in total cholesterol levels or FIB-4 scores (p = 0.071).
Conclusion: COC and BDD treatment in MAFLD patients resulted in regression of ALT, triglycerides, steatosis, and fibrosis over 24 weeks, with a slight increase in AST within the reference range. Despite these promising results, further studies are needed to fully assess the efficacy of COC and BDD.

SAT-429

The synergistic effects of 4 weeks of resistance exercise and whey protein supplementation on liver health in individuals with metabolic dysfunction-associated liver disease

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Background and aims: Exercise and diet are effective non-pharmacological treatments for metabolic dysfunction-associated liver disease (MASLD), reducing hepatic fat. Resistance exercise helps prevent muscle loss in MASLD patients, while whey protein reduces hepatic fat accumulation. However, the combined effects of exercise and whey protein supplementation are unclear. This study examines their individual and combined effects on hepatic fat and liver enzymes in MASLD.
Method: Individuals with MASLD (n = 45) were randomly assigned to four groups: exercise protein (ExPro, n = 14), exercise placebo (ExPla, n = 12), control protein (ConPro, n = 11), and control placebo (ConPla, n = 8). ExPro and ConPro consumed 0.7 g of whey protein/kg of body weight, while ExPla and ConPla consumed an equal amount of placebo for 4 weeks. ExPro and ExPla performed supervised resistance exercise five times per week for 40 minutes, with intensity gradually increasing from 50% to 75% of 1-RM. All participants received packed meals containing 30% fewer calories than their daily requirement (measured by gas analysis of RMR multiplied by physical activity level), containing 0.8 g of protein/kg of body weight. Hepatic fat content was assessed weekly by controlled attenuation parameter (CAP) and plasma samples were collected biweekly to analyze AST, ALT, and GGT. Data were analyzed using generalized estimating equations with a log-gamma model, with ConPla as the reference.
Results: A significant time-by-group interaction was observed for CAP. In the ExPro, reductions were significant at 1 week (beta = −0.061, p = 0.028), 2 weeks (beta = −0.092, p = 0.001), 3 weeks (beta = −0.083, p = 0.008), and 4 weeks (beta = −0.111, p < 0.001). In ExPla, reductions occurred at 2 weeks (beta = −0.054, p = 0.041) and 4 weeks (beta = −0.082, p = 0.011). ConPro showed a reduction at 4 weeks (beta = −0.089, p = 0.002). For ALT, significant reductions in ConPro occurred at 2 weeks (beta = −0.311, p = 0.026) and 4 weeks (beta = −0.322, p = 0.002). AST showed significant time-by-group interaction, with a reduction in ConPro at 2 weeks (beta = −0.198, p = 0.040), but increase in ExPro at 2 weeks (beta = 0.327, p = 0.044). No significant interaction was found for GGT.
Conclusion: Both resistance exercise and whey protein supplementation, both individually and in combination, improve liver health in individuals with MASLD. The combination may offer synergistic benefits compared to each treatment alone.

SAT-430

Population pharmacokinetic/pharmacodynamic modelling of novel thyroid hormone receptor beta agonist ALG-055009 reveals statistically significant correlation between exposure and key efficacy endpoints

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Background and aims: ALG-055009 is a novel next generation thyroid hormone receptor (THR)-beta agonist with beta selectivity and in vitro potency exceeding that of first-generation drugs. In the randomized, double-blind, placebo-controlled Phase 2a HERALD study, 12 weeks of once daily ALG-055009 treatment in subjects with presumed metabolic dysfunction-associated steatohepatitis (MASH) and F1-F3 fibrosis was well-tolerated and met the primary endpoint, demonstrating significant reductions in liver fat (Loomba et al. AASLD 2024). This analysis was conducted to inform Phase 2b dose selection.
Method: ALG-055009 pharmacokinetic (PK) data were collected from two healthy volunteer studies (n = 91 subjects and 2233 samples) and one MASH patient study (n = 78 subjects and 726 samples), after single or multiple once-daily dosing of 0.1–4.0 mg ALG-055009. Nonlinear mixed effects modeling was used to characterize the population PK. Individual exposure parameters were used to investigate the relationship with efficacy parameters and key safety parameters. The exposure-efficacy dataset consisted of 97 subjects receiving daily oral administration of ALG-055009 at 0.3 (n = 18), 0.5 (n = 21), 0.7 (n = 20) or 0.9 mg (n = 17) or placebo (n = 21). Non-linear regression and logistic regression were used to model the exposure-response relationships. Key efficacy endpoints included change from baseline in liver fat as measured by MRI-PDFF and proportion of responders of ≥30% relative liver fat reduction. Covariate analysis was conducted on the population PK and exposure-response relationship.
Results: Greater change from baseline in liver fat at Week 12 ($p < 2.35 \times 10^{-6}$) and proportion of subjects achieving more than 30% relative liver fat reduction (p < 0.001) showed statistically significant association with increased ALG-055009 exposure. ALG-055009 steady-state area under the plasma concentration-time curve (AUC) between 500–1500 ng.h/mL appeared to have optimal efficacy profile. Covariates included demographics, weight, baseline liver fat, and relevant concomitant medication use (statins or GLP-1 receptor agonists) did not have a statistically significant effect on the exposure-efficacy relationship. A simulation study of PK and key efficacy endpoints in a virtual population of 1000 subjects with covariate distributions from the HERALD study provided rank order of efficacy for dosing regimens with and without dose cut-offs at selected body weights.
Conclusion: Population PK and exposure-response models were developed for ALG-055009. There was a statistically significant correlation between exposure and key efficacy endpoints of change from baseline in liver fat and proportion of responders of ≥30% relative liver fat reduction. These models will be used to provide guidance for dose selection for a Phase 2b study in patients with MASH.

SAT-431

Effectiveness of a smartphone app in promoting weight loss in patients with metabolic dysfunction-associated steatotic liver disease: a pilot randomized controlled trial

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Background and aims: Although achieving weight loss is the cornerstone of treatment for patients with metabolic dysfunction-associated steatotic liver disease (MASLD), it is only achieved in <20% of patients. Mobile technology is being increasingly used to promote health. We aimed to evaluate the effectiveness of a self-developed smartphone app (*AppLiver*) for promoting weight loss in Chinese adults with MASLD.
Method: We conducted a non-blinded two-arm parallel 1:1 randomized controlled trial (NCT05180760) and recruited adult MASLD patients age <70 who could operate a smartphone and understand Chinese or English. Patients with decompensated cirrhosis were excluded. The control arm consisted of standard of care (SOC) with intensive group counselling and monitoring by non-invasive tests (NITs). The interventional arm consisted of the use of *AppLiver* + SOC. *AppLiver* is a smartphone app developed by our study team which consisted of data tracking function (anthropometric, liver and metabolic parameters), interactive function (dietary log and feedback, activities log) and knowledge enrichment. At baseline and 6-monthly intervals, all patients were monitored by NITs including vibration-controlled transient elastography to determine controlled attenuation parameter (CAP) and liver stiffness (LS), and bioelectrical impedance analysis (BIA) to determine skeletal muscle index (SMI), visceral fat index (VFI) and visceral body fat % (VBF). The primary outcome was weight loss ≥5% at 6 months.
Results: In this interim analysis, a total of 141 participants were recruited, with 72 in SOC arm and 69 in the app arm, who were matched in baseline age (median 56 years, IQR 47–62), gender (53.2% male), body mass index (BMI, 27.3 kg/m^2, IQR 25–30), diabetes (38.3%), steatosis and fibrosis stage. The baseline SMI, VFI and VBF was 7.8 kg/m^2(IQR 6.9–8.6), 13 and 34.6%, respectively. At 6 months, the primary outcome was achieved in 9.1% in the SOC arm and 7.9% in the app arm ($p = 0.533$). Significant CAP reduction (defined as ≥40 dB/m decline), downstaging of steatosis and fibrosis was seen in 13.2%, 15.9% and 14.3% in the app arm and 19.4%, 18.2% and 21.2% in the SOC arm, respectively, (all $p > 0.05$). Compared to baseline, the whole group demonstrated significant increase in SMI (+7.6 kg/m^2, IQR 0–9.4, $p < 0.001$), decrease in LS (-0.6 kPa, IQR −1.7 to +0.5 $p = 0.004$), reduced total cholesterol (-0.15 mmol/L, IQR −0.6 to +0.3, $p = 0.035$), reduced LDL-cholesterol (-0.1 mmol/L, IQR −0.5 to +0.2, $p = 0.018$) and reduced HbA1c (-0.1%, IQR −0.3 to +0.1, $p = 0.014$) at 6 months, while no significant change in body weight, BMI, CAP, ALT, VFI and VBF was observed. No patients dropped out from the study at 6 months.
Conclusion: Intensive group counselling and monitoring with NITs promoted changes in SMI, LS and metabolic profile with or without the aid of mobile technology in Chinese adult patients with MASLD.

SAT-432
Effects of Berberine Ursodeoxcholate (HTD1801) in chinese patients with T2DM and presumed MASLD

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Background and aims: T2DM typically coexists with other metabolic abnormalities such as hyperlipidemia, obesity, and MASH that can exacerbate T2DM and lead to a worse prognosis with increased risk for mortality and cardiovascular outcomes. As such, treatments are needed that can be simultaneously effective across multiple metabolic abnormalities. Berberine ursodeoxycholate (HTD1801) is a gut-liver anti-inflammatory metabolic modulator being developed for the treatment of T2DM and MASH. HTD1801 was effective in improving key cardiometabolic parameters in a Phase 2, double-blind, placebo (PBO)-controlled study in Chinese patients with T2DM (NCT06411275). Based on the latest diagnostic criteria, it is likely that a substantial subgroup in this study may have had concurrent MASLD. The purpose of this analysis is to evaluate the benefits of HTD1801 in Chinese patients with T2DM and presumed MASLD.
Method: 113 patients were randomized 1:1:1 to PBO (n = 38), HTD1801 500 mg BID (n = 37), and 1000 mg BID (n = 38) for 12 weeks. The primary endpoint was change from baseline in HbA1c at Week 12. The presence of MASLD was identified by baseline controlled attention parameter (CAP) values >288 dB/M (correlated to 5% liver fat content) and T2DM.
Results: Presumed MASLD, occurring in 40% of patients at baseline, was evenly distributed between treatment groups (PBO, n = 16; HTD1801 500 mg BID, n = 14; HTD1801 1000 mg BID, n = 15). At baseline, HbA1c was 8.1–8.5%, GGT was 40–43 U/L and LDL-C was 119–124 mg/dL. After 12 weeks of treatment, HbA1c was reduced by −0.4% (0.7), −0.8% (0.8), and −1.0% (0.5) in the PBO, HTD1801 500 mg BID and 1000 mg BID groups, respectively. Substantial improvements in GGT were observed with changes of 2.7 U/L (10.8), −8.7 U/L (6.9), and −9.9 U/L (17.6) and the change from baseline in LDL-C was 1.7 mg/dL (16.8), −7.5 mg/dL (15.9), and −9.4 mg/dL (19.1), in the PBO, HTD1801 500 mg BID and 1000 mg BID groups, respectively.
Conclusion: HTD1801 treatment has demonstrated both cardiometabolic and hepatic benefits in Chinese patients with T2DM and presumed MASLD with dose dependent improvements in HbA1c, GGT and LDL-C. These data suggest HTD1801 can comprehensively address metabolic and cardiovascular risk factors beyond glycemic control. Further evaluation of HTD1801 continues in 3 Phase 3 studies of T2DM and a Phase 2b study of patients with MASH and T2DM/pre-diabetes.

SAT-433-YI
Multidisciplinary management combining hepatologist counseling, cognitive/behavioral therapy, and nutritional support (the "CoCoNut" protocol) significantly improves metabolic and clinical outcomes of MASLD patients

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Background and aims: Metabolic dysfunction-associated Steatotic Liver disease (MASLD) is a systemic disorder severely burdened by various extra-hepatic complications. In this context, acute cardiovascular events (ACE) represent a real plague dramatically affecting mortality, suggesting the cruciality of holistic approaches. Although several drugs have been tested to target dysmetabolic comorbidities, lifestyle modifications remain the cornerstone intervention. Unfortunately, the dietary-behavioral prescription is constantly limited by poor compliance, and, despite emerging evidence supporting behavioral therapy's relevance, the real benefits of offering motivational support to MASLD individuals remain unexplored in real life. Considering this, we aimed to evaluate the effectiveness of a multidisciplinary (hepatologist-nutritionist-psychologist- "CoCoNut") management in improving clinical outcomes in MASLD, via ameliorating adherence to specialistic tailored indications.
Method: MASLD patients (n.286) were consecutively enrolled and randomized in three cohorts: 72 followed generic hepatologist-provided advice ("H"), 71 also received a nutritionists-prescribed individualized intervention ("HN") (H+N = "standard of care"), and 143 were treated with an approach additionally involving cognitive/

behavioral-based psychological support ("HNP") ("experimental-group"). Baseline anthropometric, biochemical, clinical, liver stiffness (LSM), controlled attenuation parameter (CAP), lifestyle habits, and body composition values were recorded. Along 18 months, semestral hepatological (for all), nutritional (H and HN), and psychological (HNP) follow-ups reassessed parameters and evaluated compliance.
Results: After 18 months, the prevalence of patients achieving a ≥10% decrease in body weight was significantly higher in HNP (HNP:62.09%; HN:44.9%; H:35.8%; HNP vs HN, p:0.01; HNP vs H, p:0.0002). In HNP, a significant improvement in Homeostatic-model-assessment-for-insulin-resistance (p:0.001), HDL (p < 0.0001), LSM (p:0.007), CAP (p:0.002), and fat-mass (p < 0.0001) was observed. Loss of compliance rate was significantly lower in HNP (HNP:12.08%; HN:34.7%; H:45.8%; HNP vs HN, HNP vs H, p:0.001) Relevantly, HNP patients presented a significantly lower risk of ACEs [HR: 0.497, IC (0.236–0.751) 95%, p:0.04)]. Logistic regression analysis (adjusted for sex, age, drug administration, and cardiovascular risk factors) revealed that HNP adherence was significantly associated with lower ACE occurrence (aOR: 0.81; C.I. 95%: 0.55–0.97; p:0.02). Large family, dynamic work, and city life emerged as social factors influencing compliance (OR: 2.11, 1.78, 1.12) (all p < 0.05).
Conclusion: Integrating standard hepatological-nutritional with psychological support significantly improves the metabolic and clinical outcomes of MASLD patients.

SAT-434-YI

Efficacy of pharmacotherapy in improvement of liver fibrosis and steatohepatitis in patients with metabolic dysfunction associated steatotic liver disease (MASLD): a network meta-analysis

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Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is common cause of chronic liver disease. Apart from lifestyle changes including dietary restriction and exercise, several pharmacologic therapies are in pipeline and there is a major need to clarify the comparative efficacy of these therapies. The aim of this study was to estimate the relative rank-order efficacy of different pharmacological therapies in metabolic dysfunction–associated steatohepatitis (MASH) resolution and fibrosis improvement.
Method: Randomized-controlled-trials (RCTs) comparing pharmacological interventions in patients with biopsy-proven MASH and assessing fibrosis improvement or MASH resolution were included. The primary outcome was ≥ 1 stage improvement in fibrosis. Secondary outcomes were comparing different pharmacological interventions for MASH resolution and assessing different interventions for fibrosis improvement and MASH resolution in patients with liver cirrhosis.
Results: Total 44 trials (with a total of 9779 patients and comparing 28 different drugs) met the eligibility criteria. Pegozafermin, Lanafibrinor, Obeticholic acid, Resmetirom, Vitamin E and Pioglitazone were significantly better than placebo in achieving ≥ 1 stage fibrosis improvement. Pegozafermin (P-score = 0.91), Pebelfermin (P-score = 0.72), and Lanafibrinor (P-score = 0.71), had the highest probability of being ranked the most effective intervention for achieving ≥ 1 stage of fibrosis improvement, respectively. Efruxifermin, Pegozafermin, Tirzepatide, Semaglutide, Aldafermin, Pioglitazone, Resmetirom and Lanafibrinor were significantly better than placebo in achieving MASH resolution. Efruxifermin (P-score = 0.94), Pegozafermin (P-score = 0.92), Tirzepatide (P-score = 0.91) and Semaglutide (P-score = 0.75) had the highest probability of being ranked the most effective intervention for achieving MASH resolution. In cirrhotic patients, none of the therapies were found to be better than placebo in achieving fibrosis improvement or MASH resolution.
Conclusion: This study provides an updated relative rank-order of various therapies in terms of their efficacy in fibrosis improvement and MASH resolution. In future, therapies that improve liver fibrosis in patients with MASLD may be combined with therapies which achieve MASH resolution for better treatment response.

SAT-435-YI

A comparative analysis of metabolic dysfunction-associated steatotic liver disease and Mediterranean diet across different races

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Background and aims: While previous studies have highlighted the benefits of Mediterranean diet in reducing liver steatosis, these investigations have primarily been conducted in Western populations, overlooking the unique dietary factors of other populations. This study aims to evaluate the association between steatotic liver disease (SLD) and adherence to the Mediterranean diet across different racial groups, with a particular focus on Asians.
Method: This case-control study utilized a nationally representative dataset from the National Health and Nutrition Examination Survey 2017–March 2020, which included vibration-controlled transient elastography measurements for quantifying liver steatosis and fibrosis. Our inclusion criteria include age 18 years or older and complete controlled attenuation parameter, alcohol and nutrient intake data. Case group comprised participants meeting the consensus nomenclature for metabolic dysfunction-associated steatotic liver disease (MASLD), defined as CAP ≧ 288 dB/m with at least 1 metabolic factor. Control group consisted of individuals with a CAP < 288 dB/m (non-SLD). For predictor variable, we extracted information from NHANES dietary questionnaires to evaluate participants' adherence to the Mediterranean diet. Adherence was quantified into aMED score, ranging from 0 to 9, with higher scores indicating greater adherence, categorized into three groups: 0–2, 3–4, and 5–9. Effect modification by race was examined. Confounding factors considered in the multivariate analysis include age, sex, anti-HBC, HCV RNA, alcohol intake, physical activity, ALT, total bilirubin, platelet, and liver stiffness.
Results: Of the 15,560 participants, 3,600 MASLD (case) and 2,777 non-SLD (control) individuals were selected. The MASLD group was predominantly non-Hispanic white (37.2%), followed by Hispanic (25.9%) and Asian (8.5%). The non-SLD group comprised primarily non-Hispanic white (36.2%), followed by non-Hispanic black (31.2%) and Asian (9.7%). While there was little difference in the number of people with high aMED scores between the two groups, the MASLD group had a higher proportion of people with middle aMED scores (3–4) compared to the non-SLD group (42.2% vs. 39.3%). Because a significant effect modification by race was observed, results from adjusted analysis with an interaction term showed a significantly lower MASLD risk among non-Hispanic white individuals compared to Hispanic individuals with high aMED scores (aOR: 0.53, p = 0.002). This association was absent in other races, including non-Hispanic Asians (aOR: 0.66, p = 0.23).
Conclusion: A lower risk of MASLD was observed among non-Hispanic Whites with high adherence to the Mediterranean diet, but this association was not evident in other racial groups. Future research should explore how the Mediterranean diet affects MASLD risk across different races and ethnicities.

SAT-436

Efficacy of Imeglimin in MASLD with type 2 diabetes: a multicenter study

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Background and aims: Imeglimin is a novel oral hypoglycemic agent for the treatment of type 2 diabetes mellitus (T2DM) that protects mitochondrial function from oxidative stress and promotes lipid oxidation, thereby normalizing glucose tolerance and insulin sensitivity. Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with metabolic risk factors such as insulin resistance, T2DM, obesity, and dyslipidemia, and represents a significant public health concern. To date, various medications have been utilized for MASLD, but no definitive therapeutic agent has been established. Therefere, this study aimed to investigate the therapeutic efficacy of imeglimin for MASLD in patients with T2DM across multiple centers.
Method: This study included 131 patients with MASLD and T2DM who received imeglimin treatment at our institution and affiliated facilities. Among them, 40 patients who continued treatment for at least six months were analyzed. To evaluate the effects of imeglimin, changes in liver function markers such as AST, ALT, γ-GTP, controlled attenuation parameter (CAP), liver stiffness measurement (LSM), and FibroScan-aspartate aminotransferase (FAST) score were assessed. Furthermore, changes in these markers were evaluated monthly, from baseline up to six months, to examine early effects.
Results: AST and ALT levels significantly decreased at four weeks after imeglimin administration. γ-GTP also showed a significant decrease at four weeks. Although other biomarkers, including type IV collagen, autotaxin, and the AST-platelet ratio index, did not show significant reductions after imeglimin treatment, the FIB-4 index showed a significant decrease at six months. CAP and LSM did not exhibit significant reductions, but the FAST score significantly decreased at 24 weeks. Additionally, in a subgroup analysis based on baseline HbA1c levels (≥8 vs. <8), AST, ALT, and γ-GTP significantly decreased from four weeks after treatment in the HbA1c <8 group, while the FIB-4 index significantly decreased at 12 weeks. These results represent the first multicenter report indicating that imeglimin improves liver function and fibrosis markers and is effective against hepatic steatosis, inflammation, and fibrosis in patients with MASLD and T2DM.
Conclusion: Imeglimine may be a novel treatment for T2DM complicated by MASLD.

SAT-437

Denifanstat improves multiple qFibrosis-based collagen features linked to major adverse liver outcomes in patients with metabolic dysfunction-associated steatohepatitis patients and high polygenic risk

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Background and aims: Denifanstat (DENI) is a fatty acid synthase inhibitor in development for metabolic dysfunction-associated steatohepatitis (MASH). It met statistical significance in histology endpoints in a phase 2b trial, showing antifibrotic effect. Liver fibrosis, several genetic variants, and 5 qFibrosis parameters features in the periportal and portal zones (digital pathology) have been associated at baseline with major adverse liver outcomes (MALO). We assessed the antifibrotic effect of DENI in different genotypes.
Method: The FASCINATE-2 phase 2b trial (NCT04906421) randomized 168 patients with biopsy-proven MASH, NAS ≥ 4, and NASH-CRN fibrosis stage 2 or 3, to receive either oral once-daily DENI 50 mg or placebo (PBO) (2:1) for 52 weeks. *PNPLA3* rs738409, *MBOAT7* rs641738, and *TM6SF2* rs58542926 were genotyped in consenting patients. Relative changes from baseline in qFibrosis were calculated using steatosis correction as well as features previously linked to MALO: IntersectionPT (#1), LongStrPeriPortalAgg (#2), ThinStrPeriPortal (#3), ThinStrPeriPortalDis (#4), and StrLengthPeriPortal (#5). Treatment by polygenic risk strata (≤1 risk allele vs > 1 risk allele of the 3 above variants) interaction was tested in an ANCOVA model including terms for treatment, polygenic risk strata, interaction, and (log-transformed) baseline parameter.
Results: At week 52, in accordance with NASH-CRN scores, continuous qFibrosis was significantly decreased in DENI group (−1.0) vs PBO (−0.1, $p < 0.0001$). PBO-corrected treatment effect of DENI on qFibrosis was similar across polygenic risk strata. PBO-corrected relative change from baseline of DENI was −30% ($p = 0.03$), −31% ($p = 0.02$), −27% ($p = 0.01$), −25% ($p = 0.02$), and −30% ($p = 0.01$) in qFibrosis features previously linked to MALO #1, #2, #3, #4, and #5, respectively. Notably, the PBO-corrected treatment effect of DENI on these features was more pronounced in carriers of at least 2 risk alleles vs non-carriers or carriers of 1 risk allele (#2: $p = 0.01$, #3: $p = 0.04$, #4: $p = 0.06$, #5: $p = 0.01$). In the subgroup of patients classified as "no change" by conventional pathology, continuous qFibrosis provided more granularity on DENI effect showing a significant decrease (−0.9) vs PBO (−0.1; $n = 52$, $p < 0.001$). Within this subgroup, 4 out of 5 qFibrosis-based collagen features were significantly decreased compared to PBO: −30% ($p = 0.02$), −32% ($p = 0.02$), −30% ($p = 0.03$), and −29% ($p = 0.02$) in features #2, #3, #4, and #5, respectively.
Conclusion: Digital pathology showed antifibrotic effect of DENI in qFibrosis-based collagen features previously linked to MALO and recapitulated NASH-CRN fibrosis staging. Pronounced changes were seen with DENI in the difficult-to-treat population with several risk variants associated with MALO. Further research is warranted to discern the specific effect related to DENI mechanism of action within the polygenic risk population.

SAT-438

General characteristics of the patients prescribed Resmetirom: data derived from six tertiary care centers in the United States

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Background and aims: Resmetirom was recently approved by the FDA as the first medication intended for non-cirrhotic patients with metabolic dysfunction-associated steatohepatitis (MASH) and stage F2-F3 fibrosis. The approval was based on histological improvement and patients were selected for the phase 3 trial based on liver biopsy. However, in the real world, most patients with MASH do not undergo liver biopsy and the diagnosis is based on noninvasive tests. Here, we aimed to describe the general characteristics of the MASH patients prescribed resmetirom including noninvasive tests and concomitant medications derived from six hepatology clinics in the United States.
Method: The data of MASLD patients derived from six tertiary care centers were collected between March and Nov 2024 (265, 15, 32, 48, 27, and 37 patients from six centers, respectively, total 424 patients). The demographic and laboratory data were recorded during the baseline visit.
Results: The cohort had a median age of 58 years (IQR: 49–67), with 179 males (42.0%). A total of 88 patients (20.8%) were diagnosed via liver biopsy, while the majority (88.9%) were assessed using transient elastography; 56 (13.2%) had ELF testing. The median liver stiffness measurement (LSM) was 11.0 kPa (IQR: 8.9–13.4) and the median ELF was 9.7 (IQR: 9.4–10.3). Obesity was prevalent in 356 patients (84.0%), while 185 patients (43.6%) had type 2 diabetes (T2D). Cardiometabolic comorbidities were common, with 40.3% on statins, 19.3% on GLP-1 analogs, and 33.3% on metformin. Patients prescribed resmetirom were predominantly on 80 mg (50.9%) or 100 mg (47.2%) doses. Only 1.9% were prescribed 60 mg. The number of patients with 0, 1, 2, 3, and ≥4 cardiometabolic risk factors were 6.8%, 23.3%, 28.3%, 29.2%, and 12.3%, respectively.
Conclusion: This large real-world cohort of MASH patients prescribed resmetirom reflects the high burden of cardiometabolic comorbidities typical of MASLD populations, with obesity and T2D being especially prevalent. Most patients were diagnosed with advanced fibrosis (F2-F3) using noninvasive methods, such as transient elastography, highlighting a shift from biopsy reliance in clinical trials to real-world practice. These findings underline the importance of integrated management of cardiometabolic risk factors and reinforce the potential of resmetirom as a critical therapy for MASH in real-world settings.

SAT-439

The impact of metabolic surgery on metabolic dysfunction-associated steatotic liver disease

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Background and aims: Obese people with fatty liver are diagnosed as MASLD. Chronic liver inflammation can progress to cirrhosis and liver cancer. Therefore, controlling persistent inflammation is crucial for improving the prognosis of patients with MASLD. Metabolic surgery is known to induce dramatic weight loss and significant metabolic improvements. This study aimed to examine the impact of obesity-related metabolic abnormalities on MASLD and evaluate the effects of metabolic surgery on MASLD.
Method: We enrolled 66 severely obese patients with MASLD undergoing laparoscopic sleeve gastrectomy from July 2020 to April 2022. Blood samples were obtained preoperatively and one year after surgery. Blood cytokines were analyzed using multiplex assay, adiponectin and leptin by ELISA, BCAA by HPLC, liver stiffness by shear wave elastography (SWE), and visceral/subcutaneous fat areas by CT. Liver biopsies were performed intraoperatively, and histological evaluation was performed.
Results: Fourty-two patients (64%) were female. The median age was 45 years, body mass index (BMI) was 43.6 kg/m², systolic blood pressure (sBP) was 143 mmHg, ALT was 47 (10–231) U/L, and the HbA1c was 6.2 (5.2–11.1) %. Compared to non-obese healthy age-mathced adults, 25 blood cytokines, including TNF-α, were higher in the obese patients, indicating that systemic inflammation exists in obese patients. One year after metabolic surgery, there was a decrease in BW, BMI, visceral and subcutaneous fat area, and sBP, ASL, ALT, SWE, type-4 collagen, HbA1c, HOMA-IR, TG and BCAA. After surgery, Leptin decreased, while adiponectin increased. We observed the effects of metabolic surgery on metabolic factors and liver inflammation. Next, we tried to investigate the factors associated with liver inflammation in obese patients. Preoperative ALT > 30 U/L group (45 cases) was compared to preoperative ALT ≦ 30 group (21 cases). The ALT > 30 group was characterized by younger age, a higher proportion of men, elevated systolic blood pressure (sBP), higher AST and gamma-GTP (GGT), increased HbA1c and HOMA-IR, higher BCAA, lower HDL cholesterol (HDL-C), and reduced adiponectin levels. Advanced fibrosis (F2 or higher) was significantly more common in the ALT > 30 group (76%) than in the ALT ≦ 30 group (48%), suggesting an association between liver inflammation and metabolic abnormalities. Among the patients with the preoperative ALT > 30, 5 cases were still ALT > 30 at 1 years after metabolic surgery. To explore the factors contributing to postoperative ALT > 30, we analyzed the preoperative factors in the postoperative ALT > 30 group. In the multivariate analysis, high preoperative HbA1c was an independent contributing factor for postoperative ALT > 30.
Conclusion: Liver inflammation in severely obese MASLD patients was associated with metabolic abnormalities, and metabolic surgery showed beneficial effects.

SAT-440

Effects of Berberine Ursodeoxycholate (HTD1801) in patients with at-risk MASH and T2DM

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Background and aims: Berberine ursodeoxycholate (HTD1801) is a gut-liver anti-inflammatory metabolic modulator with a unique molecular structure which has been shown to significantly reduce liver fat content (LFC) as determined by MRI-PDFF in an 18-week, placebo (PBO)-controlled Phase 2 study in patients with MASH and T2DM (NCT03656744). The primary focus of clinical development in MASH due to the ongoing unmet medical need focuses on patients who are at a higher risk of disease progression and outcomes due to the presence of moderate to advanced fibrosis (defined as at-risk MASH). The purpose of this analysis was to assess the effects of HTD1801 in patients with at-risk MASH and T2DM.
Method: 100 patients were randomized and treated with PBO (n = 33), HTD1801 500 mg BID (n = 33), or HTD1801 1000 mg BID (n = 34) for 18 weeks. The primary endpoint was change in LFC. This analysis focused on patients with at-risk MASH as identified by baseline MRI cT1 > 875 ms and was only assessed in patients randomized to PBO and HTD1801 1000 mg BID.
Results: 66% of patients were considered as having at-risk MASH at baseline, and were evenly distributed between the PBO (n = 23) and HTD1801 1000 mg BID (n = 21) groups. At baseline, LFC, cT1, and body weight were all generally balanced between groups at approximately 20%, 970 ms, and 100 kg, respectively. After 18 weeks of treatment,

the relative change from baseline in LFC was −7.3% (25.0) and −26.2% (21.7) with 22% vs 43% of patients achieving ≥30% reduction in LFC for PBO and HTD1801 1000 mg BID, respectively. The change from baseline in cT1 was −28.7 ms (70.6) and −67.1 ms (83.1) with 17% vs 48% of patients achieving ≥80 ms reduction in cT1 for PBO and HTD1801 1000 mg BID, respectively. In addition, after 18 weeks of treatment the change from baseline in body weight was −1.5 kg (3.2) and −4.2 kg (4.5) in the PBO and HTD1801 1000 mg BID groups. Improvements were also observed in ALT, HbA1c, and LDL-C with HTD1801 treatment.

Conclusion: Eighteen weeks of treatment with HTD1801 resulted in substantial improvements in key hepatic and cardiometabolic parameters in patients with probable at-risk MASH and twice as many patients achieved a reduction in LFC or fibroinflammation that have been associated with improvements in liver histology. These data are particularly insightful as HTD1801 continues to be evaluated in an ongoing paired biopsy study of patients with at-risk MASH and pre-diabetes or diabetes.

SAT-445

Sustained improvements in non-invasive biomarkers with the novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist survodutide: longitudinal analysis from a phase 2 trial in people with metabolic dysfunction-associated steatohepatitis and fibrosis

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Background and aims: We performed a longitudinal analysis of the effects of survodutide, a novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist, on non-invasive biomarkers in a phase 2 trial in participants with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and F1–F3 liver fibrosis (NCT04771273).

Method: 295 people aged 18–80 years were randomised to once-weekly subcutaneous injections of survodutide 2.4, 4.8, or 6.0 mg or placebo (PBO) (escalated over up to 24 weeks). In this analysis, we evaluated absolute change in enhanced liver fibrosis (ELF™) score and its components, relative change in propeptide of type III collagen (PRO-C3), total cytokeratin 18 (M65) (CK18-M65), Fibrosis-4 index (FIB-4), and glucagon longitudinally from baseline (BL) up to Week 48. Longitudinal analyses were performed on treated participants with BL and ≥ 1 post-BL biomarker value. Changes in biomarker levels over time were analysed using restricted maximum likelihood based mixed model for repeated measures (MMRM) with visit as the repeated measure and an unstructured covariance matrix. Due to their skewed distribution, a logarithmic transformation was applied to all biomarkers (except for the ELF score). Model estimates were back transformed and are reported in the original scale. The MMRM included fixed categorical effects of sex and diabetes at BL, fixed continuous effects of BL body weight, age, and magnetic resonance imaging proton density fat fraction liver fat fraction, and interaction terms for visit and BL biomarker values and for visit and actual treatment (dose at start of maintenance or planned dose up from that received at pre-maintenance discontinuation). P-values are nominal.

Results: Longitudinal absolute reduction in ELF score from BL was 0.57–0.61 with survodutide vs 0.05 for PBO at Week 48 ($p < 0.0001$ all doses). There was a significant reduction in the 3 components of the ELF score with survodutide vs PBO ($p < 0.01$ all doses). The estimated relative change in PRO-C3 was 0.71–0.74 (BL: 39.52–41.73 micrograms/L) with survodutide vs 1.01 (BL: 41.67 micrograms/L) with PBO ($p < 0.001$ all doses). Estimated relative change in total CK18 was 0.29–0.40 (BL: 640.51–672.27 U/L) with survodutide vs 0.90 (BL: 722.72 U/L) with PBO ($p < 0.0001$ all doses). Estimated relative change in FIB-4 was 0.80–0.85 (BL: 1.06–1.12) with survodutide vs 1.04 (BL: 1.22) with PBO ($p < 0.01$ all doses). Estimated relative change in glucagon was 0.73–0.84 (BL: 60.87–65.24 pmol/L) with survodutide vs 1.01 (BL: 61.18 pmol/L) with PBO ($p < 0.0001$ all doses).

Conclusion: Participants who received survodutide vs PBO had significant improvement in multiple non-invasive biomarkers for MASH and liver fibrosis (ELF score and its components, PRO-C3, glucagon, and FIB-4) and significantly reduced levels of total CK18, suggesting increased hepatocyte survival with survodutide treatment.

SAT-446

Survodutide activates cAMP signaling and reduces steatosis and fibrosis through its glucagon component in human liver spheroids

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Background and aims: Survodutide, a novel glucagon receptor/glucagon-like peptide-1 receptor dual agonist is currently in Phase 3 clinical trials in people with metabolic dysfunction-associated steatohepatitis (MASH) and for people living with obesity. Recent Phase 2 trials in people with MASH demonstrated anti-steatotic and anti-fibrotic effects of survodutide. Here we report the in vitro characterisation of survodutide in liver spheroids as models for healthy and diseased human liver.

Method: Human liver spheroids resembling phenotypes of healthy and MASLD human livers were investigated for dose-responsive increases in intracellular cAMP upon treatment with survodutide; semaglutide (mono GLP-1R agonist) and tirzepatide (dual GLP-1R/GIPR agonist) were included for comparison. In addition, increases in cAMP was assessed in hepatocytes monolayers from multiple healthy donors. Healthy control and MASH spheroids were incubated with survodutide and total triglyceride content and secretion of pro-collagen 1 (PC-1) were determined after 10 days.

Results: Survodutide increased cAMP in primary hepatocytes mono layers with EC_{50} = 0.581 micromolar. Survodutide (at 1 micromolar) significantly increased cAMP levels in control and MASLD spheroids showing a 3-fold higher potency in MASLD spheroids. Semaglutide and tirzepatide (both 1 micromolar) did not increase cAMP. Compared to control spheroids, MASH spheroids showed a statistically significant increase (9.8 fold, $p < 0.0001$) of triglyceride content and PC-1 secretion (10.3 fold, $p < 0.0001$). In MASH liver spheroids, survodutide significantly reduced intracellular triglyceride content by 23.8% ($p < 0.05$) at a concentration of 0.3 micromolar (EC_{50} = 0. 655 micromolar) and PC-1 secretion by 35.0% ($p < 0.05$) at 1 micromolar (EC_{50} = 0.662 micromolar).

Conclusion: Survodutide showed increased cAMP signalling in spheroids as a model for healthy and MASLD human hepatocytes, while the incretin analogues semaglutide and tirzepatide did not show a response. Survodutide significantly lowered triglyceride as well as PC-1 secretion in MASH spheroids. Human liver spheroids represent a robust in vitro model for human liver cells to study glucagon receptor agonism.

SAT-447

Comprehensive intensive lifestyle intervention to reverse significant liver fibrosis in overweight and obese patients with metabolic dysfunction-associated steatotic liver disease: data from a multicenter randomized controlled trial

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Background and aims: Liver fibrosis, rather than steatosis, is the vital driver of adverse outcomes in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). This study aimed to evaluate the effectiveness of a 12-week comprehensive intensive lifestyle intervention (ILI) to reverse significant liver fibrosis among overweight/obese patients diagnosed with MASLD.

Method: We analyzed participants with significant liver fibrosis, defined as liver stiffness measurement (LSM, by transient elastography) ≥8 kPa, from a 12-week randomized controlled trial (ClinicalTrials.gov identifier: NCT03972631) involving well-characterized overweight/obese patients with MASLD (aged 18–65 years, BMI 25–35 kg/m²). Eligible participants were assigned to the ILI or control groups in a 1:1 ratio. During the 12 weeks of the trial, patients in both groups were asked to follow a restricted-energy content (initial weight × 25 kcal/kg × 0.7); after randomization, the ILI group received an intensive intervention, following a low-carbohydrate, high-protein diet (20–25 energy percent [E%] carbohydrates, 30–35 E % fat, and 40–45 E% protein), while the control group adhered to a balanced CRD (45–55 E% carbohydrates, 20–30 E% fat, and 20–30 E% protein). All outcomes were collected at baseline and 12 weeks after the intervention started. The primary outcome was the proportion of patients who reversed significant fibrosis from baseline to week 12. Secondary outcomes including changes in weight, liver enzymes and other metabolic indicators.

Results: A total of 33 participants from six university hospitals were enrolled, with 18 in the ILI group and 15 in the control group. Baseline characteristics were comparable between the two groups. The mean ± SD age and BMI in the ILI group (12 [63.2%] male) were 38.0 ± 9.5 years and 29.38 ± 2.41 kg/m², respectively, and in the control group (17 [85.0%] male), they were 38.9 ± 6.5 years and 30.95 ± 2.75 kg/m², respectively. Both groups showed significant changes from baseline to week 12 in LSM, BMI, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), triglycerides (TG), fasting insulin (FINS), HOMA-IR, and HOMA-β (all $p < 0.05$). Notably, the ILI group achieved a significant higher proportion of reversal in significant liver fibrosis compared to the control group (88.9% vs. 53.5%, $p = 0.047$). Additionally, the ILI group showed greater improvements in key metabolic and liver-related parameters, with mean differences of BMI: −1.53 kg/m² (95% CI: −2.41 to −0.65), ALT: −10.25 IU/L (95% CI: −20.42 to −0.09), GGT: −8.67 IU/L (95% CI: −16.45 to −0.90), fasting insulin: −3.04 μU/mL (95% CI: −5.88 to −2.12), HOMA-β: −42.95 (95% CI: −78.65 to −7.24), all with $p < 0.05$.

Conclusion: The ILI approach was more effective than the traditional balanced diet to reverse significant liver fibrosis in overweight/obese patients with MASLD.

SAT-448

A 10-week, randomized, double blind, placebo-controlled exploratory proof of concept study of Utreglutide (GL0034) in individuals with overweight and obesity

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Background and aims: Utreglutide (UTG, GL0034), a potent glucagon-like peptide-1 receptor agonist, has been demonstrated to be safe in a phase 1 program in individuals with obesity. A reduction of body weight (BW) up to 3.3 kg resulted upon single dose administration in obese subjects and sustained till day 22. Further, in multiple ascending dose studies, improvements in liver injury, metabolic and lipid biomarkers were observed. Here, we present safety and efficacy data in a 10-week, randomized, double blind, placebo (PBO) controlled exploratory Proof of Concept study of UTG in individuals with overweight and obesity.

Method: The study was carried out in 20 male and female individuals with overweight or obesity and BMI between ≥ 28 and ≤45 kg/m², which were randomized (16:4) to weekly subcutaneous UTG (400, 2 × 800, 3 × 1400, 4 × 2000 μg) or placebo following an up-titration scheme. Safety along with efficacy biomarkers were assessed viz., liver enzymes [alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT)], lipids [low-density lipoprotein cholesterol (LDL-C), Apolipoprotein B (ApoB), fatty liver index (FLI), very-low density lipoprotein cholesterol (VLDL-C)], free fatty acids (FFA), and β-hydroxybutyrate as well as BW.

Results: Most common adverse events were gastrointestinal including nausea, decreased appetite and vomiting. BMI (kg/m²) at baseline was 33.7 ± 3.1 for UTG treatment group and 34.5 ± 3.5 for PBO. UTG treatment for 10 weeks caused a significant improvement in liver enzymes, lipids, and ApoB. The change in liver enzymes were, ALT [42.6 to 29.5 U/L ($p = 0.02$)], AST [28.9 to 22.9 U/L ($p = 0.004$)], GGT [29.7 to 22.3 U/L($p < 0.001$)], and ALP [75.9 to 71.6 U/L($p > 0.05$)]. These changes reflected in as a significant decrease in the non-invasive marker of fatty liver disease, FLI [77.6 to 62.1 ($p < 0.001$)] along with LDL-C [128.0 to 110.2 mg/dL ($p = 0.03$)], ApoB [0.99 to 0.81 g/L ($p = 0.001$) and VLDL-C [29.9 to 29.4 mg/dL ($p > 0.05$)]. No significant change was observed in FFA (0.34 to 0.33 mmol/L) and β-hydroxybutyrate (0.43 to 0.50 mmol/L). Reduction in BW from baseline was sustained with significance until the end of study [UTG: − 5.9 ± 3.2 kg ($p < 0.001$); PBO: 0.3 ± 0.9 kg].

Conclusion: Utreglutide was safe and well tolerated by individuals with overweight and obesity. The observed pharmacodynamic effects

on liver enzymes and lipid profile, FLI along with body weight reduction at a total dose of 14.2 mg in 10-weeks, suggest potential therapeutic benefits in MASLD patients.

SAT-449

Saroglitazar vs. vitamin E in metabolic-dysfunction associated fatty liver disease related compensated chronic liver disease- a cohort study

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Background and aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) is an emerging cause of chronic liver disease with limited pharmacotherapeutic options. We aimed to investigate the efficacy of saroglitazar (SARO) compared to vitamin E (VitE) on non-invasive surrogates of liver fibrosis and portal hypertension in patients with MAFLD-related compensated chronic liver disease (CLD).

Method: Retrospective cohort of patients with MAFLD, all having liver stiffness measurements (LSM ≥ 10; n = 264, 39% biopsy-proven), were treated with either SARO (n = 92) or VitE (n = 172). Patients were followed with assessments of LSM and spleen stiffness measurement (SSM) performed at baseline and follow-up of every 3–6 months. Progression was defined as a worsening of LSM by 10% and SSM by 20% from baseline at 6 months, while response was defined as a reduction by 20% from baseline to last assessment.

Results: Patients with MAFLD, mean age 48.8 ± 11.2 years, 76% males, 15% hypothyroid, 80% with body mass index (BMI) >23.5, 6% with a family history, and patatin-like phospholipase domain-containing 3 (PNPLA3 rs738409; n = 117) (43%-GG, 34% CG, 22.2% CC genotype) were enrolled. These patients had a mean controlled attenuation parameter (CAP) of 245.5 ± 51.1, LSM 32.9 ± 19.5, SSM 49.9 ± 27.2, HOMA-IR 2.8 ± 2.7, Fib-4 4.7 ± 3.7, and CRP 5.1 ± 10.5, and were followed. Of the 102 patients with hepatic venous pressure gradient (HVPG) measurement, the majority (76%) had HVPG >10 mm Hg (mean 13.2 ± 5 mm Hg).Patients in the VitE group had significantly higher LSM [(29 ± 17.32) vs (34.99 ± 20.29); p = 0.01], FIB4 [(4.14 ± 3.07) vs. (5.05 ± 3.92); p = 0.05], AST [(47.1 ± 24.2) vs. (63.2 ± 57.9); p = 0.01], and lower LDL [(89.8 ± 49.5) vs. (78.9 ± 32.2); p = 0.005] compared to SARO, respectively. The proportion of patients with weight reduction was also similar [(≥10%) 6% vs. 11%, (5–9%) 15% vs.15%; (<5%) 38% vs. 35%; p = 0.65) including response in LSM (50% vs. 41%; p = 0.60) and SSM (14% vs. 15%; p = 0.83) at last assessment; median follow-up of 301(180–642) days. At 6-months, 12% had progression of disease which was comparable (8% vs. 14%; p = 0.24) between SARO and VitE, respectively. Binary logistic regression analysis showed lower ALT (p = 0.02, OR 0.96, 0.93–0.99), presence of hypothyroidism (p = 0.008, OR 4.19, 1.46–12.01), higher BMI (p = 0.03, OR 1.11, 1.01–1.22), and fasting blood sugar (p = 0.04, OR 1.01, 1.00–1.02) were independent determinants of disease progression.

Conclusion: Saroglitazar is comparable to vitamin E in improving metabolic and clinical outcomes, as well as non-invasive surrogates of liver fibrosis and portal hypertension in patients with MAFLD-related cirrhosis. Patients with hypothyroidism, lower ALT, higher BMI, and higher fasting blood sugar are at a higher risk of disease progression and require targeted pharmacotherapy.

SAT-450

ALG-055009, a novel thyroid hormone receptor beta (THR-beta) agonist, demonstrated robust reductions in liver fat at Week 12 across subgroups including glucagon-like peptide-1 (GLP-1) receptor agonist users in non-cirrhotic MASH patients in the Phase 2a HERALD study

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Background and aims: ALG-055009, a next generation THR-beta agonist with enhanced beta selectivity and in vitro potency, previously demonstrated favorable Ph1 safety, pharmacokinetic (PK) and pharmacodynamic (PD) effects in healthy volunteers/hyperlipidemic subjects. In the Ph2a HERALD (NCT06342947) randomized, double-blind, placebo-controlled study, the efficacy, safety, PK and PD of 12-week once daily ALG-055009 were evaluated in non-cirrhotic adults with presumed MASH and F1-F3 fibrosis. As reported previously, the primary endpoint was met, demonstrating significant reductions in liver fat (Loomba et al. AASLD 2024). Subgroup analyses for the primary endpoint are reported here, including those associated with a worse prognosis (e.g., type 2 diabetes).

Method: 102 subjects (~20/arm) were randomized to receive 0.3, 0.5, 0.7 or 0.9 mg ALG-055009 or placebo, orally once daily for 12 weeks. Only subjects with body weight >85 kg were enrolled in the 0.9 mg arm, with no weight restrictions for other arms. The primary endpoint was relative change from baseline in liver fat by MRI-PDFF at Week 12 and was analyzed across subgroups, defined according to baseline characteristics, e.g., gender, body weight, GLP-1 agonist use, statin use and type 2 diabetes status. Subjects on glucagon-like peptide-1 (GLP-1) receptor agonists at a stable dose for ≥12 weeks prior to dosing were included.

Results: Baseline characteristics were generally similar across arms and representative of the MASH patient population: 62% female, mean age 50 yrs, mean BMI 39 kg/m2, 47% Hispanic, 18% GLP-1 use, 35% statin use, 46% Type 2 diabetes. The mean time of GLP-1 use before first dose of ALG-055009 was 130 weeks. ALG-055009 dose groups met the primary endpoint, with statistically significant placebo-adjusted median relative reductions in liver fat of up to 46.2% at Week 12. Median placebo-adjusted liver fat reduction by selected subgroups were as follows: gender (male: up to 49%; female: up to 48%), body weight (up to 39% for >100 kg and up to 52% ≤100 kg), statin use (yes: up to 55%, no: up to 36%), GLP-1 agonist use (yes: up to 52%; no: up to 36%), or type 2 diabetes status (yes: up to 46%; no: up to 39%). Notably, subgroup analysis indicated that there were no clinically relevant differences in liver fat reduction among participants with or without GLP-1 agonist use.

Conclusion: 12 weeks of once daily ALG-055009 treatment in MASH subjects demonstrated significant reductions in liver fat, with efficacy observed across the baseline factors evaluated. This supports evaluation of longer durations of ALG-055009 and its effects on liver histology and indicates liver fat reductions with the next generation THR-beta agonist ALG-055009 may be observed across various baseline characteristics in the MASH patient population, including those associated with a worse prognosis.

SAT-451

ALG-055009, a novel thyroid hormone receptor beta agonist, demonstrated significant reductions in atherogenic lipids/lipoproteins, including lipoprotein (a), in patients with presumed metabolic dysfunction-associated steatohepatitis in the Phase 2a HERALD study

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are associated with atherogenic dyslipidemia, with cardiovascular disease (CVD) being the leading cause of mortality in this patient population. While statins reduce low density lipoprotein cholesterol (LDL-C), they have no effect on lipoprotein (a) (Lp(a)). ALG-055009 is a novel next generation thyroid hormone receptor (THR)-beta agonist with beta selectivity and in vitro potency exceeding that of first generation THR-beta drugs. In the randomized, double-blind, placebo-controlled Phase 2a HERALD study, 12 weeks of once daily ALG-055009 treatment in subjects with presumed MASH and F1-F3 fibrosis was well-tolerated and met the primary endpoint, demonstrating significant reductions in liver fat (Loomba et al. AASLD 2024). An analysis of the effects of ALG-055009 compared to placebo on lipid/lipoprotein levels, including Lp(a), a key secondary endpoint, is reported here.
Method: 102 subjects (~20/arm) were randomized to receive 0.3, 0.5, 0.7 or 0.9 mg ALG-055009 or placebo orally once daily for 12 weeks. Only subjects with body weight >85 kg were enrolled in the 0.9 mg arm, with no weight restrictions for other arms. Blood samples were collected to evaluate change from baseline in levels of the following lipid/lipoproteins: total cholesterol, high density lipoprotein cholesterol (HDL-C), LDL-C, non-HDL-C, triglycerides, apolipoprotein B (apoB), A1 and CIII (apoCIII), Lp(a), and very low-density lipoprotein cholesterol (VLDL).
Results: Baseline characteristics were generally similar across arms: 38% male, mean age 50 yrs, mean BMI 39 kg/m^2, 46% with Type 2 diabetes, 54% with dyslipidemia, 18% with stable glucagon-like peptide-1 (GLP-1) agonist use (mean duration of 33 months prior to dose), and 35% with stable statin use. Significant median reductions compared to baseline at Week 12 in levels of LDL-C (up to –15.9% vs. –3.6%; $p < 0.05$), Lp(a) (up to –26.8% vs. +6.1%; $p < 0.005$) and apoB (up to –18.3% vs. –1.5%; $p < 0.005$) for ALG-055009 vs. placebo, respectively, were observed at the highest ALG-055009 dose levels evaluated; reductions in triglycerides (up to –15.4% vs. –5.9%), VLDL (up to –14.8% vs. –6.3%) and apoCIII (up to –12.8% vs. –3.5%) were also observed. These lipids/lipoproteins reductions were observed with or without stable GLP-1 agonist or statin use.
Conclusion: The statistically significant improvements in atherogenic lipids achieved with 12 weeks of ALG-055009 treatment may suggest an added benefit for patients at risk for CVD in addition to the previously reported liver fat lowering properties in a MASLD/MASH population. This data supports evaluation of longer duration ALG-055009 treatment in a dedicated clinical trial of patients with dyslipidemia (including those with MASLD/MASH) to better characterize the extent of reduction in atherogenic lipids/lipoproteins.

SAT-452

GLP1 agonist and metabolic dysfunction-associated steatohepatitis (MASH): systematic review and meta-analysis

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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is one of the most prevalent liver diseases. However, pharmacological treatments for this disease have been limited. This meta-analysis aims to evaluate the benefits and limitations of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RA) in the treatment of MASH.
Method: MEDLINE and EMBASE was searched on 17th May 2024 for articles comparing GLP-RA with placebo or active comparators. Outcomes included resolution of MASH and ≥1 point reduction in fibrosis stage without worsening of MASH after administration of the drug. Pairwise meta-analysis was conducted to obtain the odds ratio (OR) and mean difference (MD) for dichotomous and continuous outcomes respectively.
Results: In total, 16 studies and 2557 patients were included in the analysis, with 924 MASH patients and 1633 MASLD patients. GLP-1 RA significantly increased the odds of MASH resolution (OR: 5.36, 95% CI: 3.08–9.34, $p < 0.01$, $I^2 = 36.80\%$) and improved fibrosis stage (OR: 2.08, 95% CI: 1.40–3.07, $p < 0.01$, $I^2 = 4.40\%$). However, improvement in fibrosis was only significant for non-cirrhotic patients. There was a reduction in liver fat content (MD = –3.82, 95% CI: –5.4 to –2.23, $p < 0.01$, $I^2 = 0.00\%$), AST (MD = –18.32 U/L, $p = 0.02$, $I^2 = 98.50\%$), ALT (MD = –27.34 U/L, $p < 0.01$, $I^2 = 98.80\%$), and GGT (MD = –35.57 U/L, $p = 0.01$, $I^2 = 98.80\%$) and other metabolic indices.
Conclusion: This meta-analysis has provided strong evidence for the use of GLP-1 based therapies for treatment of MASH/MASLD.

SAT-453

MASH resolution index, a novel, highly sensitive non-invasive measure of histologic improvement, predicts high rates of MASH resolution with pemvidutide treatment of metabolic dysfunction-associated steatohepatitis (MASH)

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Background and aims: Pemvidutide is a long-acting, GLP-1/glucagon dual receptor agonist under development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and obesity. We previously reported that pemvidutide led to >75% relative reduction in liver fat content (LFC) by MRI-PDFF after 24 weeks, with up to 50% of subjects achieving LFC normalization. Here, we utilized the MASH resolution index (MASHResInd), a novel score based on changes in non-invasive measures of MRI-PDFF, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with high sensitivity for detecting MASH resolution without worsening of

fibrosis (area under the curve [AUC] 0.81 for MASHResInd ≥−0.67), to predict MASH resolution with pemvidutide treatment.
Method: 64 subjects with metabolic dysfunction-associated steatotic liver disease (MASLD), defined as LFC ≥ 10% by MRI-PDFF, were randomized (1:1:1:1) to receive 1.2 mg, 1.8 mg, 2.4 mg pemvidutide, or placebo weekly for 24 weeks. Subjects with baseline ALT > 75 IU/L or evidence of advanced fibrosis, defined as liver stiffness measurement (LSM) by Fibroscan® ≥ 10 kPa, were excluded. The outcome measure was the proportion of subjects who achieved a MASHResInd response (≥−0.67, Loomba 2024) at Week 24. Combined MASHResInd response and corrected (c)T1 response (≥80 ms reduction, AUC 0.72, Alkhouri 2024) was assessed in a subset of 19 subjects who also underwent cT1 imaging.
Results: Median baseline BMI, LFC, ALT, and LSM, were 36.8 kg/m^2, 20.6%, 31.0 IU/L, and 6.5 kPa, respectively. 53% were female and 27% had diabetes. MASHResInd response was achieved by 22.2%, 69.2%, 92.3%, and 90.9% of subjects receiving placebo, pemvidutide 1.2 mg, 1.8 mg, and 2.4 mg, respectively ($p < 0.05$, $p < 0.001$, $p < 0.001$ vs. placebo) at Week 24. Combined MASHResInd with cT1 responses were achieved in 0.0% of placebo vs. 71.4%, 75%, and 100% of pemvidutide-treated subjects, respectively ($p < 0.05$) at Week 24, further discriminating placebo from active treatment.
Conclusion: Pemvidutide administered for 24 weeks was associated with significantly greater MASHResInd and cT1 responses. These findings suggest a high probability of achieving MASH resolution with pemvidutide in biopsy-driven trials.

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SAT-454

Therapeutic Effects of GLP-1 agonist versus SGLT2-i on patients with T2D and MASLD

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Background and aims: Type 2 diabetes (T2D) has a bidirectional relationship with metabolic dysfunction-associated steatotic liver disease (MASLD). Common pathophysiological pathways, such as insulin resistance, both adipose tissue and mitochondrial dysfunction, low-grade inflammation, and dysbiosis, are the cause of this strong correlation. It remains unclear how the coexistence of MASLD and T2D influences each disease's prognosis in both directions. Considering this, research on the medications that lower glucose affect MASLD has been significant. The aim was to evaluate the comparative effects of oral Semaglutide therapy (GLP-1 agonist) versus Dapagliflozin (SGLT2 inhibitor) in patients with T2D and MASLD.
Method: This was a prospective study. Thus, 72 consecutive patients with MASLD and T2D received oral Semaglutide, and 76 consecutive patients received Dapagliflozin therapy. The median follow-up period was 24 weeks. Dose adjustments of oral Semaglutide and Dapagliflozin were determined by each physician while monitoring efficacy and adverse events.
Results: At 24 weeks, there were notable improvements in body weight, lipid profile, liver enzymes, and glycemic control when compared to baseline values in both groups ($p < 0.01$). Regarding glycated hemoglobin, a notable decrease was observed in the Semaglutide group ($p < 0.001$) when compared to the Dapagliflozin group ($p = 0.011$). Between baseline and 24 weeks, the values of the Controlled Attenuation Parameter (CAP) lowered significantly in Semaglutide group ($p < 0.01$). The variation of body weight index and abdominal circumference were strongly correlated with changes in alanine aminotransferase concentrations ($r = 0.36$, $p < 0.01$) and CAP values ($r = 0.44$, $p < 0.01$). The liver stiffness measurement (LSM) according to Vibration Controlled Transient Elastography was improved significantly in the Semaglutide group from 9.06 ± 1.80 kPa at baseline to 7.41 ± 2.06 kPa ($p < 0.001$). Regarding the factors associated with improving LSM, it was observed that the decrease of CAP by one unit determined a decrease of LSM values by 0.08 kPa, and the decrease of blood glucose by one unit determined the decrease of LSM by 0.07 kPa.
Conclusion: Therefore, the metabolic effects were superior in the group treated with Semaglutide in contrast to the group that received Dapagliflozin. This can be explained by the more important weight loss and improved glycemic control in the first group. Further studies conducted in an ideal time frame are needed to confirm the evidence presented in this research.

SAT-455

A single centre, comparative study of Saroglitazar combined with vitamin E versus Saroglitazar alone in managing steatotic liver disease and/or metabolic dysfunction among liver transplant recipients

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Background and aims: The prevalence of post-transplant metabolic dysfunction (MD) has been rising as advancements in the long-term care of liver transplant (LT) recipients enhance survival rates. Management strategies remain centered on lifestyle interventions and pharmacological treatments to address the associated metabolic risks. Saroglitazar, a dual peroxisome proliferator-activated receptor α/γ agonist, is a potential therapeutic option for MASLD or metabolic associated steatohepatitis (MASH).
Method: This single-center retrospective analysis focuses on liver transplant (LT) recipients treated with Saroglitazar for managing MASLD or metabolic dysfunction (MD), including diabetes and/or dyslipidemia. Post-transplant steatotic liver disease (SLD) was diagnosed through imaging (ultrasonography) and/or liver biopsy. Patients were prescribed lifestyle modifications along with pharmacotherapy, which included Vitamin E, Saroglitazar, or a combination of both. The study included 54 patients who had been on Saroglitazar therapy for a minimum of 3 months.
Results: 54 individuals(50 Male and 4 Female) with the mean age of 52.7 ± 8.8 years were included in this study. Out of 54 patients 72.3% patients received Saroglitazar along with Vitamin E, and 27.7% received Saroglitazar alone. MASLD was seen in 38 (70%) patients [de novo in 21(55.3%) and recurrent in 17(44.7%) patients]. Saroglitazar (4 mg/day) was initiated at a median period of 56(IQR 33–82) months after LT. Biochemical and metabolic parameters before and after Saroglitazar initiation are shown in Table 1. Over a median follow-up of 9 months(IQR 5–16.5), notable reductions were observed in total cholesterol, TG, BMI, HbA1C and LDL levels across both groups treated with Saroglitazar. Saroglitazar was generally well tolerated, with no significant adverse events reported.
Conclusion: Saroglitazar, when used independently of Vitamin E, has shown effectiveness in mitigating metabolic risk factors associated with steatotic liver disease in liver transplant recipients. Further studies including MR-PDFF are needed to assess reduction in hepatic fat content with Saroglitazar.

SAT-456

Current evidence on dietary interventions in people with metabolic-dysfunction associated fatty liver disease and MetALD – a systematic review and meta-analysis of randomized controlled trials

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Background and aims: Metabolic-dysfunction associated fatty liver disease (MASLD) and MetALD are highly prevalent. The management relies on lifestyle changes. Dietary interventions are recommended as first line treatment. A number of them, including mediterranean diet, intermittent fasting, low-fat high-carbohydrate diet and vice versa, and the DASH diet have been suggested to be beneficial. The aim of this systematic review with meta-analysis was to provide a comprehensive description and quantitative assessment of the evidence of dietary interventions in improving MASLD and MetALD.
Method: In August 2024, a systematic literature search was performed across multiple databases, including Medline, Embase, the International Clinical Trials Registry Platform, ClinicalTrials.gov, and Web of Science. The review focuses on randomized controlled trials published between 2018 and 2024.
Results: The search yielded n = 1459 records, of which n = 182 were selected for full-text screening by two independent reviewers. Records were grouped into different categories according to dietary patterns. Identified studies included the Mediterranean Diet (n = 23), the DASH diet (n = 6), plant-based diets (n = 3), low-carbohydrate (n = 7) or low-fat diets (n = 2), and ketogenic diet (n = 10). Additional interventions include fasting protocols (n = 20), only focusing caloric restriction (n = 2), the utilisation of diverse plant-oils (n = 8) and supplementation with vitamins and minerals (n = 6), omega 3 fatty acids (n = 8), pre- and probiotics (n = 14), and nutraceuticals (n = 6) such as Silymarin. Moreover, the influence of antioxidant-rich substances (n = 13) e.g. resveratrol, was also investigated. However, no trials focusing on MetALD could be identified. Liver-related endpoints included were enzymes (ALT, AST, GGT) in 85%, liver stiffness in 26.7%, controlled attenuation parameter (CAP) in 25%, and magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) in 11.7% of studies. Furthermore, the duration of the interventions was highly variable ranging from four weeks up to 24 months. Quality of life was only incompletely assessed.
Conclusion: A large number of dietary interventions in MASLD have been published. Overall, the heterogeneity is high. Studies vary significantly with regards to duration and endpoints. Standardization of these interventions will be required to allow to compare and grade recommendations for patients with MASLD.

SAT-461-YI

The early impact of bariatric surgery on liver fibrosis and steatosis in MASLD patients

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Background and aims: Metabolic-dysfunction-associated-liver disease (MASLD) affects more than half of obese subjects. To date, weight reduction by diet and physical activity is recommended to improve liver injury. Recent studies have shown that bariatric surgery induces stable weight loss and ameliorates metabolic parameters. The aim of this study is to evaluate the effect of bariatric surgery on liver steatosis and fibrosis.
Method: This is a monocentric prospective study including all patients with severe obesity and MASLD candidates for bariatric surgery in a single Italian-center. Other causes of chronic liver disease were exclusion criteria. Clinical and biochemical data were collected. Liver fibrosis and steatosis were non-invasively assessed with Liver Stiffness Measurements (LSM) and Controlled Attenuation Parameter (CAP) by Fibroscan at three time-points: before surgery, 6- and 12-months after surgery.
Results: A total of 112 patients (63.4% female, mean age 41.5 years) were enrolled. Before bariatric surgery, the BMI was 43.6 ± 6.2 kg/m², the LSM was 8 ± 5.8 kPa and the CAP was 319.7 ± 57.8 dB/m. Ninety-six patients continued follow-up up after surgery. These patients demonstrated a significant reduction in BMI and CAP as early as 6-months post-surgery, while a significant decrease in LSM was observed only after 12-months. Specifically, the mean BMI was 31.9 ± 5.1 kg/m² after 6 months and 28.0 ± 3.5 kg/m² after 12-months, representing an overall decrease of 35.9% from baseline ($p < 0.0001$). The mean CAP was 264.5 ± 57 dB/m after 6-months and 214.8 ± 47.8 dB/m after 12-months, reflecting an overall decrease of 32.8% from baseline ($p < 0.0001$). Finally, the mean LSM was 6.3 ± 2.5 kPa after 6-months and 5.8 ± 1.9 kPa after 12-months, showing an overall decrease of 21.6% from baseline ($p = 0.02$).
Conclusion: This study demonstrated a significant weight loss and liver steatosis decrease already at 6-months after surgery, while liver fibrosis reduction takes longer at 12-months after surgery. Therefore, in adults with MASLD and severe obesity, bariatric surgery should be considered as a valid therapeutic option for improving liver damage.

SAT-462

First-in-human single and multiple ascending dose study of AZD2389, a potent inhibitor of fibroblast activation protein, in healthy participants to evaluate safety, tolerability, pharmacokinetics and target engagement

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Background and aims: Fibroblast activation protein (FAP) is an endopeptidase whose increased hepatic expression correlates with liver fibrosis severity and development. FAP cleaves proteins that regulate extracellular matrix turnover and metabolism, such as denatured collagens, α2-antiplasmin, and FGF21. Pharmacological inhibition of FAP in animal models of liver fibrosis shows anti-fibrosis benefit. This study reports the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of AZD2389, a potent FAP inhibitor, in healthy participants.
Method: In a single-blind, phase 1 study with single-ascending (SAD) and multiple-ascending dose (MAD) parts, AZD2389 was evaluated in participants (18–55 years). Each cohort had 6 active and 2 placebo participants. In the SAD, 35 participants across 6 cohorts received from low to high single doses of AZD2389, including one cohort of 5 participants which were dosed twice with AZD2389 to explore effect of food upon PK. In the MAD, 24 participants received AZD2389 or placebo for 10 days at low, medium and high repeated doses across 3 cohorts. FAP inhibition was assessed by percentage inhibition, and mechanistic insights were evaluated through the FAP cleavage product α2-antiplasmin (Asn-α2AP).
Results: AZD2389 was well tolerated with no safety concerns at all doses. No serious adverse events, discontinuations, or clinically significant adverse events (AEs) related to AZD2389 were reported. In the SAD part, one mild AE was observed, and in the MAD part, five mild AEs were reported, all resolving without issues. No clinically relevant trends in ECGs, physical exams, or lab results were found. AZD2389 was rapidly absorbed (Cmax 0.5 to 1 hours post-dose). Systemic exposure increased proportionally with dose across single and repeated dosing. Following administration of AZD2389 with food, AUC was similar and Cmax was 33% lower in fed state compared to fasting state. There was no accumulation in plasma Cmax or AUCtau or time-dependency in AZD2389 PK. AZD2389 inhibited FAP activity by >90% at Cmax in both SAD and MAD parts, with 47%, 74%, and 92% inhibition at trough after low, medium, and high doses, respectively. AZD2389 caused dose-dependently reduced %Asn-α2AP, returning to baseline after washout.
Conclusion: In healthy participants, there were no safety or tolerability concerns up to the highest dose of AZD2389 tested in both the SAD and MAD parts. AZD2389 is a selective FAP inhibitor and is being studied further as a treatment for liver fibrosis.

Non-invasive assesment of liver disease except MASLD

TOP-505
Evaluation of a non-invasive pathway for advanced fibrosis detection and liver-related outcomes prognosis in the general population from China, United Kingdom, and United States

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Background and aims: Population-based management of chronic diseases is of paramount importance, as this could identify undiagnosed cases at early disease stages. Recently, EASL-EASD-EASO proposed a non-invasive pathway for case finding of advanced fibrosis. This study aims to evaluate the diagnostic accuracy of the pathway for fibrosis detection and its association with liver-related events (LREs) in the general population.
Method: We included 468999 adult general population (age ≥18 years) from four prospective cohorts: China cross-sectional cohort (n = 8943), United States (US) cross-sectional cohort (n = 6756), United Kingdom (UK) prognosis cohort (n = 411120, median follow-up time: 14.7 years), and US prognosis cohort (n = 42180, median follow-up time: 10.4 years). According to the latest EASL-EASD-EASO guideline, the first step was to screen for primary risk factors. Individuals without type 2 diabetes, or elevated liver enzymes, or the simultaneous presence of obesity and one or more additional cardiometabolic risk factor(s) are classified as minimal-risk group. Further, individuals were categorized into low-, medium-, and high-risk groups according to fibrosis-4 index. Advanced fibrosis was defined by liver stiffness measurement ≥10 kPa, assessed using FibroScan®. Associations with LREs (comprising liver-related hospitalization, cirrhosis, liver cancer, and liver-related death), and cardiovascular-related death were investigated.
Results: The prevalence of advanced fibrosis in minimal-, low-, medium-, and high-risk groups was 1.1%, 2.9%, 6.4%, and 20.9% in the China cross-sectional cohort, and 0.8%, 6.9%, 9.8%, and 37.1% in the US cross-sectional cohort. In the UK prognosis cohort, hazard ratios (HRs) for LREs compared to the minimal-risk group were 2.25 (95% CI 2.14–2.36), 2.95 (95% CI 2.79–3.10), and 11.15 (95% CI 10.29–12.08) for the low-, medium-, and high-risk groups, respectively. Compared with the minimal-risk group, HRs for liver-related hospitalization, cirrhosis, liver cancer, and liver-related death in the high-risk group were 11.1 (95% CI 10.23–12.04), 50.75 (95% CI 43.73–58.91), 20.72 (95% CI 16.3–26.34), and 42.39 (95% CI 35.47–50.67), respectively. The risk groups within the pathway were associated with a progressively increasing risk of cardiovascular-related death, with HRs of high-risk group reaching 6.43 (95% CI 5.86–7.06) in the UK prognosis cohort and 11.89 (95% CI 9.67–14.61) in the US prognosis cohort. Notably, subgroup analysis indicated that among participants with and without high alcohol consumption, increased risk stratification was also associated with a higher prevalence of advanced fibrosis and a higher incidence of LREs and cardiovascular-related death.
Conclusion: The stepwise non-invasive pathway appears suitable for identifying individuals at risk for advanced fibrosis and future LREs in the general population.

WEDNESDAY 07 MAY

WED-499-YI

Validation of small transient elastography device for liver fibrosis and steatosis detection in a population-based study

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Background and aims: International guidelines recommend early identification of liver fibrosis as an attempt to decrease the burden of chronic liver diseases. Vibration controlled transient elastography (VCTE) on FibroScan devices is one of the most accurate tests to assess liver stiffness (LSM) in general population as well as in high-risk populations. However, VCTE is not widely available in a primary care setting. FibroScan 230 device (FS230) is a new model of Fibroscan (CE marked in April 2021 by Echosens) able to pilot from a personal computer, more accessible, smaller and with smarter connectivity than the conventional VCTE (FS530). The aim of this study was to assess the concordance between both devices in evaluating the presence of liver fibrosis by LSM and steatosis by controlled attenuation parameter (CAP) in the general population.

Method: Prospective cross-sectional population-based study that included subjects above 40 years without previous known liver disease. A medical history, physical examination, VCTE and blood tests were performed. LSM and CAP were measured with FS530 and FS230 in random order. Patients with LSM ≥8 kPa with at least one of the devices or with ALT ≥1.5 UNL were considered as high-risk group and were referred to a hepatologist. Only reliable values of LSM were included in the analysis. Categoric and quantitative variables were represented in percentages, median and interquartile range (IQR). Pearson's correlation was used to assess concordance between devices.

Results: 1962 patients were screened in 5 primary care centers in Catalonia during an 18-month period from 2021 to 2022: 47 met exclusion criteria, 173 did not have available blood tests and 106 had an unreliable VCTE value in any or both devices. Finally, 1628 patients were included for the analysis. Median age 61 years (IQR 52–69), 55% women, 7% at-risk alcohol consumption (≥20 g/day women and ≥30 g/day men), 28% type 2 diabetes (T2DM), 41% arterial hypertension and 42% dyslipidemia. Median LSM was 4.7 Kpa (IQR 3.8–5.8) in FS530 and 4.7 Kpa (IQR 3.8–5.7) in FS230 and CAP 251 dB/m^2 (IQR 218–296) in FS530 and 249 dB/m^2 (IQR 216–292) in FS230. The number of subjects with LSM ≥8 kPa was 109 (7%) in FS530 and 96 (6%) in FS230. The correlation between both devices was R = 0.88 for LSM (CI 95% 0.87–0.89, p < 0.001) and R = 0.84 for CAP (CI 95% 0.83–0.86, p < 0.001). A closer look to subjects with risk factors for chronic liver diseases (T2DM, obesity, at-risk alcohol consumption) showed that correlation for LSM and CAP was above 0.85 and 0.81 respectively in all subgroups (p < 0.05).

Conclusion: There is a good correlation between LSM and CAP values with FS230 and FS530 devices. Repeated measurements showed low variability and good reproducibility in patients with and without risk factors for chronic liver diseases suggesting that both devices may be good tools to screen for liver fibrosis and steatosis in a primary care setting.

WED-500-YI

Evaluation of novel point-of-care ultrasound for hepatitis "PUSH" for healthcare workers managing hepatitis B infection in Zambia

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Background and aims: Hepatitis B is a leading cause of mortality in Africa. However, many people with chronic hepatitis B (CHB) in Africa cannot access treatment because key laboratory tests required for eligibility are lacking at some health facilities. Point-of-care ultrasound (POCUS) has emerged globally as a versatile, inexpensive tool used by various healthcare professionals. To support HBV guidelines implementation, a new POCUS for hepatitis (PUSH) was created. Here we evaluated the accuracy of PUSH in Zambia.

Method: We performed a real world validation study of PUSH at a hepatitis clinic at University Teaching Hospital in Lusaka, Zambia, from March to June 2024. Over 3 days, we trained 4 nurses and 6

physicians not experienced in ultrasound in the PUSH protocol. Trainees learned to visualize 3 liver windows (epigastric, subcostal, and right transverse), identify 4 cirrhosis-suggestive liver features (enlarged caudate lobe, nodular liver surface, coarse echotexture, tortuous vascularity), and liver lesions suspicious for hepatocellular carcinoma. Post-training, participants were evaluated with PUSH if had CHB assessed by HBV S antigen positivity, and 18+ years of age. They were excluded if currently/recently pregnant, with hepatitis C or in the acute phase of HBV infection. Participants also underwent reference standard tests (RST) for cirrhosis: liver stiffness (LS), and a comprehensive abdominal ultrasound by an experienced radiographer. Trainees performing PUSH and staff performing the RST were blinded to participants ' clinical information. The performance of PUSH was calculated for cirrhosis (LS >12.5 kPa), significant fibrosis (>7.0 kPa), and lesions, and we used nonparametric analysis of ROC curve, adjusted for PUSH operator (doctor vs. nurse), sex, and HIV status to examine diagnostic performance.

Results: The participants included were 202. Median age was 38 years, 57% males, 28% HIV-positive, 69% on HBV antiviral therapy. Physicians did 61% of PUSH assessments. According to RSTs, 12% of participants had cirrhosis, 30% had significant fibrosis, and 4% had lesions. Alpha fetoprotein in participants with lesions ranged from 350 to 5,703 ng/mL. PUSH had moderate accuracy for cirrhosis, with sensitivity of 56% (34.9–75.6), specificity of 97.7% (94.3–99.4), and an overall ROC area under the curve (ROC-AUC) of 0.77(0.70–0.82). For significant fibrosis, accuracy was poor with sensitivity of 28.3% (17.5–41.4), specificity of 99.3% (96.1–100), and ROC-AUC of 0.64 (0.57–0.70). PUSH excelled in diagnosing lesions, with 85.7% (42.1–99.6) sensitivity, 93.5% (88.9–96.6) specificity, and ROC-AUC of 0.90 (0.84–0.94).

Conclusion: Newly trained nurses and physicians at an HBV clinic in Zambia identified cirrhosis with moderate accuracy and lesions with high accuracy using PUSH, suggesting that this approach could identify advanced cases of HBV disease. To eliminate HBV in Africa, new strategies like liver POCUS are needed to face challenges in applying international treatment guidelines.

WED-501

Prognostication of liver disease patients via ARFI-based liver stiffness measurement using the WFUMB "Rule-of-4" algorithm

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Background and aims: Shear wave elastography (2D-SWE) is a novel ARFI-based technology for measuring liver stiffness (LSM), emerging as a valuable risk assessment tool for portal hypertension (PH). The WFUMB proposed a "rule-of-4" for ARFI-LSM, categorizing patients with advanced chronic liver disease (ACLD) using LSM cut-offs at 5, 9, 13, 17, and 21 kPa. ACLD can be ruled in at ≥13 kPa, while LSM > 21 kPa indicates a high probability of clinically significant portal hypertension (CSPH). We aimed to validate the prognostic value of the WFUMB "rule-of-4".

Method: We prospectively enrolled 125 patients with compensated (cACLD) and decompensated (dACLD) ACLD who underwent same-day 2D-SWE-LSM using the Aixplorer SuperSonic Imagine system and measurement of hepatic venous pressure gradient (HVPG). Patients were stratified via "rule-of-4" kPa into three groups, <13 kPa, 13–21 kPa and >21 kPa. Demographic, clinical, and laboratory as well as follow-up data on decompensation events (cACLD: first decompensation; dACLD: further decompensation/ACLF) were collected.

Results: 22 (17.6%) patients had LSM <13 kPa (non-ACLD); 25 (20%) LSM 13–21 kPa (ACLD); while 78 (62.4%) exhibited LSM > 21 kPa (CSPH) - the corresponding median HVPG were 6.00 [IQR: 4.25–8.00] vs. 10.0 [7.00–12.00] vs 17.0 [13.00–20.00] mmHg, respectively. The CSPH prevalence was 18.2%, 64% and 94.9%. During a median follow-up period of 18.5 months [7.56–24.00], the rate of decompensation significantly increased with the ARFI-LSM rule-of-4 categories: 4.5% in the non-ACLD group, 20% in the ACLD group, and 34.6% in the CSPH group ($p = 0.013$). In ROC analysis for predicting decompensation, HVPG (AUC: 0.78) performed best, while ARFI-LSM (AUC: 0.67) performed similarly to LSM via vibration-controlled transient elastography (VCTE: AUC: 0.72; $p = 0.225$). In competing risk regression, we observed a hazard ratio of 1.01 (95% CI: 1.00–1.02) per kPa for ARFI-LSM ($p = 0.007$), indicating a continuous increase in the risk of decompensation with increasing ARFI-LSM.

Conclusion: The recently proposed WFUMB "rule-of-4" allows for ARFI-LSM based risk assessment in patients with chronic liver disease. Specifically, the risk of decompensation starts to increase at ARFI-LSM 13–21 kPa and is significant at ARFI-LSM > 21 kPa (indicating a high risk for CSPH). Since ARFI-LSM provides comparable prognostic accuracy as VCTE, a wider application of ARFI-LSM in clinical practice should be encouraged.

WED-502

Patient-reported experience measures of EUS-guided and percutaneous liver biopsy. A prospective observational study

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Background and aims: Liver biopsy is a critical procedure for diagnosing and staging liver diseases. Traditionally, percutaneous liver biopsy (PC-LB) has been the standard method. Endoscopic ultrasound-guided liver biopsy (EUS-LB) has emerged as a promising alternative. While clinical efficacy and safety have been well-documented, less is known about the patient-reported experience associated with this approach. This study aims to compare patient-reported experience measures between EUS-LB and PC-LB, providing insight into its impact on patient comfort and satisfaction.

Method: This is a prospective observational study. Within the study period from January to August 2024, we included all consecutive non-targeted EUS-LB and PC-LB at our tertiary liver center. A modified questionnaire based on the validated Newcastle ENDOPREM was used. The questionnaire comprises multiple domains including general demographic information, pain severity (scale 1–10) and duration (scale 1–5), patient discomfort (scale 1–10), well-being, as well as patient satisfaction. Clinical data were recorded from electronic hospital files.

Results: This study included 87 patients, of whom 56 underwent EUS-LB and 31 PC-LB. Median age was 54 years (18–74), most patients were male (n = 46, 53%). Most common indications for biopsy were either after liver transplantion (n = 33, 39%) or for diagnosis of liver disease (n = 33, 39%). Technical success was 100%. There was only one major postinterventional complication in the EUS-LB group (bleeding without need for transfusion). Patients in the EUS-LB group (0(0–8)) reported significantly ($p < 0.001$) less pain during and after the procedure compared to PC-LB group (3(0–10)). Also, duration of pain was significantly ($p < 0.001$) shorter in EUS-LB (1(1–4)) compared to

PC-LB (2(1–4)). Finally, patients reported significantly ($p = 0.006$) lower rate of overall discomfort after EUS-LB (0 (0–7)) vs. PC-LB (2(0–8)), while no significant differences were observed in the other domains of the questionnaire.
Conclusion: Pain severity, duration and overall discomfort was significantly reduced in EUS-LB compared to PC-LB. The results support the use of EUS-LB as a patient-preferred method for liver biopsy, which could enhance patient compliance and satisfaction.

WED-503
Clinical decision tree for non-invasive diagnosis of graft steatosis in liver transplant patients
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Background and aims: Patients after liver transplantation (LT) are at high risk of developing hepatic steatosis, an early form of pathological graft alterations. While liver biopsy remains the gold standard for detecting graft steatosis, it carries risks of peri-interventional complications such as bleeding and pain, necessitating non-invasive alternatives. This study aims to develop an algorithm for non-invasive detection of graft steatosis.
Method: LT patients with available liver histology were included. Three ultrasound-based methods were evaluated: Attenuation PLUS (AttPLUS) and Speed of Sound PLUS (SSpPLUS) using the Hologic Mach 30 ultrasound machine, and the Controlled Attenuation Parameter (CAP) using the Fibroscan 630 Expert. Additionally, the serum-based Hepatic Steatosis Index (HSI) was calculated. Histopathological assessment of steatosis served as the reference standard.
Results: A total of 111 patients were included in the study (39% female, median age 59 years [45–68], median time since LT 7 years [2–21]). All methods showed significant correlations with histological steatosis grades ($p < 0.05$). For detecting any steatosis ($S \geq 1$), SSpPLUS demonstrated the highest accuracy with an AUC of 0.758, followed by CAP (0.718), AttPLUS (0.715), and HSI (0.715). When assessing significant steatosis ($S \geq 2$), AttPLUS outperformed other methods, achieving an AUC of 0.801, with CAP (0.763), HSI (0.700), and SSpPLUS (0.672). For severe steatosis ($S \geq 3$), AttPLUS again showed the best performance (AUC: 0.749), followed by CAP (0.747), while HSI (0.535) and SSpPLUS (0.453) exhibited poor results. Consequently, the decision tree was developed using AttPLUS and SSpPLUS. First, the cut-off value for S1 steatosis was determined using the maximum Youden index (if SSpPLUS <1572 m/s, then S1 steatosis; otherwise, no steatosis). Subsequently, the threshold for S2/S3 steatosis was identified (if AttPLUS > 0.568 dB/cm/MHz, then S3 steatosis; otherwise, S2 steatosis.
Conclusion: This study demonstrates that ultrasound-based methods, particularly AttPLUS and SSpPLUS, show promising potential in detecting and grading graft steatosis in liver transplant recipients. By providing a decision tree algorithm, we might demonstrate a feasible alternative to liver biopsy, maintaining diagnostic reliability.

WED-504
Multi-omic machine learning for risk prediction of cholangiocarcinoma in population-based cohorts
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Background and aims: Cholangiocarcinoma (CCA) is a highly fatal malignancy most frequently diagnosed at advanced stages, presenting with dismal prognosis. We previously reported a highly accurate machine learning model for HCC-risk prediction and aimed to apply similar methodology to stratify and assess CCA-risk, given the complete lack of risk scores and screening except for patients with primary sclerosing cholangitis.
Method: We trained machine learning models using multimodal data from the UK Biobank (UKB), a population-based cohort encompassing over 500,000 participants. The UKB provides extensive phenotypic characterization, including lifestyle and physical measurements, genomic data (~500,000 participants each), and metabolomic data (~250,000 participants), as well as linkage to electronic health records (EHR)and death registries, with up to 15 years of follow-up. We trained random forest classifiers using a five-fold cross-validation approach on participants from England, with independent validation performed on participants from Scotland and Wales. To address the heterogeneity of CCA($n = 666$), we further developed separate models for intrahepatic CCA (iCCA, $n = 428$) and extrahepatic CCA (eCCA, $n = 113$). Demographic variables, EHR, blood parameters, genomics (18 single nucleotide polymorphisms associated with CCA) and metabolomics were hereby incrementally incorporated into our models to reflect clinically relevant scenarios, ranging from daily clinical practice data to comprehensive multi-omics perspectives. From these, we then derived a final model comprising of only the 10 most relevant features throughout demographics, lifestyle-, EHR- and blood data using systematic ablation studies.
Results: Our models achieved AUROCs of 0.7 in the validation set, with no additional benefit of addition of genomics or metabolomics over a model consisting of demographic variables, EHR and blood parameters alone. The iCCA-only and eCCA-only models achieved AUROCs of 0.7 and 0.66, respectively. Interpretability analysis highlighted age as the most relevant feature, followed by ICD-codes like "complication of cirrhosis," "obstruction of bile duct," and blood parameters, e.g. "HbA1c," "Gamma-GT," "IGF-1," "AP," but also lifestyle factors such as "Pack years." The final model, comprising only 10 ubiquitously available and affordable clinical features showed similar performance to more complex scenarios and is currently undergoing external validation in the All Of Us Research Program (849,000+ participants) as well as the Penn Medicine Biobank (~60,000 Participants).
Conclusion: Our work presents the first-ever risk score for CCA in a general population by using machine learning. Our model, for which we provide all code and weights, can hereby serve as baseline for further prediction efforts for early detection of CCA in the general population.

WED-509
Decoding the dynamics: minimal detectable difference in non-invasive tests may exceed proposed thresholds for meaningful changes
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Background and aims: Non-invasive fibrosis tests (NITs) are widely used in primary, secondary and tertiary care. As monitoring becomes increasingly important, robust NITs with minimal random variation are essential for evaluating true changes in disease state over time. This study aimed to evaluate the test-retest reliability and minimal detectable change (MDC) of commonly used NITs across different clinical settings and patient populations.
Method: We retrospectively studied test-retest reliability of VCTE, Agile 3+, Agile 4, FIB-4, APRI, LiverPRO, CORE score, ELF and LiverRisk score in the following clinical scenarios: Cohort I: n = 52 patients with hepatic steatosis and metabolic dysfunction. Cohort II: n = 146 patients undergoing liver biopsy for suspected hepatic fibrosis. Cohort III: n = 45 patients with clinically significant portal hypertension undergoing repeated hepatic venous pressure gradient (HVPG) measurement to assess response to non-selective betablockers.
Laboratory parameters and VCTE were measured in fasting condition on the same day within 14 days (cohort I), 90 days (cohort II) and 28 days (cohort III). We used intraclass correlation coefficient (ICC) to study agreement, and quantified the minimal detectable change (MDC, i.e., minimal difference exceeding measurement error with 95% confidence) with the absolute and relative repeatability coefficient.
Results: Median VCTE was 5.3 kPa (IQR: 4.4–5.9), 10.5 kPa (9.1–14.2) and 55.7 kPa (32.9–75.0) in cohorts I, II and III. All NITs exhibited good to excellent agreement, with the lowest ICC for VCTE and highest for FIB-4: VCTE 0.623–0.846, Agile 3+ 0.704–0.889, Agile4 0.672–0.887, FIB-4 0.898–0.957, LiverPRO 0.900–0.955, CORE 0.652–0.935, LiverRisk score 0.924 (cohort I), and ELF 0.875 (cohort II). The MDC (original scale) in cohorts I, II and III was: 2.1/6.6/32.6 kPa for LSM; 8.6/11.5/4.1% for Agile 3+; 2.0/8.7/17.4% for Agile 4; 0.21/0.22/2.62 points for FIB-4; 6.2/5.0/19.0% for LiverPRO; 0.4/1.4/11.9% for CORE; 0.59 for LiverRisk score (cohort I); 0.64 points for ELF (cohort II). On a relative scale, this translated into a MDC of 38.3/88.3/70.8% for LSM; 93.3/124.9/4.3% for Agile 3+; 137.5/178.2/26.6% for Agile 4; 20.6/35.8/38.5% for FIB-4; 53.1/45.7/40.6% for LiverPRO; 83.0/104.8/100.9% for CORE; 11.8% for LiverRisk score (cohort I), and 12.3% for ELF (cohort II).
Conclusion: Despite strong agreement across NITs, their MDC - both absolute and relative - varies significantly with disease severity and clinical context. This underscores the critical need to account for specific settings and background disease populations when interpreting disease dynamics over time, as universal rules for NIT interpretation are not applicable. In screening settings, thresholds for meaningful changes may exceed >6 kPa (>70%) for VCTE, >0.2 (>35%) for FIB-4, and >0.65 (>12%) for ELF.

WED-510
Repeated transient elastography measurements for the assessment of liver fibrosis

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Background and aims: The advent of non-invasive tools to evaluate liver fibrosis has dramatically reduced the need for liver biopsies. Apart from the obvious benefit of being a non-invasive procedure, transient elastography is aimed at reducing sampling error attributed to liver biopsy, owing to the ability to evaluate a significantly larger area of liver tissue. Correspondingly, most liver diseases feature well established spatial heterogenicity, pointing to a potential benefit for multiple areas of evaluation by transient elastography. While the Baveno VI Consensus recommended performing two measurements on different days to avoid false-positive results, this issue has not been specifically addressed in the succeeding Baveno VII workshop, and currently only one liver stiffness measurement (LSM) is performed during an examination in most centers. We sought to evaluate, whether simultaneous transient elastography measurements in duplicates or triplicates may result in clinically significant discrepancies in the evaluation of liver fibrosis, which can be overlooked using a single measurement.
Method: FibroScan tests reports have been retrospectively retrieved from the Tel-Aviv Sourasky Medical Center repository between the years 2006–2020. Patients whose diagnoses were not specified, or tests in which only one measurement was performed, were excluded from analysis.
Results: Within the study period 16,000 FibroScan tests were performed, of which 8,438 were eligible for analysis. LSM was performed in duplicates in 2,695 (31.94%) and in triplicates in 5,743 (68.06%) of the examinations. 3,901 (46.2%) examinations were performed on female patients and the mean age was 60.53 (±13.87). Etiologies shifted in proportions throughout the study period: between 2006–2012 HCV constituted 75.31% of the examinations and MASH only 9.16%, while between 2013–2020 HCV proportions dropped to 46.30% and MASH increased to 36.00%. Discordance between liver stiffness measurements, which resulted in assignment into different fibrosis grades was observed in 2,205 (26.13%) tests, of which 1,831 (83.04%) exhibited a gap of one category, 331 (15.01%) exhibited a gap of two categories and 43 (1.95%) exhibited a gap of three categories. Most cases of discrepancies were observed in results within the spectrum of F1–2 (44.85%), however in 37.55% of cases discrepant results spanned between mild (F1–2) to advanced (F3–4) fibrosis. The proportions of discordant measurements were etiology-dependent, and ranged from 9% for alcoholic liver disease to 35% for autoimmune hepatitis.
Conclusion: Evaluation of multiple liver areas, rather than a single measurement, in liver transient elastography can potentially detect cases of clinically significant misclassification in fibrosis grade. Means to technically optimize measurements and reconcile discrepancies warrant further studies.

WED-511
FIB-4 for identifying chronic liver disease patients requiring HCC surveillance

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Background and aims: The fibrosis-4 (FIB-4) score is a non-invasive tool developed to estimate the risk for liver fibrosis. Patients with compensated advanced chronic liver disease (cACLD), as defined by a liver stiffness measurement (LSM) ≥10 kPa, are at increased risk for clinically significant portal hypertension (CSPH) and hepatocellular carcinoma (HCC). A FIB-4 score ≥1.75 has been shown to be the equivalent of the LSM cACLD cut-off in tertiary care settings. However, the utility of FIB4 ≥1.75 for identifying those requiring HCC surveillance remains uncertain. This study aims to investigate whether the FIB-4 score is similarly predictive of *de-novo* HCC as compared to LSM, and explore possible thresholds for HCC surveillance.

Method: We retrospectively analyzed 6,143 patients with (suspected) chronic liver disease (CLD) who underwent both FIB-4 and LSM assessments at a tertiary care center. The baseline was defined as the first FIB-4 and LSM assessment. Patients were stratified into two groups: FIB-4 <1.75 (~LSM<10 kPa; n = 4404) and FIB-4 ≥1.75 (~LSM≥10 kPa, n = 1739) as well as FIB-4 <2.67 (~LSM<15 kPa; n = 5245) and FIB-4 ≥2.67 (~LSM≥15 kPa, n = 898).
Results: Patients with FIB-4 ≥1.75 were significantly older (mean age: 57.4 years vs. 44.6 years, p < 0.001) and were more commonly male (62.0% vs. 53.0%, p < 0.001). Viral hepatitis (60.9% vs. 47.8%, p < 0.001) and alcohol-related liver disease (11.0% vs. 3.7%, p < 0.001) were more frequent in the FIB-4 ≥1.75 group, while metabolic dysfunction-associated steatotic liver disease was more common in the FIB-4 <1.75 group (34.4% vs. 15.9%, p < 0.001). The median follow-up duration was 55.4 months, with 91 individuals developing HCC, 41 undergoing liver transplantation, and 526 deaths. Time-dependent ROC analysis showed that FIB-4 is an accurate predictor of de-novo HCC within one (AUC: 0.79, 95%CI: 0.65–0.94), two (AUC: 0.85, 95%CI: 0.76–0.94), and three years (AUC: 0.87, 95%CI: 0.81–0.92), which was similar to LSM (at year 1: AUC: 0.78, 95%CI: 0.62–0.93; year 2: AUC: 0.86, 95%CI: 0.76–0.96; year 3: AUC: 0.85, 95%CI: 0.80–0.91). The 3-year cumulative incidence rates were 0.13% vs. 2.28% (0.05 vs. 0.75/100 person-years) and 0.29% vs. 3.34% (0.09 vs. 1.13/100 person-years) for those with FIB-4 <1.75 vs. ≥1.75 and FIB-4 <2.67 vs. ≥2.67, respectively. A higher incidence of HCC within 3 years was observed in the FIB-4 ≥1.75 group (SHR: 15.8 for HCC, 95% CI: 6.2–40.6) and for the FIB-4 ≥2.67 group (SHR: 11.8 for HCC, 95% CI: 5.9–23.5).
Conclusion: In patients with CLD, the FIB-4 score is similarly predictive of *de-novo* HCC, as compared to LSM, indicating that LSM for staging fibrosis is not needed to identify those at-risk/in whom HCC screening is indicated. Thresholds of FIB-4 ≥1.75 (equivalent to ≥10 kPa) and ≥2.67 (equivalent to ≥15 kPa) may identify the target population for HCC surveillance, depending on health care systems' pay policies and cost-effectiveness considerations.

WED-512-YI
Validation of Baveno VII criteria for non-invasive diagnosis of clinically significant portal hypertension: systematic review and individual patient data meta-analysis

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Background and aims: In people with compensated advanced chronic liver disease (cACLD), clinically significant portal hypertension (CSPH) may be screened by using non-invasive criteria (Baveno VII). However, these rules leave a substantial proportion of unclassified individuals, especially those with obesity and metabolic dysfunction-associated steatohepatitis (MASH). The ANTICIPATE models (ANTICIPATE and ANTICIPATE-NASH) can predict the risk of CSPH and could improve the screening of CSPH. Our objective was to validate Baveno VII criteria and refine them by using the ANTICIPATE models.
Method: We conducted a systematic review of studies designed to validate Baveno VII criteria of CSPH in Medline, WoS, Google Scholar and Embase. The search strategy was "CSPH" (AND) "Baveno VII," reaching from the Baveno VII consensus till December 2023. We performed a meta-analysis of Baveno VII criteria (rule-in: LSM (liver stiffness measurement) ≥25 kPa and rule-out: LSM ≤15 kPa and platelets ≥150×10^9/L). We further used individual patient data to assess performance by etiology. We also explored the use of different values of risk of CSPH of the ANTICIPATE models for a positive (PPV) and negative (NPV) predictive value of ≥90%.
Results: We identified 566 reports, with a final selection of 5 studies accounting for 1433 cACLD patients (prevalence of CSPH 34% to 62%) with different etiologies, including hepatitis C, hepatitis B, alcohol-related liver disease, MASH, and a heterogeneous group of mixed etiologies, MetALD and cholestatic diseases. LSM ≥25 kPa had an excellent PPV (92%) pooled by studies and in all etiologies, except in MASH individuals with obesity. We identified a value of ≥75% risk of CSPH by the ANTICIPATE models as the most adequate threshold for ruling-in, with a pooled PPV of 94%, improving prediction in MASH-obesity (from 0.67 to 0.83; p < 0.001), with a parallel increase in patients classified as having CSPH from 40% to 45% and a 5% reduction of unclassified patients. The pooled NPV for the rule-out criteria (LSM ≤15 kPa and platelets ≥150×10^9/L) was of 99%, without differences across different etiologies.
Conclusion: Baveno VII criteria for CSPH adequately classify all patients, except patients with obesity and MASH. Using a ≥75% risk threshold by ANTICIPATE models to detect CSPH improves the global diagnostic performance, especially in obese MASH patients, supporting its implementation.

WED-513
Role of liver and spleen stiffness in predicting hepatic decompensation following transarterial chemoembolization in patients with hepatocellular carcinoma

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Background and aims: Transarterial chemoembolization (TACE) may influence portal pressure in patients with hepatocellular carcinoma (HCC). Liver and spleen stiffness measurements (LSM and SSM) have emerged as promising tools for assessing portal hypertension. However, limited data exist regarding the effects of TACE on LSM and SSM. This study aims to evaluate the impact of TACE on LSM and SSM and to assess the association between LSM and SSM values and the development of hepatic decompensation within six months following TACE.
Method: This study prospectively enrolled consecutive patients with HCC who underwent TACE. All patients were assessed for LSM and SSM using two-dimensional shear wave elastography (Supersonic Imaging) at baseline, 10 days, and 30 days after TACE. Hepatic decompensation was defined as a composite endpoint, including ascites, variceal bleeding, and overt hepatic encephalopathy.
Results: A total of 93 patients with HCC were included: 28 (30.1%) had Barcelona-Clinic Liver Cancer (BCLC) stage A, 58 (62.4%) had BCLC stage B, and 7 (7.5%) had BCLC stage C. The mean LSM remained unchanged from baseline to day 10 and day 30 after TACE, with values of 26.4 ± 17.0, 26.2 ± 16.6, and 25.4 ± 16.8 kilopascals (kPa), respectively ($p \geq 0.05$). Similarly, mean SSM did not show a significant change from baseline (39.8 ± 17.4 kPa) to day 10 (37.3 ± 15.6 kPa) or day 30 (42.2 ± 16.7 kPa). Significant increases in LSM and SSM (≥10% from baseline) were observed in 30.1% (n = 28) and 25.8% (n = 24) of patients on day 10, and 32.3% (n = 30) and 47.3% (n = 44) on day 30. During the six-month follow-up, 14 (15.1%) patients developed hepatic decompensation. Patients who experienced decompensation had significantly higher baseline LSM (41.0 ± 18.7 vs. 23.8 ± 15.4 kPa, $p < 0.001$) and SSM (55.0 ± 19.3 vs. 37.1 ± 15.7 kPa, $p < 0.001$) compared to those without decompensation. Multivariate analysis identified HCV infection [adjusted Odds Ratio (aOR) = 7.92, 95% CI: 1.04–60.50, p = 0.03], Child-Pugh score (aOR = 2.69, 95% CI: 1.34–5.43, p = 0.006), and baseline SSM (OR = 1.06, 95% CI: 1.01–1.10, p = 0.01) as independent predictors of hepatic decompensation following TACE. Baseline SSM demonstrated good predictive accuracy for liver decompensation, with an area under the receiver operating characteristic curve (AUROC) of 0.76 (95% CI: 0.60–0.91, $p < 0.001$). A baseline SSM > 60 kPa yielded 89.2% accuracy, with 57.1% sensitivity, 94.9% specificity, a 66.7% positive predictive value, and a 92.6% negative predictive value for predicting hepatic decompensation within six months of TACE. Baseline LSM or SSM were not associated with post-TACE syndrome.
Conclusion: TACE did not affect LSM and SSM. Baseline SSM was identified as an independent predictor of hepatic decompensation following TACE, particularly in patients with SSM > 60 kPa. These findings highlight the potential role of SSM for risk stratification for HCC patients undergoing TACE.

WED-514
Prediction of esophageal varices in fontan associated liver disease (FALD)

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Background and aims: Though up to half of patients with Fontan-associated liver disease develop esophageal varices, guidance on endoscopic surveillance is lacking. This study aimed to identify clinical features associated with presence of esophageal varices to aid in tailored surveillance for high-risk patients.
Method: We performed a retrospective cohort study using the Mayo Clinic Fontan Outcomes in Liver Disease database, which includes consecutive patients with Fontan physiology from 1984 to 2020. Patients were included if an esophagogastroduodenoscopy (EGD) was performed from January 1984 to July 2024. Laboratory values, imaging findings and hepatic hemodynamics within one year of EGD were analyzed. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression and a repeated measures model was used to account for patients with multiple EGDs. Multivariate analysis was performed with predictive variables.
Results: Among 113 patients meeting inclusion criteria, 211 EGDs were performed, 97 with varices detected and 114 without. There was no difference in type of heart defect (most common tricuspid atresia), sex, or median age at Fontan between the two groups. Majority of patients had portosystemic collaterals (96.1% of patients with varices and 94% without). In patients with varices, 18.6% were large and 81.4% were small. Two of 50 patients with varices developed variceal bleeding (4%). Alkaline phosphatase (ALP) level (OR 1.01, 95% CI 1–1.02, p = 0.005), total bilirubin (TB) (OR 1.05, 95% CI 1.04–1.05, $p < 0.001$), mean spleen size (14.9 cm vs. 13.7 cm, p = 0.023) and time from Fontan to EGD (OR 1.04, 95% CI 1–1.07, p = 0.031) were associated with presence of esophageal varices. A multivariate model combining these 4 variables showed a C-statistic of 0.88. No significant difference was found in hepatic venous pressure gradient (HVPG) (median 2.0 mmHg), Fontan pressure and platelet count.
Conclusion: Our findings identify a potential model leveraging noninvasive markers to identify patients with Fontan at risk for esophageal varices. While our model has demonstrated excellent performance, external validation is required. If validated, this tool may be used to tailor endoscopic surveillance in this at-risk population.

WED-515
Phase angle by BIA is useful for screening for malnutrition in patients with cirrhosis

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Background and aims: Malnutrition and sarcopenia are critical predictors of poor prognosis in patients with liver cirrhosis. Phase angle (PhA), derived from bioelectrical impedance analysis (BIA), is a non-invasive and simple parameter that reflects cellular membrane integrity and nutritional status. This study aimed to evaluate the utility of the PhA in screening for malnutrition and sarcopenia in patients with liver cirrhosis.
Method: This retrospective observational study included 224 patients with liver cirrhosis who were treated at our hospital between April 2019 and April 2023. Nutritional status was assessed using body mass index (BMI), serum albumin, zinc levels, and the presence of sarcopenia (based on the EWGSOP2 criteria). Malnutrition was defined by using the Geriatric Nutritional Risk Index (GNRI). Patients were randomly divided into training (n = 112) and validation (n = 112) sets. Correlations between PhA and nutritional indicators were analysed in the training set, and decision tree analysis was performed to identify the optimal PhA cut-off values for malnutrition screening. These cut-offs were validated using the validation datasets.
Results: In the training set, the median PhA was 4.6 in males and 4.2 in females. PhA was positively correlated with all nutritional indicators in males and with BMI and albumin levels in females. Multivariate analysis identified PhA and Child-Pugh classification as independent factors associated with malnutrition. Decision tree analysis determined PhA cut-offs of 4.3 for males and 4.1 for females.

Malnutrition was observed in 51 patients (45.5%) in the validation set. Using the PhA cut-off values, the screening performance showed a sensitivity of 0.54, specificity of 0.75, positive predictive value (PPV) of 0.58, and negative predictive value (NPV) of 0.72.
Conclusion: PhA-based screening may be a useful tool for detecting malnutrition in patients with liver cirrhosis. PhA offers a simple and non-invasive approach to assess nutritional status, contributing to early intervention and management. Further studies with larger cohorts are required to validate these findings.

WED-516
Bile acids drive fibroblast activation, fibrogenesis, interstitial matrix fibrosis and outcomes in PSC
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Background and aims: Fibrosis often originates from an insult that damages epithelial and endothelial cells and activates chronic pro-inflammatory processes that impair the regular course of tissue repair. Fibrosis initial stages exhibit extensive remodeling of the basement membrane to allow immune cell recruitment and initiate a pro-inflammatory response that propagates to the interstitial layer of the extracellular matrix (ECM). In this process, fibroblast activation induces an excessive production of type I, III and VI collagens leading to fibrogenesis. Several drivers of fibroblast activation including TGF-beta have been reported. Bile acids have previously demonstrated to correlate with fibroblast activation marker PRO-C3 in biliary diseases, however, their role in fibrogenesis remains unclear. We aimed to investigate the relationship between bile acids and ECM formation and degradation markers during anti-fibrotic therapy (FGF-19) and related prognostic ability of fibroblast activities in PSC.
Method: Markers of fibroblast activation (nordicPRO-C3 from type III and nordicPRO-C6 from type VI collagen), fibrosis resolution (nordicCTX-III from MMP degraded crosslinked type III collagen), ECM remodeling (type VIII, XVI and XVIII collagen), the ELF score and bile acids were measured in serum from 62 patients with primary sclerosing cholangitis (PSC) at baseline (BL) and after 12 weeks treatment with Aldafermin (FGF-19))(NCT02704364), and in 167 PSC patients with 4 years transplant free survival. Spearman correlation coefficients (r) were obtained between bile acids and collagen biomarkers at BL, and between delta values reflecting the difference in levels of individual bile acids and PRO-C3 from BL to 12 weeks. Odds ratios for transplant free survival of PRO-C3 in tertiles were calculated.
Results: Aldafermin reduced the levels of hydrophobic bile acids, PRO-C3 and PRO-C6 after treatment, but not other collagen markers. Strong correlations ($r = 0.5$) were observed between bile acids and fibroblast activation marker PRO-C3, ECM degradation by CTX-III and the ELF score at BL. The correlation, post FGF19 therapy between PRO-C3 and bile acids, was borderline significant $r = 0.24$, $P = 0.08$. The correlation of conjugated bile acids, in particular glycine conjugated bile acids (cGCA), at baseline was very strong, (GCA, $r =$ of 0.62, $P < 0.0001$; GCDCA, $r = 0.55$, $P < 0.0001$) and notably, between delta cGCA and PRO-C3 was 0.33, $P > 0.0001$, as previous published. PRO-C3 was highly prognostic for outcome in PSC, with an odds ratio of 8.5 in the upper tertile ($P < 0.001$).
Conclusion: Fibroblast activation and collagen formation is important for outcomes in PSC. These data suggest that bile acids activate fibroblast driving fibrogenesis, and that lowering of bile acids attenuate the fibrotic drive. Lowering fibroblast activity may have positive effects on liver related outcomes in PSC.

WED-517
Weight dependent, weight independent and non-pharmacological effects on fibroblast activity in metabolic dysfunction associated steatotic liver disease (MASLD)
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Background and aims: Fibroblasts are activated by metabolic dysfunction and are a central component of liver function decline. Fibroblast activities, both type III and type VI collagen formation, have been shown to be highly prognostic for outcome of liver, heart and kidney related events in MAFLD populations. Fibroblast activity, may both be inhibited by weight dependent and independent mechanisms, which allows finding optimal combination treatments. Recent data showing that pharmacological interventions leading to a substantial weight loss can significantly improve MAFLD, and fibroblast activity, at least halting MASH progression. In similar context, weight independent mechanisms such as Resmiterom and FGF-19/21 mediated mechanisms also provide strong deactivation of fibroblasts. Weight loss has also been indicated to have negative impact on bone and muscle, and we need to investigate and understand the patient centric most optimal approach for detecting fibroblasts. To shed light on the effect of weight loss on other organs, we analyzed data from elderly subjects and investigated the relationship between weight loss and bone loss using the biomarker of bone resorption CTX-I. Additionally, we used recently published data on the liver fibrosis biomarker PRO-C3 and the cardiovascular marker PRO-C6, from both weight loss studies, and pharmacological interventions by Resmiterom, GLP-1 receptor agonists, and Survodutide.
Method: 806 subjects were included in the analyses. Their baseline age was 64 years, and the baseline BMI was 29 kg/m^2. The were categorized by baseline BMI (lean, overweight, obese) and two-year weight change (gain/loss ≥5%), and the changes in biomarkers were monitored and related to changes in CTX-1. A weight loss study using VLCD, and data from pharmacological interventions with Resmetirom, GLP1RA and Survodutide previously analyzed for changes in either PRO-C3 and PRO-C6.
Results: Non-pharmacological intervention led to a 30% decreased in PRO-C3, with no reduction in PRO-C6. Weight dependent pharmacological interventions lead to significant reductions in PRO-C3. Weight independent mechanisms such as FGF-21/19 led to large reductions in PRO-C3 and smaller reductions in PRO-C6. The bone resorption biomarker CTX-I increased 1.58-fold [95% CI 1.39, 1.81], 1.37-fold [1.28, 1.47] and 1.11-fold [0.95, 1.28] in the weight loss, stable and weight gain groups.
Conclusion: Pharmacological and non-pharmacological induction of weight loss results in different deactivation of fibroblasts activities, which may have divergent efficacy on heart and liver related outcomes. Furthermore, weight dependent and independent mechanisms of deactivation fibroblasts may result in additional effects on bone and muscle. This understanding may be needed when designing the optimal intervention strategy, including possible combination regimens, for the individual MAFLD patient.

WED-518
Comparing ultrasound and magnetic resonance imaging for hepatocellular carcinoma screening in high-risk populations: a systematic review and meta-analysis of prospective cohorts
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Background and aims: Magnetic resonance imaging (MRI) is known for its higher accuracy in detecting hepatocellular carcinoma (HCC) compared to ultrasound (US). Despite this, guidelines recommend biannual HCC screening with US in cirrhosis patients due to its cost-effectiveness, availability, and non-invasiveness. Our meta-analysis aims to clarify the implications of choosing one modality over the other in routine HCC surveillance.
Method: We searched online databases for prospective cohorts in which the same participants were submitted to both US and MRI as screening for HCC. Per-patient sensitivity and specificity were calculated for each modality. To synthesize the test accuracy across studies, we employed a Bayesian bivariate random-effects model. Expected and predicted diagnostic metrics, as well as their 95% credible intervals (CrI), were then used for comparisons. A decision curve analysis (DCA) was performed to assess the clinical utility of each screening modality with the predicted diagnostic parameters, utilizing a simulated cohort of 1000 participants with a 5% prevalence of HCC.
Results: Four studies, with a total of 823 participants who prospectively underwent both US and MRI, were included. For MRI, the expected sensitivity was 77% (95% CrI: 34%–95%), with a predictive sensitivity of 73% (95% CrI: 1%–100%). The expected specificity for MRI was 92% (95% CrI: 61%–98%), and the predictive specificity was 88% (95% CrI: 13%–100%). For US, the expected sensitivity was 50% (95% CrI: 10%–92%), with a predictive sensitivity of 50% (95% CrI: 0%–100%). The expected specificity for US was 86% (95% CrI: 35%–98%), and the predictive specificity was 81% (95% CrI: 1%–99%). In DCA, MRI demonstrated a higher net benefit than US across all threshold probabilities. The net benefit for US screening dropped to zero at a 12% threshold, while MRI maintained a non-zero net benefit up to a 24% threshold. Based on the predictive accuracy, we estimated that for each 100 screenings in a high-risk (5%) population, 18 individuals without HCC are misclassified as having HCC by US, and 11 by MRI. Additionally, 3 HCC-bearing individuals are misclassified as negative by US, and 1 by MRI. The predictive positive predictive value for MRI in a high-risk population (5%) was 24% (95% CrI: 0%–95%), and for US, it was 12% (95% CrI: 0%–100%). The negative predictive value for MRI was 98% (95% CrI: 71%–100%), while for US, it was 97% (95% CrI: 9%–100%).
Conclusion: This meta-analysis demonstrates that MRI offers superior accuracy compared to US for HCC screening. MRI was more effective in ruling-in HCC and had lower false-positives, which may prove to be cost-effective when applied to populations with high incidence. US displayed considerable variability in its performance, highlighting its potential limitations for HCC screening.

WED-520
Prognostic utility of serum ammonia in cirrhosis: a systematic review and meta-analysis

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Background and aims: There is conflicting evidence regarding the prognostic utility of serum ammonia in patients with cirrhosis. This systematic review and meta-analysis evaluate its ability to predict mortality as a primary outcome in patients with stable cirrhosis, acutely decompensated cirrhosis and acute-on-chronic-liver-failure (ACLF). Secondary outcomes included all cause decompensation and progression to ACLF.
Method: The protocol was registered on PROSPERO (CRD42024567671). Comprehensive searches of Medline, Embase, Scopus, Web of Science and Pubmed were performed with no limits on publishing period on 02/05/2023 and updated on 10/07/2024. Two reviewers independently screened studies from abstract to full text, that included adult patients with cirrhosis of any aetiology. Studies involving acute liver failure, liver transplantation or single decompensation events as a secondary outcome were excluded. Data extraction was conducted using the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Factor Studies (CHARMS-PF) and a risk of bias assessment was made using the Quality in Prognostic Factor Studies (QUIPS) checklist.
Results: Forty-three studies were included in the final review, of which 31 provided useable data for meta-analysis of hazard ratios (HR) using a random effects model. The pooled HR for all stages of cirrhosis (n = 8480) was 1.12 (95% CI 1.04–1.21), with significant heterogeneity. (I^2 = 92.2% (95% CI 90.0–93.9). Subgroup analysis using a fixed effects model showed no significant difference in effect estimate among the three cirrhosis groups. However, ammonia predicted a significantly higher risk of mortality in studies including participants with a Model for End Stage Liver Disease score less than 16, compared to those with a higher score (p = 0.0405). Multiple meta regression revealed that cirrhosis category, study size, survival outcome definition and ammonia handling in statistical models accounted for 51% of the heterogeneity (p = 0.0017).
Conclusion: Serum ammonia is a modest, yet significant biomarker for predicting mortality in cirrhosis, and this may have greater utility in patients with less severe disease at baseline. Future studies should standardize survival definitions and statistical models to reduce heterogeneity and improve comparability.

Nurses and Allied Health Professional

TOP-522-YI
Health-related quality of life, events of decompensation and mortality – effectiveness of the quality liver nursing care model

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Background and aims: Patients with cirrhosis report difficulties in understanding how to cope with their disease. Registered nurse involvement has potential to improve the quality of outpatient cirrhosis care. The benefit of nursing care on health-related quality of life (HRQoL), incidence of decompensation and mortality is scarcely studied. The primary aim of this study was to compare HRQoL in patients receiving either standard medical outpatient care or adjunctive registered nurse-based Quality Liver Nursing Care Model (QLiNCaM) intervention. Secondary aims were to compare decompensation events and mortality.
Method: A pragmatic, multicentre randomised controlled study (www.clinicaltrials.gov NCT02957253) involving six Swedish hepatology outpatient clinics in Sweden. One hundred and sixty-seven participants were allocated to either standard medical care or adjunctive registered nurse-based intervention (QLiNCaM), which was based on person-centred care and Orem's self-care theory of nursing. HRQoL was measured with RAND-36, of which the physical and mental component scores were compared between the study groups in a linear mixed-effects model for repeated measures. Primary and secondary outcomes were assessed after 12 and 24 months.

Results: Differences of the physical and mental component scores of RAND-36 after 24 months were non-significant between the groups (−1.1, p = 0.53; and −0.7, p = 0.67, respectively). There was also no difference in numbers of decompensation events (p ≥ 0.05), but, the intervention reduced the time for identification of a decompensation event with 112 days. After 24 months, mortality was three times higher in the control group compared to the intervention group (12 *vs* 4, p = <0.05).
Conclusion: Adjunctive nurse-led care was not superior to standard medical outpatient care concerning HRQoL, malnutrition or decompensation. Nevertheless, RN involvement reduced the time for identification of decompensation and mortality.

THURSDAY 08 MAY

THU-496-YI
Allied health professionals are essential for facilitating initial evaluation and optimisation of patients for liver transplantation

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Background and aims: Assessment for Liver Transplantation (LT) involves a multi-disciplinary approach where allied health professionals (AHP) undertake evidence-based approaches to assess risk and suitability for LT and give individualised advice to allow optimisation of their candidacy.
Method: A multidisciplinary assessment clinic (MAC) at our centre (physiotherapist, dietician, specialist nurse in drug and alcohol misuse, hepatologist and anaesthetist) provides evaluation of patients referred for consideration of LT where concerns around frailty, fitness and alcohol history are raised. Data were collected on sequential patients seen in the MAC between June 2022 and May 2023, to include evaluation (hand grip strength (HGS), Liver frailty Index (LFI), alcohol relapse risk), outcome and where appropriate subsequent listing outcome.
Results: Seventy-six patients were seen (50-male), median age 58-years. Aetiology was alcohol (54%), MASLD (16%), Autoimmune (16%), viral (6%) and other (8%). Indications for assessment were decompensated cirrhosis (82%), HCC (5%), variant syndromes (13%). Of the patients seen in the MAC, 26/76 (29%) did not see an AHP. Reasons included no indication, absolute contraindication or advanced palliative stage of disease. These 26 patients did not proceed on a LT pathway. Fifty patients thus underwent full evaluation by AHP's in the MAC following which 22/50 (44%) were booked directly for LT workup of which 19/22 (86%) proceeded to be listed for LT. Between initial MAC and LT workup, LFI and HGS improved significantly, with mean improvement of −0.43 (p < 0.05) and 8.8 KG (p < 0.05) respectively. Twenty-eight patients were deemed to be either too frail or too high risk from an alcohol perspective to proceed to LT work up. After a median time of 17-weeks (range 5–46 weeks), 36% (n = 10/28) improved sufficiently to proceed to LT workup, of which 7/10 were subsequently listed. LFI and HGS improved significantly over this period with mean improvement of −0.45 (p < 0.05) and HGS 9.8KG (p < 0.05) respectively, and subjective alcohol relapse risk reduced.
Conclusion: This data highlights that a MAC approach allows optimisation and identification of patient for LT as evidenced by, identification and optimisation of those patients suitable for immediate LT work up result in high listing proportion (86%); optimisation to facilitate listing of patients deemed initially to be too frail for work-up (35%) and finally aid identification of those patients in which a full LT work-up would be futile (29%). The clinic thus ensures timely and appropriate management plans, intensive optimisation where appropriate and cost saves on futile LT work up. Our centre feels this should be considered as the gold standard for candidacy for LT work up.

THU-497
The challenge of adherence in Wilson disease: a prospective study

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Background and aims: Wilson disease (WD) is a rare genetic disorder that promotes copper accumulation in the body, which can lead to hepatic and neurological symptoms and heterogeneous phenotypes. Despite the availability of effective drugs for copper control, which must be taken daily and lifelong, some studies have shown decreased compliance in a significant proportion of WD patients, being this fact related to worse clinical outcomes. Our aim was to assess pharmacological compliance among WD patients in our setting and aid in designing individualized educational interventions.
Method: Prospective, single-center study, including patients with confirmed WD followed at the Liver Unit, Hospital Clínic (Barcelona) and a signed informed consent form. Specific nursing visits were scheduled to assess self-reported adherence (by means of the validated ARMS-e questionnaire) and develop an individualized educational intervention according to the score. Objective adherence data were also obtained from the Pharmacy Service dispensing records at a blinded manner. Low adherence was defined as ARMS-e score ≥16 or medication uptake ≤80%.
Results: 50 WD patients were included: 52% female, median age 38 (IQR 29–47) years, median time since diagnosis 19 (IQR 13–28) years, 70% with hepatic phenotypes. 50% of patients received treatment with chelators and 50% with zinc, with a median current treatment duration of 12 (IQR 2–20) years. According to the ARMS-e questionnaire, 21 patients (42%) reported low adherence mainly associated to medication intake; treatment collection was not reported as a major concern. We observed no statistical differences on adherence according to type/ duration of treatment, phenotype or educational level. Low adherence was associated with higher levels of ALT (p = 0.015) and exchangeable copper (p = 0.058), suggesting poorer metabolic control. According to pharmacy records, 14 patients (31%) were objectively classified as low compliant (≤80% registered collection). No concordance was detected between the two adherence assessments (ARMS-e vs pharmacy records, p = 0.197).
Conclusion: At least one third of our WD patients show low adherence to medication and this seem to be related with worse copper control. No concordance was detected between the two prospective adherence assessments, outlining the limitations of both strategies. These results support the need to design educational tools among these patients, which we have implemented in the nursing practice.

THU-498-YI

Demonstration of the success of a nurse led service surveying for hepatocellular carcinoma and other cirrhosis associated complications

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Background and aims: Hillingdon Hospital hepatology service is predominantly nurse led, comprising one consultant hepatologist, three Clinical Nurse Specialists (CNS) and one Hepatology Assistant Practitioner (HAP). >5000 patients are managed in the Hepatology department annually. Of those, approximately 30% require six monthly Hepatocellular Carcinoma (HCC) surveillance due to the increased risk of HCC with their underlying liver condition. We assessed whether HCC surveillance intervals were being met within National Institute for Clinical Excellence (NICE) guidelines across the CNS, consultant and registrar (SPR) out-patient Hepatology Clinic. We also reviewed requesting rates for gastroscopies for variceal surveillance and bone health (DEXA).
Method: May–August 2024 data for: Clinic date, aetiology, clinician, whether HCC surveillance was required and whether ultrasound (USS), gastroscopy and DEXA had been requested/performed. USS 'did not attend' (DNA) data sourced by radiology to compare against Hepatology figures. HCC diagnoses between this time sourced from the cancer team.
Results: Of 1197 patients reviewed in a three-month period, 30% (362) required HCC surveillance. 86% (311) of those requiring surveillance were seen by the CNS, 8% (29) by SPR and 6% (20) by consultant. In the SPR clinic 68% had an USS requested prior to the planned due date, 83% in the consultant clinic and 98% in the CNS clinic (results for 86% were available in planned clinic review). Six HCC's were detected during this period, four during clinic surveillance, two on inpatients (66% were surveillance detected). The Hepatology USS DNA rate over a five-month period was 27%, versus a total out-patient USS DNA rate across the hospital of just 3%. Of the patients who required and consented to a gastroscopy: 99% requesting rate by CNS, consultant 100% and SPR 77%. 275 patients required a DEXA, only 55% were requested. Out of 97 completed DEXA's, 57% had low bone density. Thus, a 'wash-up' clinic established: HAP filtered through the clinicians' clinics to ensure the appropriate tests have been requested after each clinic. Where gaps were identified, the CNS has since requested all appropriate tests to ensure patient safety.
Conclusion: >30% of patients in the SPR clinic had a delay in their HCC surveillance and 22% a delay in variceal surveillance. HCC surveillance and other cirrhosis related investigations are more likely to be requested from the nurse-led clinic, in line with NICE guidelines. The USS DNA rate is significantly higher for Hepatology compared to all hospital requests, which can lead to further delays in surveillance, thus USS DNA rates will be addressed locally to improve adherence. The overall requesting rate for DEXA was suboptimal within the department, thus the wash-up clinic will ensure a 100% requesting rate moving forward.

THU-499

Health-related quality of life in patients with chronic hepatitis D receiving bulevirtide and pegylated interferon: interim results from the SEE-D clinical trial

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Background and aims: At the outpatient clinic of Infectious Diseases at Karolinska University Hospital, Sweden, approximately 150 patients with hepatitis D are under care. This study is part of the clinical trial SEE-D (EU 2023-504414-29-00), evaluating the treatment of hepatitis D with bulevirtide (BLV), pegylated interferon (peg-IFN), and nucleos(t)ide analogues. BLV and peg-IFN are administered as daily and weekly subcutaneous injections, respectively. Peg-IFN treatment is associated with frequent side-effects. We aimed to evaluate health-related quality of life (HRQOL) in patients receiving BLV and peg-IFN combination therapy.
Method: HRQOL was assessed using the Hepatitis Quality of Life Questionnaire (HBQOL) with 7 domains, RAND-36 with 8 domains, and the Fatigue Severity Scale (FSS). A total of 19 patients with advanced fibrosis or cirrhosis completed these questionnaires at baseline (BL) and treatment week 24 (w24). Interim data at w24 are presented. HRQOL scores are expressed as mean (±SD) values, and comparisons between BL and w24 were conducted using the Wilcoxon signed rank test. Subgroup analyses were performed for men and women.
Results: Baseline characteristics included a mean (±SD) age of 42.6 (6.7) years, with 60% men and 40% women, and a mean body mass index (±SD) of 25 (3.4) kg/m^2. Median (IQR) liver elasticity was 12.1 (8.6) kpa. Median HDV RNA level (log10) was 5.4 (5.5) IU/ml at BL, with 21.1% of patients achieving undetectable HDV RNA at w24. No statistically significant changes were observed in psychological well-being, anticipation anxiety, transmission concerns, vulnerability or viral response. However, vitality (HBQOL) significantly worsened, with scores increasing from 42.1 (22.8) at BL 48.4 (28.1) at w24 ($p = 0.048$). Stigma scores did not change significantly in the whole group, but men showed a significant improvement, decreasing from 36.5 (16.9) at BL to 27.4 (18.3) at w24 ($p = 0.046$). In RAND-36, significant improvements were noted in role limitations due to physical health, pain, social functioning and vitality (all $p < 0.05$), while physical functioning worsened significantly ($p = 0.02$). Improvements in vitality and pain were particularly pronounced in men. A borderline significant improvement in role limitations due to emotional problems was seen, with scores improving from 68.7 (46.3) at BL to 41.3 (44.9) at w24 ($p = 0.058$). Physical function (RAND-36) declined significantly, with more pronounced changes in women ($p = 0.02$). Significant worsening of fatigue could be shown in FSS, with worsening of mean 3.7 (1.9) to 4.3 ($p = 0.008$), driven primarily by significant worsening in women ($p = 0.03$).
Conclusion: Combination therapy with BLV and peg-IFN shows varying effects on HRQOL, with improvements in several domains, but worsening fatigue and physical functioning, particularly in women. More data are needed to guide targeted support during treatment.

THU-500

Community liver health checks are a valuable tool to support early diagnosis of liver disease

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Background and aims: A Community Liver Health Check (CLHC) pilot is being delivered in England via the National Health Service (NHS) Cancer Programme to address the rising incidence of liver cancer. Early detection of chronic liver disease and referral onto surveillance pathways is vital to diagnose liver cancer at an earlier, potentially treatable stage. 18 pilot sites across England were commissioned, with approaches individualised locally. We discuss our novel service using a Community Liver Specialist Nurse.
Method: The CLHC pilot offers a FibroScan to people considered 'at risk' of liver disease in various community settings (long-term excess alcohol intake; diabetes/obesity; previous exposure to viral hepatitis B/C). Our team consists of a Community Liver Nurse Specialist, a Community Liaison Officer and Consultant Hepatologist. All attenders are given liver health guidance and education. Anyone with a FibroScan reading ≥11.5 kPa is offered a second validatory scan within a 2–4 week period. Those with a repeat result of ≥11.5 kPa are referred into liver clinics to consider appropriate follow-up, including cancer surveillance. Further assessment, including liver screen blood tests

and ultrasound are arranged by the nurse specialist so the results are available at the time of Consultant review. Those with FibroScan result 8.5–11.4 kPa are offered a repeat scan in 12 months.
Results: Since April 2023, 2760 people underwent FibroScan. 8.1% (n = 223) had an elevated result; 4.5% (n = 125) were ≥11.5 kPa. After validation scan, 61/125 had confirmed cirrhosis (2.2% overall cohort), 19/125 (0.7%) improved to moderate fibrosis, 29/125 (1.0%) had a normal result and were discharged, and 16/125 (0.6%) await review. In addition to identification of undiagnosed cirrhosis, we identified one case of treatable hepatocellular carcinoma at initial ultrasound, one treatable renal cell carcinoma idenitified during surveillance, and cases of Hepatitis B and Primary Biliary Cholangitis via liver screen tests. 98 patients with moderate fibrosis have had a 12-month repeat scan. Of these, 2 (0.1% overall cohort) progressed to advanced fibrosis, and 30 (1.1%) had a normal result and were discharged.
Conclusion: The nurse-led service offers a unique approach to early identification of liver disease, aiming to improve outcomes, provide tailored, specialist-led education, and ensure smooth referral directly into secondary care. We found that a confirmatory scan is vital, to reduce the risk of unnecessary commitment to long-term surveillance. The prevalence of advanced fibrosis identified through the pilot suggests that thousands of people across the UK are likely to be living with undiagnosed liver disease, and we recommend ongoing expansion of the scheme, which should be accompanied by access to appropriate interventions to limit progression of liver disease.

THU-501-YI
Malnutrition, sarcopenia and inadequate dietary intake before liver transplant: a time for action
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Background and aims: Malnutrition and reduced muscle strength are important prognostic indicators in liver transplantation (LT) leading to adverse waiting list and post-transplant outcomes. The period awaiting LT offers a crucial period for intervention for those requiring optimization. We aimed to describe nutritional parameters, dietary intake and functional muscle strength in a cohort of patients with decompensated cirrhosis referred for LT.
Method: Consecutive patients referred to our centre for LT in 2022–2023 were assessed by a specialist dietitian. Nutritional status (via subjective global assessment), handgrip strength (HGS), dietary energy (kcal) and protein intake were measured and compared to established nutritional targets.
Results: One hundred patients (54% male) with median age 55 years (IQR 45.5, 61.25) and MELD 24 (18, 26) were included. Seventy-four per cent of patients were malnourished (60% moderately malnourished, 14% severely malnourished) with median HGS 18.1 kg (14.4, 23.2) and 31.1 kg (26.4, 34.9) for females and males, respectively. Only 14% of patients had a HGS above their gender and age-matched normative value. Median dietary intake was 22.8kcal/kg (18.1, 26.6) for energy and 0.9 g/kg (0.7, 1.1) for protein; well below the recommended 35kcal/kg and 1.2–1.5 g/kg for this patient population. Only 17% of patients were meeting the lower end of protein requirements (>1.2 g/kg), whilst only 1 patient had a dietary protein intake greater than 1.5 g/kg.
Conclusion: Patients with decompensated cirrhosis referred for LT have a high prevalence of malnutrition and reduced functional muscle strength, contributing to sarcopenia and frailty in this population. Inadequate dietary intake appears to be universal. Aggressive nutritional prehabilitation in the period awaiting LT should be undertaken for all patients with decompensated cirrhosis referred for LT, with specific oral and enteral nutrition interventions aiming to bridge the significant gap between baseline dietary intake and elevated energy and protein targets.

THU-502
Non-weight-based ribavirin dosing for hepatitis E in immunosuppressed patients: a single-centre experience
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Background and aims: Hepatitis E virus (HEV) can progress to chronic infection in immunosuppressed patients, causing morbidity and mortality. Whilst ribavirin (RBV) is not licensed for HEV treatment, it is used off-label in this context. Licensed dosing for RBV in hepatitis C (HCV) typically follows a weight-based approach, but optimal dosing for HEV patients remains unclear. This single-centre retrospective analysis evaluates the use of virologically and symptomatically guided RBV dosing in immunosuppressed patients focusing on dosing, duration, tolerability, and outcomes.
Method: Dispensing data from April 2017 to October 2024 were analysed to identify immunosuppressed patients treated with RBV for HEV. Clinical documentation and biochemistry were reviewed to assess RBV dosing, duration, tolerability, and virological response.
Results: 11 patients (mean age: 44.5 years, 55% male) received RBV for HEV. Of these, 73% (8/11) were transplant recipients on a median of 2.5 immunosuppressive agents; renal transplants accounted for 75% (6/8). There were 2 cases of donor derived HEV. 27% (3/11) were on/had recent immunosuppression for non-transplant indications. At treatment initiation, median ALT, AST, and bilirubin were 80 U/L (20–1477), 41 U/L (13–707), and 10 μmol/L (4–180) respectively. RBV was initiated at a median daily dose of 400 mg (100–1000) or 5.5 mg/kg (1.4–13.9). Dose was reduced if not tolerated and increased if there was a lack of response in HEV titres. Side effects included fatigue/tiredness (60%), anaemia/low Hb (50%), headache (40%), GI symptoms (30%) and insomnia or mood disorders (20%). Dose adjustments guided by virological and symptomatic responses were required in 70% of patients with 3 patients on a lower dose at completion. Median dose at completion was 400 mg (100–1000). 100% (10/10, 1 patient currently on treatment) of patients achieved viral clearance. Median treatment duration was 80 days (29–538). There was no significant correlation between median daily dose on initiation and treatment duration ($r = 0.49$, $p = 0.15$).
Conclusion: This tertiary centre experience demonstrates that reducing RBV dosage in the context of side effects and a virological response does not lead to breakthrough or relapse. HEV clearance can be achieved at doses much lower than those used in weight-based HCV therapy. Additionally, proactive symptom and response-guided RBV dose adjustments can achieve better tolerability without compromising outcomes.

THU-503
Internal consistency and diagnostic validity of SARC-F questionnaire in chronic liver disease patients with sarcopenia on liver transplant wait list
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Background and aims: The study investigated the utility of Sarcopenia-Functional (SARC-F) questionnaire, a subjective 5-item questionnaire to screen and rapidly diagnose sarcopenia in patients with chronic liver disease on liver transplant wait list. Internal consistency and reliability of the tool was examined based on the hypothesis that patients classified as frail, prefrail and robust using Liver Frailty Index (LFI) will score high, median and low on SARC-F tool. Diagnostic validity of the tool was examined using performance-oriented measures like Short Physical Performance Battery(SPPB) and LFI derived from balance score of SPPB, hand grip strength, and 5 rep sit to stand (5STS)test. The study also examined the association between frailty and frequency of hospitalization.

Method: 60 subjects (24 females, 36 males with avg Body mass Index 28.10, 31.89 and mean age 60, and 54 respectively) 54% alcoholic cirrhosis, 27% NASH cirrhosis and 19% (other) on wait list for liver transplant were part the study. After consent, subjects answered the 5-item questionnaire, and underwent hand grip measurements using JAMAR hydraulic dynamo-meter, physical performance measures using Short Physical Performance Battery.
Results: SARC-F questionnaire exhibited good internal-consistency reliability, with Cronbach's alpha of 0.82. Correlation between SARC-F and Liver frailty Index was statistically significant, with a positive Pearson co-relation (56) = 0.89, p = <0.001.Mean dominant HG(d) strength, 4 m gait speed test, 5 STS score were all low for Frail subjects 19.31 kg, 6.8 s, 42.62 s. prefrail and robust subjects had mean value of 28.60 kg, 5.6 s,13.59 s and 42.09 kg, 3.5 s, 9.7 s, respectively. The frequency of hospitalization (>3 times) was higher in frail subjects, as compared to prefrail and robust subjects.
Conclusion: SARC-F is a valuable tool in rapidly diagnosing sarcopenia exhibiting both internal consistency and diagnostic validity in these population. SARC-F score ≥4 indicated subjects were either Prefrail and Frail, in our study. The mean SARC-F score in Frail subjects in our study was ≥7. MELD score when combined with SARC-F score can assist transplant surgeons and transplant-hepatology team to make decisions to prioritize the transplant wait-list, with improved post-operative outcomes.

THU-504-YI
Negative consequences of screening for steatotic liver disease
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Background and aims: Steatotic liver disease is a major public health concern, making screening and early detection essential to prevent severe disease. While screening may promote positive lifestyle changes, it may also cause negative consequences of screening (COS): anxiety, shame and depression as seen in cancer screening. We aimed to describe whether screening for liver disease can inflict negative COS in the short- and long term. Further, we explored the impact of disease severity on negative COS.
Method: We screened individuals from the general population and a high-risk population using controlled attenuation parameter (CAP) and transient elastography (TE). Participants with TE ≥8 kPa were invited for a liver biopsy visit within 3 months. We used a modified version of COS used for lung cancer screening (COS-LC), sent to participants 7 days and 6 months post-screening. We used 7 themes: self-blame, symptoms, introvert, sleep, harm of behaviour, anxiety, and sense of dejection. We focused on "Self-blame" (blame, guilt, disappointment, and anger), using a four-point Likert scale (not at all, slightly, moderate, a lot). Frequency analysis and multinominal logistic regression were used to assess the association between TE and response categories.
Results: We screened 6,453 participants with a median age of 57 (IQR 52–63), 52% female. In total, 6.2% had TE ≥8 kPa. Response rates from baseline to day 7 and 6 months were 78–80% and 81–84% respectively. Overall the theme of self-blame faded over time. Moderate and high levels of "Blame" declined from 3.5% to 2.7%. High levels of anger persisted the most (2.9% at day 7 vs. 2.8% at 6 months). Most themes showed a reduction in negative COS over time, but moderate and high levels of "Harm of behaviour" and "Sense of dejection" increased at 6 months. When adjusting for age and gender, the odds of answering "a lot" in "Blame" is 3.6 higher for those with TE 6–8 kPa and 15.4 higher for those with TE ≥8 kPa compared to those with TE ≤6 kPa. At 6 months the odds are 2.4 and 7.4 respectively. This tendency is found for each of the themes on day 7 and persists at lower odds at 6 months.
Conclusion: Our findings reveal that while some negative COS diminish, others persist or even increase over time, particularly in individuals with higher TE. This underscores the need for targeted support to mitigate the psychological burden associated with those with advanced disease stages.

THU-509-YI
Improving clinical efficiency of Hepatology clinics by optimising patient adherence with blood test monitoring
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Background and aims: Hillingdon Hospital's Hepatology service consists one consultant hepatologist, three clinical nurse specialists (CNS) and one hepatology assistant practitioner (HAP). The service has approximately 5,000 patients on the caseload, and through evolution is now predominantly a nurse-led service managing 87% of total reviews. Blood tests are a critical requirement for chronic liver diseases and timely bloods pave the way for effective patient management, guiding treatment decisions and identifying deterioration of their condition. Having identified low adherence with blood test monitoring for Hepatology outpatients we aimed to assess and improve this.
Method: Data collected between May–August 2024, inclusive of all clinic types – face to face (F2F), paper and telephone across four clinicians – hepatologist, CNS, HAP and registrar. Aetiology, ethnicity, attendance at F2F review and blood test completion, when required, were recorded. Data analysis focused on adherence to blood tests and whether this improved after two separate interventions, as well as evaluating local DNA (did not attend) rates across aetiology and ethnicities. Baseline data collected, first intervention (reminder letter), second intervention (reminder letter and text), each a one-month period.
Results: 1496 encounters analysed May–August 2024. 52% F2F (777) and 48% (719) virtual/telephone. CNS and HAP 87% of total reviews (639 F2F, 248 telephone and 423 paper). Hepatologist reviewed 7% (103) and registrar 6% (56). Virtual clinics: 91% (652) required bloods before review; 32% adhered at baseline. First intervention increased compliance to 43%, whilst second intervention increased compliance to 50% (chi square test for either intervention versus baseline $p < 0.05$). No statistical difference in uptake of blood tests between a paper and or paper/text reminder ($p > 0.05$). Over the three-month period compliance by ethnicity: Indian, Pakistani and Bangladeshi Asians 41%, Asian Chinese 61%, Asian other 37%, black African 31%, White British 48%, white other 40%, unknown 54%. Hepatology F2F clinics overall DNA rate 20%. 82% (382) attendance for new

appointments, 77% (242) for follow up appointments. Overall DNA rate by ethnicity: Indian, Pakistani, Bangladeshi Asian 22% (60), White British 15% (42), black African 27% (23), white other 17% (14), Asian other 20% (8), unknown 38% (5) and Asian Chinese 10% (1). 16% (125) of total F2F DNAs were for CNS/HAP clinic, 2% (16) registrar and 1.5% (12) Hepatologist.
Conclusion: Our data has highlighted poor blood test adherence within Hepatology clinic attendees, with an 18% improvement with letter or text reminder. Improved clinic attendance and blood test adherence could be facilitated with configuration of electronic notification systems tailored to patient requirements, to promote effective patient care, improve clinician productivity and use of resource.

THU-510
Impact of hepatitis delta infection on quality of life: results from the Nora-hepatitis B study
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Background and aims: Hepatitis D (HDV) is an RNA virus that only affects individuals with hepatitis B virus (HBV) infection. Chronic hepatitis D (CHD) is associated with a worse prognosis than HBV mono-infection, with a higher risk of progression to cirrhosis and liver cancer. The aim of this study was to assess the quality of life using health questionnaires in individuals with HDV and compare it to subjects with chronic hepatitis B (CHB).
Method: Prospective study based on the administration of the CLDQ, FACIT-F, and EQ-5D questionnaires using a mobile application (Nora-Hepatitis B) to a cohort of patients with CHD and CHB followed in a hepatology outpatient clinic between February 2022 and April 2024.
Results: A total of 85 individuals, 62 with CHB and 23 with CHD, participated in the questionnaires. Seventy-four percent were men, with an average age of 51.9 years old (±12.5), 72% were Caucasian, and 95% were receiving nucleo(t)ide analogues. Individuals with CHD showed worse results on the CLDQ questionnaire in all dimensions, particularly in abdominal symptoms ($p = 0.001$) and concern regarding their disease ($p = 0.003$). On the FACIT-F questionnaire, only emotional well-being was significantly worse in individuals with CHD ($p = 0.042$), while the total score was similar between both groups. On the EQ-5D questionnaire, although no significant differences were observed in overall health assessment, individuals with CHB had significantly lower levels of anxiety and depression compared to those with CHD ($p = 0.007$).
Conclusion: These results indicate that, overall, patients with CHD have a worse quality of life compared to patients with CHB, particularly in terms of well-being and emotional status. Nora-Hepatitis B is a useful application for evaluating patient-reported outcomes.

THU-511
Evaluation of the utility of the Nora-hepatitis B mobile application: a comparative study between chronic infection and HBeAg-negative chronic hepatitis
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Background and aims: Mobile apps are being implemented in the management of some chronic diseases, improving follow-up and treatment adherence. In viral hepatitis, their evaluation has been limited. The aim of this study was to assess the utility of the Nora-Hepatitis B app in individuals with HBeAg-negative chronic hepatitis B infection vs those with chronic hepatitis (CHB), and to determine if the need for treatment has an influence on its use.
Method: The prospective Nora-Hepatitis B study consisted in the distribution of an app (Nora-Hepatitis B) to adults with chronic hepatitis B virus (HBV) infection who attended an outpatient consultation at an academic hospital. Patients needed to have a mobile device, internet access, and were proficient in Spanish. The app provided a chat feature for communication with healthcare staff, allowed users to complete quality of life and knowledge questionnaires, and sent medication reminders. The study was conducted between February 2022 and April 2024 and only results for HBeAg negative population were analysed.
Results: A total of 301 patients accepted to participate; of these, 250 (83%) were HBeAg negative, 147 had chronic infection, and 103 had CHB, with an average age of 50 years, 64% male, and 47% born in Spain. Participants with CHB used the chat feature significantly more frequently (51.4% vs. 34.7%, $p = 0.008$) and had a higher rate of participation in completing questionnaires (39.4% vs. 26.9%, $p = 0.036$) compared to those with chronic infection. No differences were found in patient-reported outcome results between the two groups. However, knowledge about the disease was higher in individuals with CHB (8.46 vs. 7.55, $p = 0.001$).
Conclusion: People with CHB used the chat feature and completed quality of life questionnaires more frequently, suggesting a greater need for contact with healthcare services compared to those with chronic infection. However, both groups reported similar quality of life results, indicating a comparable disease burden in terms of overall well-being.

THU-512
Long-term real-world outcomes of obeticholic acid treatment for primary biliary cholangitis: insights from a pharmacy-led single-centre study
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Background and aims: First line therapy for the management of Primary Biliary Cholangitis (PBC) is with ursodeoxycholic acid (UDCA). Non-responders or those intolerant to UDCA are entitled to second line therapy with obeticholic acid (OCA) which requires approval via a pharmacy-led regional multidisciplinary team meeting (MDM). Patients are commenced on OCA in a virtual pharmacy-led clinic. Repeat prescribing following subsequent virtual reviews take place in this clinic by a pharmacist and pharmacy technician. Our aim was to retrospectively evaluate the efficacy of OCA in our existing cohort of PBC patients, and to identify who would be eligible for alternative second-line therapies.
Method: Data collected retrospectively identified a total of 196 patients referred to the PBC MDM between November 2017 and November 2022 from 12 different centres. Data was collected for the OCA cohort which included; liver function tests at baseline and 6 monthly intervals up to 2 years, fibroscan, fib-4 & APRI scores at baseline and one year, dose changes and adverse reactions.
Results: A total of 107 (55%) were advised to commence treatment with OCA, 48 (24%) with bezafibrate, and 41 (21%) had another outcome, such as referral for clinical trial. Only 88 patients remained under our care for OCA prescribing which we analysed until at least 24 months of follow-up. Seventy-six patients (86%) were female with a median age of 56 years. A total of 22 (25%) had cirrhosis. Of the 107 patients, 77 (88%) received UDCA at a median dose of 14 mg/kg. At 24 months, 55 patients (63%) remained on OCA. A statistically significant reduction in ALP:ULN (−39.8%) and ALT:ULN (−47.8%) was observed. Response rates were 60% according to POISE criteria and 9% by normal range criteria. There was no change in bilirubin. Of the 33

patients (37%) who prematurely stopped OCA, 25 stopped due to side effects (most commonly treatment-induced pruritus), 2 stopped due to liver decompensation and 6 stopped due to no clinical response. Six patients went on to start bezafibrate. No patients were lost to follow up. Average doses of OCA increased from an average of 4.2 mg/day at baseline to 8.2 mg/day at 24 months. Month 6 saw the most significant change in dose; 48 patients increased in line with national guidance.

Conclusion: The results confirm the effectiveness and safety of OCA, with the response rate mirroring that which was reported in the POISE trial. Access to second-line treatment with OCA is widely available across our region, aided by our pharmacy-led regional MDM and virtual clinic that allow patients to remain with their local clinicians, ensuring continuity of care. Overall, virtual monitoring of response after starting OCA can be challenging as this is dependent on referring clinicians sending timely follow-up data. For those who do not respond adequately to OCA, alternative second-line treatments such as bezafibrate and elafibranor should be explored.

THU-513-YI

Should all patients referred for liver transplantation undergo a review in a dedicated multidisciplinary assessment clinic prior to formal liver transplant work up?

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Background and aims: Formally evaluating a patient for liver transplantation (LT) involves multiple investigations, specialist input and MDT discussion to determine candidacy. Correctly identifying suitable candidates allows efficient and cost-effective use of LT work up resources. Allied health professional assessments provide objective and validated measures to assess LT risk and help inform candidacy.

Method: In our centre, all potential LT candidates are discussed in principle (DIP) in the LT MDT. Those felt to be higher risk are pre-screened in a multidisciplinary assessment clinic (MAC) with access to dietetic, physiotherapy and alcohol nurse input, to identify those suitable to proceed to work up whereas those perceived after DIP to be more favourable proceed direct to LT work up.

We reviewed all patients who underwent a LT work up (excluding ALF and ACLF) over a 12-month period (June 2022–May 2023) comparing those who have been evaluated/optimised in the MAC prior to LT work up and those proceeding direct to LT work up.

Results: 144 patients underwent a formal LT work up. Median age was 56-years (range 27–71) and 50/144 (34%) were female. The indications for LT work up were decompensated chronic liver disease (74%), HCC (13%) and variant syndrome (13%). Of the 144 LT work ups, 40 (28%) were seen in the MAC prior to LT work up, the remaining 104 patients came direct to LT work up. Alcohol aetiology was higher in those patients seen in the MAC compared to direct LT work up (23/40 (58%) vs 23/104 (22%) $p < 0.01$), whereas the presence of clinical decompensation (32/40 (80%) vs 75/104 (72%) $p = 0.3$), UKELD score (55 vs. 55, p = ns) and age (57 vs 55, p = ns) were similar. Following LT work up 33/40 patients (83%) from the MAC were ultimately listed with 26/40 (65%) listed within a month of work up. The remaining 8 were listed with a median delay of 2 months (range 2–8 months). Conversely of those brought direct in for work up 67/104 (64%) were ultimately listed, with 52/104 (50%) listed within a month. The remining 16 patients were listed with a median delay of 2 months (range 2–8 months). Patients were statistically more likely to be listed if seen in the MAC prior to formal assessment (33/40 vs 67/104, $p = 0.04$) despite being identified at DIP as less favourable candidates. Of the 44 patients that underwent formal work up and were never listed, 16% (7/44) came from the MAC compared to 84% (37/44) from direct work up with common themes for decline being frailty, alcohol risk and medical contraindication.

Conclusion: These data highlight that LT work up slots are used most efficiently by patients who have been evaluated in a MAC, with a significantly higher proportion of patients listed in a timely manner compared to patients coming directly for LT work up. Pre-screening patients in a MAC can thus help avoid costly futile LT work ups. Despite this, in the direct work up group, 64% of patients were listed indicating that there is a subset of patients that can proceed direct to LT work up, although this data failed to identify any predictive markers to guide selection.

THU-514

Patient-perceived quality of care – effectiveness of the quality liver nursing care model

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Background and aims: Liver cirrhosis is a growing health problem due to obesity and excessive alcohol consumption. The disease significantly impacts the person's physical and mental health. Patients with liver cirrhosis express insufficient support from healthcare providers, which may harm patient-satisfaction with healthcare, their psychological well-being, and commitment to manage the disease. In contrast to other chronic diseases, structured registered nurse-based liver cirrhosis outpatient care programmes has not yet been widely established. The aim was to study patient-perceived quality of liver cirrhosis outpatient care after implementing a 24-month adjunctive registered nurse-based intervention, named the Quality Liver Nursing Care Model (QLiNCaM).

Method: A pragmatic, randomised controlled multicentre study (www.clinicaltrials.gov NCT02957253) involving six hepatology outpatient clinics in Sweden. One hundred and sixty-seven participants were allocated to either standard medical care or adjunctive registered nurse-based intervention (QLiNCaM), which was based on person-centred care and Orem's self-care theory of nursing. The questionnaire 'Quality of care from the patient's perspective' (22 items) was used to study patient-perceived quality of care. The response scale of each item was dichotomised into 'lacking quality' or 'good quality'. Complete case analysis with Firth's penalised logistic regression compared 'lacking quality' between the two study groups, at 12 and 24 months respectively. Study results were reported in odds ratio (OR) with 95% confidence intervals (CI).

Results: After 12 months, the registered nurse-based QLiNCaM intervention revealed an improvement in 7 of 22 perspectives of patient-perceived quality of care. The improvements applied: participation in decision-making regarding their care (OR 0.3, CI 0.1–0.8); access to the outpatient clinic (OR 0.1, CI 0.0–0.5); receiving written information (OR 0.3, CI 0.1–0.9); feeling understood (OR 0.1, CI 0.0–1.0); and having influence over their received care (OR 0.1, CI 0.0–0.9). However, these improvements were not sustained after 24 months.

Conclusion: Structured registered nurse-based outpatient care may encourage patient involvement and facilitate patients' accessibility to care, thus being a complement to physician-based care with a more person-centred approach, continuity and care coordination.

THU-515-YI

Impact of consensus guidelines on hepatitis B reactivation risk assessment and management in immunosuppressive therapy

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Background and aims: Hepatitis B virus reactivation (HBVr) can result in fatal liver failure in the setting of immunosuppressive therapy (IST). International guidelines differ in their recommendations on the use of monitoring and/or prophylaxis by class of IST. A systematic review of the available literature on HBVr risk for individual IST agents was conducted by the specialist hepatology pharmacist followed by consultant hepatologist Delphi Consensus process incorporating existing, AASLD, EASL and UK Chemotherapy Board guidelines. Guidelines were reviewed and ratified by clinical leads from key IST prescribing services before publication (rheumatology, dermatology, haematology, oncology, nephrology, gastroenterology, neurology, immunology). In January 2024, a consensus guideline was published which devolves the majority of screening, decision-making and prophylaxis prescribing in those with past HBV infection (pHBV) to the clinicians prescribing IST. The guideline, which categorises IST into risk category groups with associated advice on monitoring and/or antiviral prophylaxis, has the explicit goal of improving rates of both screening and appropriate management whilst minimizing the number of clinical services with which patients needs to engage.
Method: To assess the impact of the guidance, we reviewed referrals to the viral hepatitis multidisciplinary team for HBVr risk assessment queries pre- and post-guideline implementation (prGI and poGI, respectively).
Results: A total of 106 referrals were received between February 2022 and January 2024 and 29 between January and November 2024 indicating a decline of 2 referrals per month (on average). 78% (83/106) and 65% (19/29) of referrals were for patients with pHBV prGI and poGI. 21% (23/106) and 31% (9/29) of referrals were for patients with active infection prGI and poGI. 71% (75/106) and 76% (22/29) of referrals had a full HBV screen at baseline prGI and poGI. All IST prescribing services in our organization have adopted screening, monitoring and prophylaxis prescribing for those with past HBV infection.
Conclusion: Implementation of HBVr guidance reduces overall referrals of patients with pHBV to the viral hepatitis service, increases referrals of those with active infection, and increases proportion of patients with full HBV baseline screen; indicating more efficient use of clinical resources and improved patient experience. The proportions of those being screened, monitored and given appropriate prophylaxis needs to be assessed within IST-prescribing services. Specialist pharmacists are ideally placed to do this during clinical screening of IST.

THU-516-YI

Nurse-led clinic for patients with decompensated liver cirrhosis

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Background and aims: Patients with decompensated liver cirrhosis has a mortality of around 50% within five years of diagnosis. The risk of mortality may be influenced by the management focusing on reducing risk of cirrhosis-related complications. Many individuals with liver cirrhosis have limited health literacy, highlighting a need for tailored information and guidance. Unstructured follow-up has been associated with frequent liver-related readmissions, with structured care potentially preventing up to one-third of these readmissions.
Method: A quasi-experimental, investigator-led single-centre study was conducted from January 2022 to May 2024. The intervention involved a nurse-led clinic designed to meet the special needs of patients with decompensated liver cirrhosis. The primary aims were to reduce liver-related hospital admissions and to identify patients who would benefit the most from the intervention. Monthly data from a hospital database ($N \approx 400$) were analysed across three study periods: before, during, and after the intervention. Demographic and disease-related data were continuously collected.
Results: 55 participants were enrolled in the intervention (45% female, mean age 61 ± 11 years, 78% with alcohol-related cirrhosis, mean MELD score of 16 ± 7, mean Child-Pugh score of 9 ± 2, with 65% living alone). The median duration of affiliation with the clinic was 142 (IQR 43–224) days, and the median number of contacts was 7 (IQR 3–11). Telephone contact was the primary form of communication. Among participants, 55% were discharged from the clinic upon achieving self-management ability, 20% were deemed non-compliant, 16% died, 5% were lost to follow-up, and 4% underwent a liver transplantation. Participants who were evaluated to have achieved self-management ($n = 30$) differed significantly from those who did not ($n = 25$), with lower mean baseline MELD scores (14 ± 1 vs. 19 ± 2, $p = 0.01$), lower mean baseline Child-Pugh scores (8.2 ± 0.3 vs. 9.6 ± 0.4, $p = 0.01$), and a higher proportion had alcohol-related cirrhosis (90% vs. 64%, $p = 0.02$). Hospital data indicated a decrease in mean monthly admission rates among the wider population of cirrhosis patients from 13.6 in 2022 to 9.3 in 2023 ($p = 0.02$), with stable outpatient clinic contact rates. The results may be influenced by the Covid-19 lockdown prior to the intervention.
Conclusion: Establishing a nurse-led clinic for patients with decompensated liver cirrhosis was feasible. Patients who benefited from the clinic were characterised by lower baseline MELD and Child-Pugh scores and a higher prevalence of alcohol-related cirrhosis. The study provided valuable insights into strengthening multidisciplinary team collaboration and streamlining patient pathways within the department.

THU-517-YI

iCARE: Insights on competency advancement and recommendations for nurses managing HBV/HDV with bulevirtide – findings from a european advisory board

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Background and aims: Bulevirtide (BLV), a novel treatment for hepatitis D (HDV), offers a promising option to manage liver disease progression in patients (pt) co-infected with chronic hepatitis B. However, the requirement for long-term daily subcutaneous administration presents challenges in pt self-management. Nursing expertise may improve treatment outcomes, safety and pt adherence, requiring specialized knowledge and skills to deliver high-quality, evidence-based HDV care. iCARE was developed to address these challenges by gathering insights from experienced nurses to share best practice, and to develop training to enhance nursing skills supporting long term care.

Method: Nurses managing pt with HBV/HDV completed a written survey detailing their professional background, care settings, BLV experiences, and training needs. A descriptive analysis was conducted, followed by an online European HDV Nurse Advisory Board in September 2024, focused on the pt journey. Key findings were shared with participants.
Results: Six nurses participated, all working in specialized liver units. They had years of experience in caring for HBV/HDV pt and also managing pt on BLV. The survey revealed differences in care priorities arising from local settings and internal pathways, influencing how nurses became involved in care. Despite variations, all emphasized their role as pt advocates, focused on shared decision-making, and empowering pt to manage their disease. Nurses agreed on the importance of clear communication, logistical support and holistic assessments including evaluating social resources to ensure coordinated care. Key responsibilities include: Establishing a trusting relationship with pt, providing emotional support, evaluating treatment readiness and involving family in care. In addition, nurses support pt on BLV by teaching practical skills, such as self-injection. Written and visual materials, along with practice tools, were considered valuable for enhancing pt capabilities. Nurses have a fundamental role in follow-up care and serve as accessible points of contact across settings, facilitated by digital tools.
They require specialized HBV/HDV and BLV knowledge for management of treatment and adverse events. Equally important are skills in building therapeutic relationships-, person-centered communication, and chronic care management, focusing on adherence and motivation.
Conclusion: Liver care nurses across Europe agreed on essential skills required to manage HDV, with local differences having minimal impact on care delivery. They viewed themselves as close partners, comparable to co-pilots, guiding pt and families through their treatment journey. iCARE highlights the vital role of nurses in empowering pt to manage BLV therapy and supports the development of adaptable educational programs across diverse healthcare settings and countries.

THU-518
Multi-displinary team initiation of GLP-1/GIP agonist Tirzepatide in patients with metabolic-dysfunction associated steatotic liver disease (MASLD): single-centre UK study

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Background and aims: Tirzepatide, a dual GLP-1/GIP agonist, has shown efficacy in type 2 diabetes mellitus (T2DM) and obesity, with promising phase II trials in metabolic dysfunction-associated steatotic liver disease (MASLD). No real-world data exists in MASLD. This study evaluates tirzepatide's efficacy in patients with MASLD and T2DM in secondary care, comparing those with liver multidisciplinary team (MDT) input (inc. diabetes specialist nurse) to those managed in a general diabetes clinic.
Method: Adult patients with T2DM and MASLD prescribed tirzepatide between Jan–Nov 2024 were included. Pre and ≥3 months post initiation data of weight, BMI, HbA1c, liver function tests and liver stiffness measurement (LSM; kPa)/controlled attenuation parameter (CAP) were recorded, in parallel to (dose) changes in other T2DM medications. Statistical tests included 2-sample t-tests (parametric), Wilcoxon rank-sum tests (non-parametric), chi-square tests (binary).
Results: Of 67 patients with MASLD at baseline 32 (47.8%) were male; weight (median (IQR)) was 106.8 Kg (94.1–120.1); BMI 37.2 kg/m² (34.8–40.5); HbA1c 61 mmol/mol (49–73.5), LSM 16.1 KpA (10.7–21.3) and CAP 333.5 dB/m (313–368). 35 (57%) patients had liver MDT input. 47 (70.1%) were on only oral-hypoglycaemics and 20 (29.9%) on insulin ± oral-hypoglycaemics. After 3 months, the median change in weight was −3.9 kg (IQR −3.9; −7.1: p = 0.290), BMI −1.5 kg/m^2 (−0.1;-2.6: p = 0.242), HbA1c −10 mmol/L (−1; −18: p = 0.001), ALT −9.5 IU/L (−3.0; −19.8: p = 0.044), AST −19.5 IU/L (−10.5; −26.3: p = 0.088), LSM −10.4 kPa (−5.9; −13.5: p = 0.408), and CAP −31 dB/m (−11; −57: p = 0.047). 38.6% and 11.4% had at least 5% and 10% weight loss, respectively. 40.3% (25/62) decreased their dose or number of T2DM medications (inc. insulin). There were no safety issues reported. Patients with MDT follow-up had greater, though non-significant, weight loss (−4.9 ± 5.6 vs −3.1 ± 6.6 kg) and changes in BMI (−1.53 ± 2.20 vs −0.38 ± 8.03 kg/m²). Improvements in HbA1c (−11.1 ± 14.2 vs −11.1 ± 16.9 umol/mol) were similar between the groups, however those under liver MDT follow-up were more likely to have successful dose reduction of other T2DM medications, including insulin (56.3% vs 23.3%; p = 0.008).
Conclusion: Tirzepatide is safe and significantly improves liver enzymes, steatosis and glycaemic control in patients with MASLD after only 3 months. Those under liver MDT care significantly reduced the burden of other T2DM medications, whilst maintaining safe improvements in glycaemic control and weight.

THU-519-YI
Prescribing for pain and symptom management in hospital patients with advanced liver disease: a single centre, retrospective clinical audit

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Background and aims: Advanced chronic liver disease patients, particularly in their last year of life require adjustments to dose and choice of medication as per the British Association for the Study of the Liver (BASL) guidelines. Most hospital patients should be referred to supportive and palliative care team (SPCT) during their stay to ensure appropriate symptom control is in place. In this study, we assessed whether prescribing adhered to BASL guidelines and if this changed following intervention by SPCT.
Method: Prescribing data were collected retrospectively from the electronic prescribing system at a UK tertiary liver centre over 5 months (April–August 2024). Eligible patients had a Child Pugh score of B or C and were referred to SPCT. Data were reviewed against BASL guidelines to determine if meeting standards prior to and after SPCT review and assessed using t-tests.
Results: 30 patients (50% male) were included with a median age of 64.5 (interquartile range 57–72.5) and mixed aetiologies (53.4% alcohol-related, 20% metabolic dysfunction-associated steatotic liver disease and 26.6% other). Results were grouped by drug and route. Although paracetamol is the first-line analgesic, only 70% of patients sampled (n = 21) had oral paracetamol prescribed, of which 43% met the BASL standard (2–3 g daily) with a mean daily dose (MDD) of 3500 mg. SPCT intervention was statistically significant, reducing MDD to 2476 mg (p < 0.05). For oral morphine (n = 12) patients meeting recommendations (2.5 mg 4–6 hourly) increased from 18% to 36%, with MDD increasing by 25% post referral (p = 0.37). With subcutaneous morphine (n = 10) 80% of patients met standards (1.25–5 mg hourly) and MDD decreased from 36.2 mg to 26.2 mg after SPCT review (p = 0.14). 12 patients were prescribed oral oxycodone with an increase in standards adherence (1.25 mg 6–8 hourly) after intervention from 8.3% to 33.3% and reduction in MDD of 4.6 mg (p = 0.15). 3 patients were prescribed dihydrocodeine and all prescriptions were

stopped following SPCT review ($p < 0.05$). Metoclopramide was prescribed in 6 patients, and none met BASL standards (5 mg 8 hourly) prior to referral but 50% of patients adhered after. MDD reduced from 48.3 mg to 20.8 mg ($p = 0.12$). All prescriptions of intravenous and oral ondansetron ($n = 7$) were higher than recommended BASL doses (8 mg daily) however, no prescription was changed following review.
Conclusion: Adherence to standards varies greatly between drug and route but overall shows a lack of adjustment accounting for liver disease severity, both before and after SPCT review, with trends of improvement post review. Although first-line, safe analgesia at reduced dose, paracetamol is not prescribed for all patients. A small population limited the statistical power of this dataset. Initial findings indicate the development of local prescribing resources would improve patient safety and compliance with BASL guidelines.

THU-520
Improving the outcomes of patients with cirrhosis in a community clinic through the utilization of advanced practice providers and standardized tailored management protocol
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Background and aims: Cirrhosis continues to pose a public health burden worldwide, contributing to substantial morbidity and economic strain on healthcare resources. This is expected to increase exponentially with the current trends in rising liver disease incidence. Modifying long-term liver care is needed to meet evolving demands. The aim of this analysis is to describe the outcomes of managing patients (pts) with cirrhosis through a collaborative physician/allied health including advanced practice providers multi-level healthcare model using standardized protocols tailored to the severity of liver disease.
Method: Between January 2011 and December 2023, 5201 pts with cirrhosis were seen at a community-based single liver center serving suburban and urban communities. Pts were managed by a team of healthcare providers consisting of physicians and allied health professionals including nurse practitioners, physician assistants, nutritionists. Management was according to standardized protocols tailored to each pt's disease severity. Information from the Electronic Medical Records system was analyzed.
Results: 53.7% males. Mean age was 63.8 ± 10.1 years. 47.8% Hispanics and 83.6% whites. Preliminary analysis on 1126 pts showed: underlying etiology was primarily history of HCV (31.3%), 24.2% alcohol-related liver disease (ALD), and 19.3% steatotic liver disease (SLD). 67% were compensated at initial visit. Median follow-up: 54 months (1–144). Median number of outpatient visits: 34 visits (1–141). 10.9% required paracentesis or TIPS. 91% had no or grade 1 varices. 12.4% experienced sepsis. 8% developed Hepatocellular carcinoma. Almost 40% required hospitalization due to liver disease decompensation. Mean total number of hospitalizations was 3. Outcomes: >80% alive. <6% referred to Hospice and 4% received a liver transplant.
Conclusion: Over a 12-year follow-up period of cirrhotic pts at a community-based liver center, the prevalence of underlying etiology of HCV significantly decreased, SLD continued to increase, and ALD remained stable. Pts were managed by a dedicated team of 2 Hepatologists and 3 allied health professionals according to standardized protocols tailored to the pt's disease severity. It utilized the applicable provider's model of care. The joint effort and comprehensive approach led by a Hepatologist: 1) alleviated the reliance on them, 2) enabled early detection and diagnosis of cirrhosis complications and 3) swift management and expanded access to various specialized models of care. This had a major impact on lowering the number of decompensations and led to fewer hospitalizations, procedural interventions and decreased the need for hospice care and transplantation. It significantly improved complications-free survival and outcomes of pts. Management protocols need to be constantly updated with the evolving new therapies and guidelines.

Public Health – Except Viral Hepatitis

TOP-017
Global association between metabolic dysfunction policies and the burden of metabolic dysfunction-associated steatotic liver disease (MASLD)
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Background and aims: Although metabolic dysfunction-associated steatotic liver disease (MASLD) is intrinsically associated with cardiometabolic risk factors, evidence assessing the potential impact of MASLD-related public health policies (PHP) on reducing the burden of MASLD remains unknown. We aimed to determine the relationship between establishing MASLD-related PHP over time and the burden of MASLD worldwide.
Method: We conducted a multinational ecological study. Data on policies were obtained from the World Health Organization between

2013–2021, while age-standardized disability-adjusted life years (DALYs) due to MASLD were obtained from the Global Burden of Disease study between 2017–2021. We classified PHP into two categories: 1. Countries with the policies established by 2013 and 2. Countries with PHP after 2013 (or no policies). We estimated an incidence rate ratio (IRR) using multilevel generalized linear models with a Poisson family distribution adjusted by population structure, healthcare access and quality index, human development index, alcohol use per capita, smoking, body mass index, and physical activity.

Results: A total of 110 countries were included. The median age-standardized MASLD-related DALYs were 47.8 [IQR:33–74.3] per 100,000 inhabitants. Fifty-three percent of countries had national policies on diabetes by 2013, while 46.4% had cardiovascular disease (CVD) policies, 60.9% had nutritional policies, and 57.3% had policies on physical activity. In adjusted models, the establishment of PHP in diabetes by 2013 was associated with a significant reduction in MASLD-related DALYs (IRR 0.49, 95%CI:0.27–0.90, p = 0.021). Similar associations were observed in the establishment of national policies on nutrition (IRR 0.46, 95%CI:0.23–0.94, p = 0.034) and policies on CVD (IRR 0.43, 95%CI:0.21–0.88, p = 0.020) by 2013. However, the PHPs on physical inactivity were not significantly associated with lower MASLD-related DALYs (IRR 0.60, 95% CI:0.29–1.25, p = 0.177). A comparable effect size was observed among these public health policies in decreasing the incidence of hepatocellular carcinoma and deaths due to MASLD cirrhosis. In all the multivariable models, higher alcohol use was significantly associated with an increase in MASLD-related DALYs.

Conclusion: Establishing national PHP targeting diabetes, CVD, and nutrition may significantly reduce the burden of MASLD. Additionally, alcohol use remains a critical modifiable risk factor contributing to the global burden of MASLD, underscoring the need for integrated approaches in public health strategies and better methods to quantify alcohol use in clinical practice.

TOP-018

Examining the causal link between alcohol consumption and fatty liver disease using Mendelian randomization

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Background and aims: The prevalence of fatty liver has risen significantly in Asian countries, from 25.3% (1999–2005) to 33.9% (2012–2017). According to the WHO's 2018 Global Report on Alcohol and Health, alcohol consumption causes 3 million deaths annually, with 47.9% related to cirrhosis. Alcohol is metabolized in the liver by ADH and ALDH2 enzymes. Although alcohol consumption has been associated with fatty liver development, the causal relationship remains unclear, especially in humans. Animal studies suggest alcohol leads to liver fat accumulation, but conclusive evidence in humans is lacking. Mendelian randomization (MR) provides a powerful method to assess causality by using genetic variations as instrumental variables. This study aimed to investigate the causal link between alcohol consumption and fatty liver in the Taiwanese population.

Method: The study analyzed data from 120,143 Taiwanese adults (aged 37–60) in the Taiwan Biobank. Fatty liver was determined using the Fatty Liver Index (FLI), with scores ≥20 indicating fatty liver disease (FLD). Participants with viral hepatitis or missing data were excluded, yielding 104,802 individuals. Genetic variants in ADH1A, ADH1B, ADH1C, and ALDH2 associated with alcohol drinking ($P < 5 \times 10^{-8}$) were selected as instrumental variables. To ensure validity, MR assumptions were tested: reliable association with alcohol drinking, no link to confounders, and an effect on fatty liver solely through alcohol. Logistic regression assessed compliance, and MR analysis was conducted using a two-stage residual inclusion method.

Results: Four significant genetic variants were identified: ADH1B rs1229984, ALDH2 rs75162023, ALDH2 rs671, and ALDH2 rs6489793. Logistic regression showed that ALDH2 rs671 and rs6489793 were associated with confounders like smoking, physical activity, and income, and also directly linked to fatty liver, violating MR assumptions. Conversely, ADH1B rs1229984 and ALDH2 rs75162023 satisfied all criteria, qualifying as valid instrumental variables. MR analysis using these valid variants showed no significant causal relationship between alcohol consumption and fatty liver (rs75162023: OR = 1.6, 95% CI = 0.11–23.28; rs1229984: OR = 0.97, 95% CI = 0.11–8.83). Comparatively, analyses with invalid variants (rs671 and rs6489793) showed misleading associations, emphasizing the importance of valid instrumental variables in MR studies.

Conclusion: This study provides no evidence of a causal relationship between alcohol consumption and fatty liver disease in the Taiwanese population. These findings differ from prior observational studies suggesting an association, indicating that fatty liver risk may be influenced by lifestyle factors beyond alcohol, such as unhealthy diets. Future research should address these confounders, and genome-wide association studies (GWAS) could further clarify the complex relationship between alcohol consumption and fatty liver.

TOP-032

Prevalence of the spectrum of steatotic liver disease and associated fibrosis and cirrhosis among adults in the United States

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Background and aims: Spectrum of steatotic liver diseases (SLD), including metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic alcohol-related liver disease (MetALD), and alcohol-related liver disease (ALD), pose a significant public health challenge in the U.S. This study aimed to estimate the age-standardized prevalence of fibrosis stages and cirrhosis across SLD subtypes in U.S. adults.

Method: Data from the National Health and Nutrition Examination Survey (NHANES, 2017–2023) were analyzed. SLD was identified using a Controlled Attenuation Parameter (CAP) threshold of ≥280 dB/m. Subtypes (MASLD, MetALD, ALD) were classified per updated nomenclature. Fibrosis stages were assessed using liver stiffness measurements (LSM): significant fibrosis (LSM > 8 kPa) and advanced fibrosis (LSM > 12 kPa). We defined cirrhosis by LSM according to 2 criteria: Cirrhosis 1 (LSM > 15 kPa) and Cirrhosis 2 (LSM > 20 kPa).

Results: In 2021–2023, the age-standardized prevalence of SLD was 36.88%, including MASLD (32.99%), MetALD (1.86%), and ALD (1.16%). Prevalence was higher in men compared to women for SLD (41.92% vs. 31.72%), MASLD (36.76% vs. 29.54%), MetALD (2.54% vs. 1.15%), and ALD (1.93% vs. 0.33%) (p < 0.03). From 2017–2020 to 2021–2023, the prevalence of SLD and MASLD remained stable; however, the prevalence of significant and advanced fibrosis rose from 17.38% and 5.75% to 22.25% and 8.24% in SLD and from 17.55% and 5.72% to 21.44% and 7.79% in MASLD, respectively. The prevalence of cirrhosis, defined by two different criteria, also increased (Cirrhosis 1 increased from 3.84% to 5.59% in SLD and from 3.83% to 5.55% in MASLD, while Cirrhosis 2 increased modestly from 2.39% to 2.86% in SLD and from

2.47% to 2.85% in MASLD). Similar trends were observed in the MetALD and ALD subgroups. Logistic regression adjusted for metabolic and sociodemographic factors showed severe obesity (BMI ≥40 kg/m²) as the strongest predictor of significant fibrosis (OR = 9.96, 95% CI: 5.95–16.67) and advanced fibrosis (OR = 18.17, 95% CI: 7.83–42.15). Other predictors of significant fibrosis included obesity (OR = 2.81, 95% CI: 1.85–4.26), type 2 diabetes (T2D; OR = 2.58, 95% CI: 1.92–3.48), and hypertension (OR = 1.80, 95% CI: 1.34–2.42). These metabolic risk factors more pronounced predictors of cirrhosis.
Conclusion: While the prevalence of SLD and MASLD remained stable over time in the United States, there is a consistent increase in the prevalence of patients with high-risk disease (advanced fibrosis and cirrhosis). This underscores the need for targeted policies in the United States to avert adverse outcomes.

THURSDAY 08 MAY

THU-003-YI

One-stop shop: a bespoke single-point-of-referral clinic enhances linkage to care for ultrasound surveillance of hepatoma in patients diagnosed with advanced fibrosis and cirrhosis via targeted community screening

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Background and aims: We established a pilot project to identify advanced fibrosis/cirrhosis in patients in community settings using liver stiffness measurements (LSM) by Fibroscan. The aim is to increase ultrasound surveillance (USS) and the diagnosis of early hepatoma, in populations currently unlinked to care. Outreach teams delivered LSM in a mobile clinic van and other community locations. Patients were referred to their local hospital clinic for USS and clinical assessment but linkage to care (LTC) remained a challenge. To address this, we started a bespoke, single-point-of-referral specialist clinic in November 2023. Patients, supported by people with lived experience (peers) if potential engagement risks were identified, underwent a repeat fasted LSM, USS, and complete clinical evaluation in one visit. We aimed to evaluate the effectiveness of 1. community LSM screening to identify subjects for USS for hepatoma and 2. attendance at our bespoke clinic over 12 months compared to prior standard of care.
Method: We extracted data from our program database covering LSMs from October 2022 to September 2024 targeting groups in local drug and alcohol services, community diabetic retinopathy services, hostels, prisons and other community locations in SW London. LSM ≥11.5 kPa was used as a cut-off for advanced fibrosis and referral. We examined attendance rates over 12 months at our bespoke clinic and for USS and/or standard assessment in one hospital in the 12 months prior to the clinic set-up.
Results: In the second period, 1448 persons received community LSMs (915 male : 533 female), and 103 (7.1%) had LSM ≥11.5 kPa and were referred to our clinic, with heavy alcohol consumption in 83%, type II diabetes in 11%, and known metabolic dysfunction-associated steatotic liver disease (MASLD) in 6%. With a mean wait time of 14 days, 97/103 (94%) subjects attended their appointments compared to 28/43 (65%) in the 12 months prior to the dedicated clinic. 24% received peer support. 95/97 (98%) had repeat LSM and USS on the same visit with 54/95 (57%) revealing radiological evidence of cirrhosis. 67/95 (71%) had a concordant repeat LSM (median LSM 22 kPa). 74/85 (87%) patients with heavy alcohol consumption received a brief alcohol intervention. 78/97 (80%) were referred for ongoing USS and 19/97 (20%) were discharged. One was diagnosed with hepatoma. 30/36 (83%) attended their second 6-monthly USS appointment on time.
Conclusion: Targeted community fibroscan is successful at detecting advanced fibrosis and cirrhosis in populations that would not otherwise access liver services. The establishment of a dedicated one-stop point-of-referral service, supported by peers, can deliver excellent attendance and LTC for ongoing USS. It is however a resource intensive undertaking.

THU-004

Hospital-based and individual disparities in liver transplantation access in France: a national health data system analysis

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Background and aims: Several studies have shown that non-medical factors can determine access to liver transplantation (LT). Most of this data comes from North America, where the healthcare system has specific features that are difficult to transpose to Europe. We aimed to investigate the factors associated with access to LT in patients admitted to hospital for a first episode of decompensated cirrhosis in France and to determine whether there are treatment gaps in certain centres due to the aetiology of the underlying liver disease.
Method: In this analytical retrospective cohort, we used data from the French national health data system to extract patients between 18–70 years hospitalized for a first decompensation of cirrhosis between 2015–2022, followed until December 2023. We built a frailty model to search for factors associated with access to LT and to quantify inter-centre variability. Then, using a method derived from indirect standardization, we described the differences between the expected and observed incidence of transplantation in patients with an alcohol-related background, between hospital centres.
Results: We identified 65,771 patients, with a mean follow-up time of 36 months and 195,270 person-year. Of these patients, 73.5% were men and 82.3% had an alcohol-related cirrhosis. By December 31st, 2023, 3,596 (5.5%) had been transplanted and 35,660 (54.2%) had died. Patients with an alcohol-related liver disease (ALD) were less likely to be transplanted (HR = 0.75, CI95% = [0.69–0.81]), as were women (HR = 0.75, CI95% = [0.69–0.81]), patients with solidarity-based complementary health insurance (HR = 0.82, CI95% = [0.74–0.90]) and more socially deprived patients (HR = 0.97, CI95% = [0.94–0.99]). The poorer access to LT for ALD patients was evenly distributed between centres.
Conclusion: Our study highlights several factors contributing to unequal access to LT in France. The lower access for ALD patients suggests the presence of structural stigma. Modification of national-based policies could lead to a more equitable access to LT.

THU-005

The largest, exhaustive in-depth analysis and concerning report on 386 complementary and alternative medicinal products belonging to the Indian-systems of medicine (AYUSH) retrieved from patients that caused liver-related harm at the consumer level

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Background and aims: Complementary and alternative medicines (CAMs) are integrated into the national healthcare system in India and widely exported globally, including Europe and US. The Indian CAM system is officially known as Ayush [Ayurveda, Yoga and Naturopathy, Unani, Siddha, Sowa Riggpa (Tibetan Medicine) and Homeopathy]. Since last decade, large series of Ayush-related liver injuries were increasingly reported in medical literature from India and the West. We aimed to perform pragmatic analysis on vast numbers of Ayush-related CAMs retrieved from patients, that caused consumer-level harm in the context of hepatotoxicity.
Method: CAM products retrieved from patients underwent inductively coupled plasma mass spectrometry and triple quadrupole gas chromatography-mass spectrometry for identification of heavy metals, steroids and prescription drug adulteration and contamination along with detailed evaluation of labels for presence of hepatotoxic ingredients.
Results: From May 2021 to December 2023, we retrieved 386 CAM products consumed by 91 patients belonging to classical, proprietary, and unlabeled ayurvedic (N = 111, 99, 77 respectively); homeopathic (15, 4, 24); Siddha (7, 5, 4); unlabeled Unani (4); Tibetan medicine (5), folk medicine (6) formulations and herbal and dietary supplements (7). Males predominated (N = 69, 75.8%) with median age 49 years. Median number of products consumed per patient was 3 (minimum 1, maximum 18). Acute-on-chronic liver failure was notable in more than one-third (N = 36). We identified a total of 2387 unique compounds in 386 CAMs. After applying criteria of match-factor cut-off >70% with presence in minimum 5 products, (except for prescription drugs), a total of 391 compounds were identified. The most common botanical metabolite was stigmasterol, precursor of naturally occurring anabolic–androgenic steroid in 123 CAMs (32%). Prescription drugs including non-steroidal anti-inflammatory medications, corticosteroids, anti-microbials, cardiac drugs, narcotics, and chemotherapeutic agents were identified in 53 (14%) CAMs. Lead beyond safe limit (0.1 mg/kg) was notable in 259 (67%, highest 67616.3 mg/kg), arsenic (>1 mg/kg) in 121 (31.3%, 11262.4 mg/kg) and mercury (>0.5 mg/kg) in 149 (38.6%, 383663.4 mg/kg). Well-documented hepatotoxic botanicals giloy, turmeric, and ashwagandha were labeled in 60 (16%), 28 (7%), and 23 (5.9%) CAMs respectively, without adequate safety warnings.
Conclusion: A significant proportion of CAMs causing liver injury contain known hepatotoxic botanicals without labeled warnings, extreme levels of heavy metal contamination, adulteration with a variety of prescription drugs and potentially toxic plant metabolites. Public education and patient awareness on avoidable liver injury from non-beneficial CAMs should be normalized in routine physician-driven outpatient and inpatient discussions.

THU-006

Bridging the gap between primary care physicians and hepatology with electronic consultations

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Background and aims: Electronic consultations (e-consults) in primary care enhance communication between primary care physicians (PCPs) and specialists, offering an important tool for managing a range of medical conditions. The advantages of e-consults include reducing the amount of specialist referrals, keeping care within the community, empowering PCPs with improved knowledge, and enabling patients to remain under the care of their usual physician. This study aimed to map the needs of PCPs managing liver conditions, and to analyse their use of hepatology e-consults in the fourth-largest Health Maintenance Organization (HMO) in a small, high-income country.
Method: A random sample of 30% of all hepatology e-consults within an HMO requested by PCPs between January 1, 2023, and July 31, 2024, were categorized according to medical condition addressed, PCP query, and hepatologist response. All responses to hepatology e-consults within the HMO were provided by a single senior hepatologist.
Results: A total of 1,373 hepatology e-consults were recorded during the study period. The most common topics included imaging findings (29%), elevated liver enzyme levels (20%), and combinations of imaging and laboratory findings (12%). Diagnoses discussed in the e-consults included mostly viral hepatitis and metabolic-associated steatotic liver disease. PCPs primarily sought guidance regarding further evaluation (44% of queries), with fewer inquiries about treatment (8%) and follow-up (4%). 15% of queries regarded medication use, procedure clearance, and administrative issues. The hepatologist's responses often included recommendations for imaging (45%) and laboratory tests (35%), while fewer responses (23%) involved treatment recommendations. Only 10% of cases required referral to a hepatology clinic.
Conclusion: This analysis highlights the wide range of liver-related challenges faced by PCPs, with 62% of queries addressing the pre-diagnosis stage of management, while 26% pertain to managing diagnosed liver conditions. Since its introduction in 2019, usage of the hepatology e-consult service by PCPs has increased by 60% annually, underscoring its potential to bridge the gap between primary care and hepatology. The finding that only 10% of cases required referral to a hepatology clinic – significantly lower than figures reported in previous studies – emphasizes the service's effectiveness in reducing the need for specialist consultations. Further studies will identify knowledge gaps among PCPs, inform targeted training programs, reduce the burden on specialist clinics, and further enhance the effectiveness of e-consult services in primary care.

THU-007

Real-world experience using serial transient elastography by FibroScan in a community outreach service for the earlier detection of liver disease

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Background and aims: The *Alright My Liver?* service delivers community screening for advanced liver fibrosis in people at risk from alcohol, viral hepatitis and metabolic syndrome in the South West of England. The service targets the highest risk populations for liver disease (many who rarely access healthcare) using transient elastography (TE) by FibroScan as the initial screening modality. A personalised brief intervention is delivered alongside TE. Of 6100 people screened, 292 had initial TE indicative of suspected advanced fibrosis (LSM > 11.5 kPa). 104 of these patients have undergone repeat TE within 2 years. Here we analyse this subgroup to understand the indications and outcomes of repeated TE in this setting.
Method: Routinely collected data was analysed retrospectively from 104 patients identified over a 26 month period between August 2022 and October 2024. Data was collated on indication for repeat TE; interval change in: liver stiffness measurement (LSM), interquartile range/median value (IQR/M), controlled attenuation parameter (CAP) and alcohol intake. Interval time between TE was recorded, as was the clinical conclusion drawn from TE results alongside other investigations. Data was initially collected for 104 patients, but 27 were removed due to opportunistic rather than planned interval repeat.
Results: 77 patients (67.5% male; mean age 54, SD 13.9) were included. Mean BMI was 29.1 kg/m^2 (SD 6.9). Median interval between scans was 11 months (IQR 7). Aetiology of suspected liver disease was ALD (57.1%), MetALD (16.9%), MASLD (16.9%) and viral hepatitis (9.1%). Median LSM at first TE was 10.8 kPa (IQR 6.3) and at second TE was 7.3 kPa (IQR 5). Median IQR/M values were 21% (IQR 12) and 15% (IQR 5) respectively. The commonest indication was scheduled interval repeat post clinician assessment (n = 57/77); this was largely due to an initial assessment indicating fibrosis or possible cirrhosis with a behaviour change intervention. Other indications included clinical suspicion of inaccuracy due to discordancy of tests (n = 5/77), high IQR/M >25% (n = 12/77) or non-fasted scan (n = 3/77). The median change in LSM between TE was −3.7 kPa (IQR 5.5), median IQR/M change was −6% (IQR 19) and CAP change −10 dB/m (IQR 57). Of the 19 patients with suspected MetALD or ALD and accurate alcohol documentation, the median alcohol intake change was −44.6 units per week (IQR 140). A limitation of this analysis is the alcohol change estimate is subject to reporting bias. Clinical conclusions drawn were fibrosis regression 36.4% (n = 28/77), spurious index TE 31.2% (n = 24/77), fibrosis progression 16.9% (n = 13/77) and no clinically significant change in fibrosis 15.6% (n = 12/77).
Conclusion: We have identified a substantial reduction in the LSM and alcohol use following initial intervention with TE alongside brief intervention in these patients. Only 1.3% (n = 77/6100) of patients required repeat LSM in 2 years of a large regional pilot. Of the total dataset of 6100 people screened, only 0.4% (n = 24/6100) were discarded as spurious.

THU-008
The placebo project - comprehensive analysis of 134 commonly prescribed homeopathic remedies in India uncovers potential for severe hepatotoxicity

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Background and aims: Homeopathy is a popular alternative medical practice globally. However, homeopathic formulations can cause allergies, anaphylaxis, fatal cardiovascular events, kidney injury, and death due to their direct and indirect toxicities. Recently Homeopathic remedies were implicated in severe liver injury, liver failure and death. Despite the growing recognition of potential risks, a comprehensive analysis of commonly prescribed and over-the-counter homeopathic products is notably absent from the medical literature. This study pragmatically analyzed the toxicology of commonly prescribed homeopathic formulations from three categories: classical dilutions, mother tinctures, and proprietary products.
Method: This cross-sectional study assessed the quality and safety of popular over-the-counter homeopathic formulations. Each remedy underwent standardized and complete organic and inorganic content profiling, including heavy metal detection, alcohol quantification, and steroid detection.
Results: We analyzed 134 homeopathic remedies and found labelled evidence of insect and animal parts in alcohol, extremely high alcohol levels, and toxic heavy metals. Mislabeling discrepancies were evident, with some formulations containing higher alcohol content than disclosed. Classical formulations had the highest alcohol content (median: 91.02% v/v). Surprisingly, highly diluted formulations of arsenic and mercury had detectable lead levels. Analysis of proprietary homeopathic formulations revealed various industrial-grade solvents, and pharmaceutical intermediates, raising consumer-level toxicity concerns. Additionally, various plant-based toxic components were also identified, which included monoterpenes and sesquiterpenes such as limonene, terpinene, and phellandrene and anthraquinones and phenolic compounds that were documented to have hepatotoxicity in published literature.
Conclusion: Our findings reveal concerning levels of ethanol, detectable heavy metals, diverse bioactive plant chemicals, industrial-grade solvents, and pharmaceutical processing residues in large number of Homeopathic formulations. Furthermore, the undisclosed nature of many compounds and discrepancies in alcohol content labeling raise significant concerns regarding product transparency and consumer safety. The presence of unregulated and untested proprietary Homeopathic remedies containing irrational combinations of ingredients, including industrial-grade chemicals and animal parts, underscores the need for stringent regulatory oversight to safeguard public health, particularly in the absence of robust clinical evidence supporting their efficacy and safety. Consumers should be aware that the testimonials and anecdotal claims of homeopathic benefits lack scientific validation and can mask potentially harmful effects.

THU-009
Gender biasing and disparities in living donor liver transplant setup from a tertiary care liver transplant centre

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Background and aims: Gender disparities in accessing medical care are global issues. This multifaceted bias experienced by women has also negatively impacted them in the setting of living donor liver transplant, and more so in developing countries. To further emphasize and establish the gender inequities in living donor liver transplantation in India, we have analysed the medical records of cirrhosis patients including that of liver transplantations performed at our liver tertiary care center for gender distribution.
Method: In this retrospective study at ILBS, we analysed for gender distribution and frequency, the medical records of cirrhosis patients including that of liver transplantations performed at our tertiary care, a government apex liver care and transplant centre between Jan 2013 to Jan 2021.
Results: A total of 1523 chronic liver disease (CLD) study subjects were analysed. Of the total CLD patients who were being evaluated for liver transplant workup (n = 1117) only 147 (13.20%) were females and 970 (86.80%) were males ($p < 0.0001$). Similarly, for the CLD patients those who were getting non- transplant standard of care management (n = 406) females and male were representing 98

(24.10%) and 308 (75.90%) ($p < 0.001$) of subjects again representing overwhelming male preponderance. On the other hand, a reverse proportion but again with a negative health and social inequity was observed in living donor for liver transplant population. Of the total donor subjects (n = 627) been evaluated for donor workup only 245 (39.10%) were males while 382 (60.90%) were females.
Conclusion: The present retrospective study confirms and reestablish the overwhelming inequities and gender disparities in access to standard of liver care and lifesaving liver transplant options as evident by overwhelming preponderance of male patients, reflecting gender bias and overall, very low prevalence of habitual drinking in females in India. Similarly, females are disproportionately overrepresented in living donor for liver transplant population again reflecting a negative gender bias and altruistic behaviour of females. There is yet unrealised and unmet need for gender parity in access to liver care and liver transplant that has to be addressed in most ethical, humane and timely manner.

THU-010
Leave no one behind: an examination of how the hepatitis C elimination programme in England is reducing healthcare inequalities

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Background and aims: Hepatitis C virus (HCV) infection poses a significant public health challenge, particularly among marginalized and excluded populations. Disparities in access to diagnosis, treatment, and care can contribute to ongoing transmission and preventable morbidity and mortality. The HCV Elimination Programme in England was established as a unique co-production between NHS England, Operational Delivery Networks, people with lived experience, UK Health Security Agency, mobile outreach teams, addiction services, prison healthcare providers, GP champions, Emergency Departments, community pharmacies, needle exchanges and pharma partners. This collaborative works to eliminate HCV as a public health threat by ensuring that care reaches all individuals affected by the virus, wherever they are and regardless of their proactively accessing 'a service'. By integrating services across multiple sectors and fostering partnerships, the programme strives to deliver equitable healthcare at the patient's' convenience and setting, ensuring that no one is left behind in the fight against HCV.
Method: Retrospective review of the impact of various elimination initiatives and healthcare innovations rolled-out by the HCV elimination programme in England alongside its partners. Anonymised data collected routinely were used to assess the programmatic work's impact on healthcare inequalities. Records were matched to Indices of Multiple Deprivation (Office of National Statistics, 2019).
Results: In England, patients living in the 20% most deprived areas received 50% of all HCV treatments since 2015, and 83% of all treatments were given to the most deprived half of the country's population. One in four patients with a recorded nationality (26%) was born outside of United Kingdom. Almost half (47%) of total treatments with a recorded ethnicity, were given to minority ethnicities in England (defined by the government as not White – British). The majority of treatments were given to male patients (72.43%), 0.03% to Transgender patients and 0.001% to patients recoded as nonbinary. Information about injecting risk was recorded in 78% of cases: 76% of patients treated had injected drugs in their lifetime. Four percent of patients treated were HIV positive.
Conclusion: Through its unique co-production and scalable innovations that integrate primary, secondary and community care with partnerships with people with lived experience, addiction services, prisons and pharma, the HCV elimination programme in England provides inclusive and equitable access to healthcare and reduces health inequalities by breaking down stigma barriers, targeting the most deprived and treating (often in non-traditional settings) people at high risk such as those injecting drugs and people born in countries with higher HCV prevalence (e.g. minority white and South Asian ethnicity populations of England).

THU-011
Incidence-based mortality trends of primary liver cancer (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) in Scotland between 2000 and 2021

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Background and aims: Primary liver cancer (PLC) incidence and mortality have been increasing in European countries in recent decades. It is important to distinguish between the two main PLC subtypes, are hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), because aetiology, management and outcomes differ. This study aimed to use an incidence-based mortality approach, which can distinguish PLC subtypes, unlike conventional death certificate-based mortality, to describe PLC mortality in Scotland up to 2021.
Method: PLC death certificates (n = 9673) were accessed from the National Records of Scotland in 2000–2021 and matched with individual-level incidence records, accessed from the Scottish Cancer Registry (SCR) (n = 9358) and any not recorded as PLC incidence were excluded (n = 315, 3% of death certificates). SCR is a nationwide and population-based registry. PLC patients were defined as ICD-O-3 C22 with all morphological codes. HCC patients were defined as ICD-O-3 C22 with 8170–8175 and 8180 morphological codes and ICD-O-3 C22.0 with 8010, 8140 morphological codes. iCCA patients were defined as ICD-O-3 C22 with 8160, 8161 morphological codes and ICD-O-3 C22.1 with 8010, 8140 morphological codes. European Age-Standardised Mortality Rate (EASMR) was annually calculated. Joinpoint regression analysis was applied to examine any change in the mortality trend. 95% lower and upper confidence limits were calculated by normal distribution.
Results: There were 9358 deaths from PLC from 2000 to 2021. PLC, HCC, and iCCA increased from 2000, followed by a more recent plateau. Temporal trends in PLC mortality changed for PLC and iCCA in 2016, and for HCC in 2015. PLC mortality increased between 2000 [n = 250, EASMR = 5.9 (5.2, 6.6) per 100 000] and 2016 [n = 574, EASMR = 11.1 (10.2, 12.0) per 100 000]. PLC mortality plateaued between 2016 and 2021 [n = 650, EASMR = 11.7 (10.8, 12.6) per 100 000]. HCC mortality increased between 2000 [n = 113, EASMR = 2.7 (2.2, 3.2) per 100 000] and 2015 [n = 351, EASMR = 6.9 (6.1, 7.6) per 100 000]. HCC mortality plateaued between 2015 and 2021 [n = 382, EASMR = 6.8 (6.1, 7.5) per 100 000]. iCCA mortality increased between 2000 [n = 97, EASMR = 2.3 (1.8, 2.8) per 100 000] and 2016 [n = 216, EASMR = 4.2 (3.6, 4.8) per 100 000]. iCCA mortality plateaued between 2016 and 2021 [n = 220, EASMR = 4.0 (3.5, 4.5) per 100 000].
Conclusion: PLC, HCC, and iCCA mortality increased from 2000 followed by plateaus from the mid-2010s in Scotland. These trends might be cautiously welcomed, but further research is needed to understand whether they are driven by changes in incidence, survival, or a mixture of the two.

THU-012

Circulating metabolites, gallstones, and gallbladder cancer

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Background and aims: Gallbladder cancer (GBC) is an aggressive disease with limited treatment options but high prevention potential. Gallstone disease has been causally linked to GBC, with an estimated latency period of 15–25 years, a time frame that harbors the potential for primary prevention of GBC through gallbladder removal in gallstone patients at high risk for GBC. An efficient prevention strategy requires accurate assessment of GBC risk, and the identification of risk biomarkers is critical. However, studies aimed at identifying GBC biomarkers have generally been challenged by their small sample size, and the robustness of their results is questionable. To overcome this limitation, we capitalized on the link between gallstones and GBC and hypothesized that some metabolites associated with gallstone disease could serve as GBC risk biomarkers.
Method: A two-stage prospective study design was applied to UK Biobank targeted metabolite data using bootstrapping for robust metabolite selection. At the first stage, the association between circulating metabolites and the onset of gallstone-related clinical conditions (gallstone detection, cholecystitis, cholecystectomy) was investigated using regularized Cox regression. At the second stage, the direct association between metabolites selected in the first stage and GBC onset was examined, adjusting for gallstone onset as a time-dependent covariate.
Results: At the first stage, seventeen metabolites, selected by bootstrapping to at least 90%, were considered robustly associated with gallstone-related clinical conditions. At the second stage, four out of these seventeen metabolites were found to be directly associated with GBC. Among these, free cholesterol in small high-density lipoprotein (HDL) was linked to a reduced risk of GBC, while triglycerides in large HDL, glutamine and acetone were associated with an elevated risk of GBC.
Conclusion: Risk assessment, a critical component of disease prevention, would highly benefit from risk biomarkers. For rare diseases such as GBC, the time and cost associated to biomarker identification and measurement limit the clinical utility of biomarker-guided personalised prevention. Our research introduces a novel approach to find risk biomarkers for a rare disease capitalizing on a well-established, strong risk factor. The metabolites identified demonstrate the potential of this approach. Next, we plan to validate our findings in independent prospective cohorts and compare the high-risk-profiles in different populations. Taken together, our work may help refine current prevention strategies by prioritizing gallbladder removal in high-risk patients.

THU-013

First nations australians with cirrhosis have higher and premature mortality and multiple cofactors

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Background and aims: Liver disease is an important contributor to the mortality gap between First Nations (FN) and non-Indigenous (NI) Australian adults. We described cause-specific mortality by indigenous status in people with cirrhosis in Queensland, a large state in the north-east of Australia with a population of over 5 million.
Method: A retrospective analysis of all adults hospitalized with cirrhosis during 2007–2022 was performed using state-wide hospital admissions and mortality data. We identified admissions with cirrhosis, aetiology, and underlying cause of death based on validated algorithms. 1,909 (8.5%) FN and 20,584 (91.5%) NI patients were followed from the first admission with cirrhosis until death, liver transplant, or December-2022, whichever came first. Multivariable Cox regression assessed factors associated with mortality.
Results: Compared to NI patients, FN patients were 8.3 years younger (53.6 years, SD = 11.9 vs 61.9 years, SD = 12.8; $p < 0.01$), a higher proportion resided in most disadvantaged (46.9% vs 26.0%; $p < 0.01$) and remote areas (19.3% vs 1.5%, $p < 0.01$), had diabetes (49.5% vs 37.6%, $p < 0.01$), and cirrhosis decompensation or hepatic failure (43.8% vs 39.9%; $p < 0.01$). Alcohol was an aetiological factor in 74.1% of FN and 58.2% of NI patients ($p < 0.01$). Multiple cofactors was more common in FN patients (70.2% vs 57.8%; $p < 0.01$), alcohol/diabetes was present in 32.6% of FN patients (vs 17.5%; $p < 0.01$), and alcohol/viral hepatitis in 25.0% (vs 14.2%; $p = 0.01$). During a median follow-up of 6.9 years (IQR 3.5–11.1), 52.1% of FN and 55.2% of NI patients died. At death, 40.2% of FN patients were ≥60 years vs 70.0% of NI patients ($p < 0.01$), with a similar pattern of premature mortality due to liver ($p < 0.01$) and cardiovascular disease ($p < 0.01$), but not due to extrahepatic cancer ($p = 0.10$). The 10-year all-cause mortality was 66.8% (95%CI 63.8–70.0) and 68.5% (95%CI 67.6–69.3), respectively. Adjusting for age, sex, socioeconomic status, remoteness of residence, aetiology, decompensation, and diabetes, all-cause mortality was 10% higher in FN vs NI patients (adjusted hazard ratio (aHR) = 1.10, 95%CI 1.02–1.19, $p = 0.01$), and mortality due to cardiovascular was 68% higher (aHR = 1.68, 95%CI 1.34–2.09; $p < 0.01$), with no difference in mortality due to liver disease ($p = 0.76$) and extrahepatic cancer ($p = 0.46$).
Conclusion: FN Australians with cirrhosis have higher mortality and die at a younger age than NI Australians. The presence of multiple liver disease cofactors is a likely driver of earlier disease onset and poorer survival in FN Australians with cirrhosis and highlights the importance of early identification of chronic liver disease and rapid linkage to specialist liver care. The higher prevalence of diabetes and higher mortality due to major cardiovascular event in FN Australians reinforces the need for a holistic approach to management of metabolic comorbidities.

THU-014

Chronic liver diseases are often diagnosed at an advanced stage despite identification of risk factors: insights from a french national study

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Background and aims: Chronic liver diseases have been reported to be frequently diagnosed at an advanced stage in various country settings. However, descriptive data on chronic liver disease (CLD) in France remain scarce. Such data are essential for designing and implementing effective corrective actions. This study aims to describe the diagnostic modalities, stages at diagnosis, and health trajectories of CLD before the occurrence of complications in France.
Method: Data were collected from the National Health Data Hub covering the National Health Data System (SNDS). Patients with at least one CLD specific ICD-10 code, procedure, or drug and/or an ICD-

10 code for primary liver cancer (PLC) between 2015–2021, were extracted from the 2% SNDS sample. Socio-demographics, etiologies, risk factors, comorbidities, and severity at diagnosis were recorded.
Results: We identified 26,388 patients, including 7,016 prevalent cases in 2015 and 19,372 incident cases between 2015 and 2021. The population of incident cases comprised 57.2% males, average age 60.3 ± 18.2 years, with 43.4% experiencing social deprivation. Etiologies included alcohol (30.6%), metabolic factors (26.6%), viral infections (10.8%), rare diseases (3.7%), and etiology was undetermined in 28.3% of the cases. At diagnosis, 55.7% had non-cirrhotic CLD, 35.2% cirrhosis (of which 91% where diagnosed during an hospitalisation stay), 7.1% liver cancer, 0.1% were identified at the time of liver transplantation and 1.8% at the time of death. Risk factors for CLD (e.g., alcohol, diabetes, obesity) were identified before CLD diagnosis in 43% of patients, with 45.7% presenting severe CLD at diagnosis (e.g., decompensated cirrhosis, liver cancer). During follow-up, nearly 50% of the cohort were diagnosed with cirrhosis or decompensations. Almost 95% of patients diagnosed with cirrhosis were hospitalized at least once during follow-up. Cirrhosis complications included a majority of hepatic encephalopathy, portal hypertension, and ascites, and to a lesser extent alcoholic hepatitis. Hepatorenal syndrome and spontaneous bacterial peritonitis were observed in few patients. About 10% of patients were diagnosed with PLC during follow-up, two-thirds being hepatocellular carcinoma. Fewer than 20% of incident CPF cases were eligible for curative treatment at diagnosis.
Conclusion: This study, utilizing data from the French National Health Data System, demonstrates that nearly half of CLD cases are diagnosed at an advanced stage, despite prior identification of risk factors. These results emphasize the urgent need for enhanced prevention and early detection strategies for CLD.

THU-019

Gaps in palliative care for liver cirrhosis in Singapore: an analysis on disease burden, timing and utilization of palliative services

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Background and aims: Liver disease afflicts millions worldwide with many of these patients dying or suffering from its associated complications. In 2022, hepatocellular carcinoma (HCC) was the fifth most common cancer and third most common cancer death in Singapore. Despite this, palliative care utilization amongst cirrhotic patients remains low. We aimed to evaluate morbidity burden and palliative care utilization for end stage liver disease (ESLD) patients in our population.
Method: A single centre retrospective observational cohort study included patients with known liver cirrhosis and mortality from 1/1/2018 to 31/5/2024. Patient demographics, hospitalization lengths and palliative care utilization data were collected.
Results: 209 patients were included. Mean age was 71 years old with 68.9% males. 53.11% of patients had a Model for End-Stage Liver Disease (MELD) score between 10–19 and 26.32% had a MELD score <10. 13.4% of patients' MELD was 20–29 and 1.44% had a MELD of >30. 12 patients had missing data that precluded a complete MELD score. On average, each patient was hospitalised 6.56 times. The average length of a hospitalization was 9.59 days. Average total hospitalization days per patient from date of inclusion was 54.50 days. Majority of admissions occurred in the patient's last year of life, with an average of 4.12 admissions during the last year, compared to 1.21 admissions in the second last year of life. Cause of death (COD) was known for 113 patients. Of these, 77 (68.14%) died of liver cirrhosis and its associated complications. The top COD was HCC with 36 (31.86%) patients. 56 (26.79%) patients were referred to specialist palliative care prior to their death. Of these, 19 (33.93%) were made within 7 days of death and a further 18 (32.14%) were made within a month of death. 39 (18.66%) accessed community palliative care and 21 (10.05%) patients were admitted to an inpatient hospice. Only 21 patients (10.05%) completed advanced care planning (ACP).
Conclusion: Despite liver cirrhosis conferring a significant mortality and morbidity burden on patients, palliative care utilization remains low. Even amongst the few who had access to palliative services, these services were provided late in the disease with majority receiving it only in the last month of life. More efforts need to be made to improve access to palliative services earlier in the disease course.

THU-020-YI

Assessing awareness of fatty liver disease among people in Scotland: a cross-sectional survey study (ADIPOSE)

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Background and aims: Metabolic dysfunction-associated steatotic liver disease [MASLD], which replaced non-alcoholic fatty liver disease [NAFLD], is the commonest liver disease globally, existing within the wider metabolic syndrome. However, awareness of NAFLD/MASLD is low in both general and at-risk groups and no such awareness data exists for large UK populations. We conducted the 1st national survey assessing awareness and knowledge of "fatty liver disease" [FLD] (NAFLD/MASLD), among adults with low and high risk of MASLD in Scotland.
Method: Adults living in Scotland, registered with Scottish Health Research Register, were invited by email to complete an online survey on their awareness of liver disease. Participants self-reported demographic and health information and their knowledge of NAFLD/MASLD and related conditions. Participants were considered "at risk" for MASLD [AR] if they had ≥1 self-reported risk factor (T2D/CVD/BMI ≥25). Individuals with no risk factors were considered low risk [LR]. Analysis utilised descriptive statistics and chi-squared tests.
Results: From 01/07–23/09/24 19,763 people were invited to complete the survey. 2,114 people (11%), from all Scottish Health Boards, completed the survey (1227 [58%] female, 1178 [56%] aged 60–79). 1,586 (75%) were AR (466 [22%] T2D; 474 [22%] CVD; 1325 [63%] BMI ≥25) and 528 (25%) were LR. 217 (10%) reported a diagnosis of "FLD, NAFLD or MASLD" - 200 [13%] AR, 17 [3%] LR ($p < 0.001$).
1,495 (71%) knew of "fatty liver disease," 810 (38%) of NAFLD and 99 (5%) of MASLD. Those AR were not significantly more likely to know of these conditions relative to LR respondents ($p = 0.354$; 0.349; 0.755, respectively). Significantly more women than men were likely to know of FLD (965 [79%], $p = <0.001$) and NAFLD (588 [48%], $p = <0.001$). 86% of respondents were aware of alcohol related liver disease, 75% of viral hepatitis and >90% of other metabolic syndrome features (T2D, hypertension, obesity). After receiving information about the lack of pharmacotherapy for NAFLD/MASLD, 2,073 (98%) stated that if they had the condition, they would wish to know.
Conclusion: This national survey gives the first population-level insight into the awareness of NAFLD/MASLD in the UK. While many people report awareness of "fatty liver disease," less than half are aware of NAFLD and only 5% of MASLD. Those individuals at highest

risk are not more likely to know of these conditions compared to those at lower risk. However, significantly more of the at-risk group report a diagnosis of NAFLD/MASLD. This low NAFLD/MASLD awareness contrasts with a much higher awareness of other liver disease aetiologies and features of the metabolic syndrome. Almost all survey respondents stated that if they had MASLD they would want to be made aware of the diagnosis, even after it was explained that current management is largely lifestyle based. This study clearly demonstrates the outstanding efforts that are necessary to increase population awareness of MASLD, one of the largest public health threats of the coming decades.

THU-021

Advanced care planning (ACP) for liver cirrhosis patients in Singapore: barriers to ACP and influence of hepatocellular carcinoma diagnosis on ACP preferences

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Background and aims: The unpredictable clinical course of liver cirrhosis necessitates early advanced care planning (ACP) initiation for liver cirrhosis patients to uphold their wishes and quality of life. This study aims to investigate barriers to ACP and the influence of Hepatocellular Carcinoma (HCC) diagnosis on ACP preferences in liver cirrhosis patients.
Method: We reviewed all electronic ACP discussion records from January 2018 to December 2023 at our institution, a public tertiary hospital in Singapore. Those with diagnosis of liver cirrhosis and at least 1 hospital admission in the same period were identified. Patient data on ACP completion rate, reasons for rejection, and ACP preferences on preferred place of death (PPOD), preferred place of care (PPOC), medical intervention and CPR were reviewed in detail.
Results: In total, 53 liver cirrhosis patients with ACP discussion records were included for analysis of which 22 had HCC and 31 non-HCC. Median age was 68 of which 33 were male. 51 were of Asian ethnicity (41 Chinese, 5 Malay, 5 Indian). 50.9% (27/53) of patients rejected or did not complete ACP. Overarching themes and reasons for rejection include: death before completion, lack of readiness to discuss end-of-life (EOL)/ACP, patient denial or avoidance (perception that ACP is unnecessary, preference to discuss when situation arises), family centredness (preference to leave decision to family, family excluding patient in decision-making, family does not want to let patient know his diagnosis), and patient conditions impairing ACP discussion (dementia or encephalopathy). The most frequent reason was death before ACP completion (n = 8). The second most frequent reason was the lack of readiness to discuss EOL/ACP (n = 5). For PPOD, majority chose their own home (34.6%), followed by hospital (23.1%), and long-term care facilities such as nursing home and inpatient hospice (3.8%). An equal proportion of HCC and non-HCC patients selected the hospital (23.1%). Compared to non-HCC patients, a higher proportion of HCC patients selected own home (38.5% vs 30.8%) and long-term care facilities (7.7% vs 0%), although the difference was not statistically significant (p = 0.878). With regards to PPOC, non-HCC patients were much more likely to select the hospital compared to those with HCC (84.6% vs 15.4%, OR30.3, [3.59–254.73]; p = 0.0015). In terms of preferred medical intervention, all patients who completed ACP opted not to attempt cardiopulmonary resuscitation with majority choosing only limited intervention (HCC 84.6% and non-HCC 100%).
Conclusion: Death before ACP completion and patient lack of readiness for ACP discussion are the most significant barriers to ACP. The higher certainty of poor prognosis for liver cirrhosis patients with HCC may influence decisions on place of care, with HCC patients preferring to stay out of hospital compared to non-HCC cirrhotics preferring hospitalisation.

THU-023

Health behaviors significantly modify the sex-specific alcohol-attributable liver-related mortality in the United States. A population-based study

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Background and aims: The impact of diet quality (DQ) and physical activity (PA) on alcohol-related liver mortality is not well-studied at the population level. This study aims to explore how DQ and PA influence the relationship between alcohol consumption patterns and liver-related mortality.
Method: The study analyzed data from 60,334 adults in the National Health and Nutrition Examination Surveys (1984–2018), linked to the National Death Index through December 31, 2019. Liver-related deaths were identified using ICD-10 codes. Alcohol intake was measured as the average number of drinks per day over the past 12 months. The NIAAA guidelines classified alcohol consumption by sex: for women, light/moderate drinking was 1–3 drinks per day, and heavy drinking was more than 3 drinks per day; for men, light/moderate drinking was 2–4 drinks per day, and heavy drinking was more than 4 drinks per day. Binge drinking was defined as 4 or more drinks for women, or 5 or more drinks for men, on a single occasion within two hours. Diet quality was assessed using the Healthy Eating Index (2010), based on 24-hour dietary recalls. Physical activity levels were evaluated using the Global PA Questionnaire, classifying participants as physically active if they reported at least 150 minutes of moderate-intensity PA, 75 minutes of vigorous-intensity PA, or a combination per week. Cox regression models examined associations between these factors and liver mortality, adjusting for age, sex, race/ethnicity, smoking, BMI, diabetes mellitus, educational attainment, poverty levels, calorie intake, and the Fib-4 index.
Results: During a mean follow-up of 12.2 years, 252 liver-specific deaths were recorded. Covariate-adjusted analyses showed that any daily alcohol intake increased the risk of liver-specific mortality (adjusted Hazard ratio (aHR)-men: 1.25, 95% CI: 1.03–1.54; women: 1.88, 95% CI: 1.25–2.83) compared to abstainers. Binge drinking also increased liver-specific mortality risk (aHR-men: 1.35, 95% CI: 1.02–2.12; women: 2.56, 95% CI: 1.34–4.93) compared to non-binge drinking. Higher diet quality (DQ) levels (HEI top quartile) were linked to lower liver mortality risk among light/moderate (aHR: 0.32, 95% CI: 0.14–0.72), heavy (aHR: 0.10, 95% CI: 0.03–0.39), and binge (aHR: 0.14, 95% CI: 0.05–0.41) drinkers compared to lower DQ levels (HEI first quartile). Physically active participants had a lower risk of liver mortality among light/moderate (aHR: 0.72, 95% CI: 0.40–0.96), heavy (aHR: 0.82, 95% CI: 0.29–0.99), and binge (aHR: 0.51, 95% CI: 0.20–0.95) drinkers compared to inactive individuals. These relationships remained consistent after excluding former drinkers from the non-drinkers and those who died within the first year of follow-up.
Conclusion: Physical activity and healthy eating significantly lower the risk of alcohol-attributable liver mortality in the US population.

THU-024

Angiotensin receptor blockers and drug-induced liver injury: a cohort study using electronic-health records-based common data model database

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Background and aims: Angiotensin receptor blockers (ARBs) are one of the most commonly used anti-hypertensives in South Korea. In 2021, a need for national compensation was acknowledged by the Korea Ministry of Food and Drug Safety for a drug-induced liver injury

(DILI) after azilsartan use, the youngest drug among ARBs. Not much has been known about the association between ARBs and DILI.
Method: To further investigate ARB-induced liver injuries, we executed a retrospective new-user cohort study using electronic-health-records-based common data model database (2017–2021). In this study, patients were designated to treatment groups according to the ARB prescribed at cohort entry, i.e., azilsartan, eprosartan, telmisartan, fimasartan, valsartan, olmesartan, losartan, irbesartan, or candesartan. DILI was operationally defined by adapting the definition from the International DILI Expert Working Group. We conducted cox regression analyses to derive hazard ratios (HRs) and applied propensity score-based inverse probability of treatment weighting.
Results: A total of 229,881 ARB users from 20 university hospitals were included. The crude incidence of DILI ranged from 15.6 to 82.8 by treatment groups. In all treatment groups, the most common type of DILI was the cholestatic type and the majority were of mild severity. In overall, the risk was significantly lower in olmesartan users compared to valsartan users (HR: 0.73 [95% confidence interval (CI): 0.55–0.96]). In patients receiving monotherapy, the risk was significantly higher in azilsartan users compared to valsartan users (HR: 6.55 [95% CI: 5.28–8.12]).
Conclusion: Our findings provide insights to the methods for detecting DILI using real-world data and enhance understanding of the variations in risk of DILI among individuals using different ARBs.

THU-025-YI
Prevalence of and outcomes related to metabolic dysfunction-associated steatotic liver disease (MASLD) in a nationwide cohort: insights from over 23 million individuals in Taiwan's national health insurance research database
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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is associated with increased risk of cirrhosis, hepatocellular carcinoma (HCC) and metabolic endpoints: cardiovascular disease (CVD) and chronic kidney disease (CKD). MASLD affects 15–30% of individuals globally, with most data from Western cohorts. However, its prevalence, progression, and associated outcomes remain underexplored in unselected general populations, particularly in East Asia, where the rates of metabolic diseases are rising. Electronic Health Record data offer very wide population coverage and real-world evidence based on clinical coding. This study leverages Taiwan's National Health Insurance Research Database (NHIRD), representing over 99% of the population, to bridge these knowledge gaps.
Method: This population-based retrospective cohort study extracted NHIRD data from 1 January 2001 to 31 December 2022. Individuals were excluded if they had < 1 year follow-up post-registration, were < 18 years old, or had pre-existing conditions including alcohol abuse, alcoholic liver disease, cirrhosis, HCC, stroke, CVD, or CKD prior to MASLD diagnosis. In the absence of MASLD codes in ICD-9/10, we used NAFLD codes; shown to overlap almost completely with MASLD.
Results: In Taiwan's 23,319,977 insured individuals in 2022, 1,569,912 (6.73%) had recorded MASLD, a significant rise ($p < 0.001$) from 4.13% (N = 965,225) in 2013. The median age of patients was 49 years (IQR: 38–60), with a slight male predominance of 53.2%. Median follow-up duration ranged from 9.6 to 10.4 years for multiple metabolic endpoints analysis. Among MASLD cases, 3.6% (N = 56,394) developed cirrhosis, and 2.3% (N = 36,287) progressed to HCC. New diagnostic codes for extrahepatic outcomes were acquired during follow up: myocardial infarction (2.3%, N = 36,397), stroke (7.2%, N = 112,530), and CKD (12.1%, N = 189,750).
Conclusion: This pilot is the first MASLD study using whole population data of NHIRD, offering a near-complete depiction of MASLD codes in an East Asian population. Although there has been a marked increase in prevalence over the past decade, substantial under-diagnosis and under-recording persists compared to expected. Progression to both hepatic and extrahepatic endpoints indicates MASLD's systemic impact. The population-wide NHIRD database can advance understanding of MASLD and guide tailored public health strategies in East Asia.

THU-026
Population study of hepatocellular carcinoma survival in northest region of Spain
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Background and aims: Hepatocellular carcinoma (HCC) is the most common primary liver tumor and is considered to have a poor prognosis. At the population level, there are few studies describing the survival of this pathology, and there are no data specific to Spain. Recently, the III Spanish HCC Registry of the Spanish Association for the Study of the Liver has been published at the hospital level, describing a mortality rate of 67%. The aim is to describe the observed survival (OS) of HCC at the population level in the province of Girona (2010–2020), by sex, age, and diagnostic period.
Method: A population-based study was conducted, including all cases of HCC diagnosed from 2010 to 2020 in the province of Girona, as recorded by the Girona Cancer Registry. Cases were coded using the International Classification of Diseases for Oncology, 3rd edition (histological codes 8170–8180). Follow-up of cases continued until December 31, 2021. OS at 1, 3, and 5 years was estimated using Kaplan-Meier curves by sex, age (<50, 50–64, 65–79, and ≥80 years), and diagnostic period (2010–2013, 2014–2017, and 2018–2020).
Results: A total of 679 cases were collected, with 79.6% being male. The median age at diagnosis was 67 years [interquartile range (IQR): 59–75]. The majority of cases (62.6%) were diagnosed through imaging tests, while the rest had a microscopically confirmed diagnosis; 4 cases (0.6%) were diagnosed with combined HCC and cholangiocarcinoma. At the end of the follow-up period, 507 patients (74.6%) had died, with a median follow-up of 1.2 years (IQR: 0.2–3.4). OS at 1, 3, and 5 years was 55%, 33%, and 22% respectively, with no statistically significant differences by sex and diagnostic period. By age group, OS varied considerably after 3 years, with 5-year OS being 41% in the <50 years group and 8.9% in the ≥80 years group.
Conclusion: Population survival of HCC remains low, although age is a determining factor in medium-term prognosis. No improvement in survival has been observed in the last decade, reflecting the need for more resources to address this pathology.

THU-027

Vibration-controlled transient elastography dynamics in the general population: longitudinal results from the LiverScreen consortium

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Background and aims: Chronic liver disease is a growing global health concern driven by the rising prevalence of steatotic liver disease. Liver stiffness measurement (LSM) via vibration-controlled transient elastography (VCTE) is a recommended screening tool for liver fibrosis. However, incidence and risk factors for significant LSM changes in the general population remain poorly understood. This study examines LSM dynamics within a general population cohort and identifies risk factors for significant increases.
Method: This multicenter, prospective cohort study analyzed two population-based cohorts (Barcelona and Rotterdam) and one focused on a population with ongoing or prior moderate-to-high alcohol consumption (Odense). Participants underwent baseline and follow-up VCTE screenings over an approximate four-year interval, alongside questionnaires, anthropometric and laboratory assessments. Clinically significant LSM change was defined as a ≥30% increase or decrease from baseline, and crossing the 8 kPa threshold. Logistic regression models were used to identify risk factors for significant LSM increase, adjusting for age, sex, baseline LSM, cohort and length of follow-up.
Results: A total of 5,584 participants underwent baseline VCTE screening, of which 3,308 participants were reassessed (participation rate 75% of those eligible). At baseline, 49% were male, median age was 63 years [53–69], median baseline LSM 4.6 kPa [3.6–5.6] and 215 (6.5%) had a baseline LSM≥8 kPa. 81% had at least one metabolic risk factor. After a median follow-up of 4.2 years (3.8–4.4; 12,634 person-years), 614 (19%) experienced an LSM change of ≥30%. Among participants with baseline LSM <8 kPa (n = 3093), 2.7% (n = 82) experienced a clinically significant LSM increase, of which 14 (17%) progressed to ≥12 kPa. Independent baseline predictors of clinically significant LSM increase included obesity (aOR 3.69; 95% CI 1.66–8.17), elevated ALT (aOR 2.94; 1.72–5.04), metabolic syndrome (aOR 2.60; 1.62–4.16) and diabetes (aOR 2.44; 1.44–4.14). Of those that screened ≥8 kPa at baseline (n = 215), 87 (40%) experienced a clinically significant decrease.
Conclusion: We found a 4-year incidence of liver fibrosis close to 3%, as assessed by VCTE in this European population, suggesting that this interval is suitable for monitoring liver fibrosis development. Baseline metabolic dysfunction or elevated ALT predicted significant LSM increases, supporting current clinical practice guidelines to screen for fibrosis in at-risk populations.

THU-028

Hospital wide approach to limiting and treating alcohol use disorder

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Background and aims: Alcohol related liver disease (ARLD) is a major public health challenge and addressing alcohol use disorder (AUD) remains the cornerstone of prevention. The inpatient setting provides an ideal and underutilised opportunity to capture risky alcohol behaviours and provide brief intervention as required. Patients with AUD have double the length of stay (5.7 vs 2.3 days), are at risk for various comorbidities in their lifetime and have a significantly higher all-cause mortality. Consequently, there are obvious health, social and monetary benefits in developing a systematic approach to assessing alcohol use in the inpatient setting for the purpose of providing brief intervention to those identified as having AUD.
Method: The hospital wide approach to limiting and treating alcohol use disorder (HALT-AUD) initiative aims to address AUD with early detection and treatment. To facilitate this approach a pilot study was conducted prior to the implementation of a hospital-wide protocol using the AUDIT-C questionnaire on a medical ward. Nursing staff administered the survey upon patient admission, with results linked to a traffic light management plan. Green (< 4): No intervention required. Yellow (4–7): Brief intervention provided, including AUD resources and motivational interviewing. Red (≥ 8): Referral to the Consultation Liaison Psychiatry Alcohol Service (CLPAS) for inpatient review and further outpatient contact. The primary goal of the study was to use a quality improvement framework to evaluate the identification and management of patients at risk of alcohol-related harm. Following a 2-month period of data collection, an additional 2-month period utilised quality improvement strategies dedicated to staff assessment, education, patient feedback and workflow management. Monthly rates of compliance were collated throughout the study. The secondary measured outcomes were prevalence of significant alcohol intake (AUDIT-C ≥4), patient and staff satisfaction.
Results: 608 patients were admitted throughout the study period with 353 patients (58%) completing the AUDIT-C. Of those who completed the AUDIT C, 28% had a score ≥ 4. In the initial observation stage, the compliance in the 1st month was 51% and the 2nd month was 46%. Staff feedback, education and workflow initiatives were implemented leading to improvement to 60% and 74% compliance in the subsequent two months. Patients found the questionnaire to be comfortable and straightforward (90% agree and strongly agree), whilst after education and training 90% of nursing staff felt confident in discussing alcohol intake with patients.
Conclusion: Utilising AUDIT-C through a hospital wide approach is a simple, fast and effective tool to address AUD through a public health lens. Automation, education and focus on workflow practices improve compliance and effectiveness of AUD pathways.

THU-029

Awareness of metabolic dysfunction-associated steatotic liver disease (MASLD) in four cities in the United States, including among people with diabetes and primary care providers

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Background and aims: Despite an estimated metabolic dysfunction-associated steatotic liver disease (MASLD) prevalence of 38.2% (33.72–42.89) in the global population aged above 20 years and an estimated prevalence of 7–14% among children, public awareness remains low. This study evaluates MASLD awareness among adults in the general population, a leading at-risk population (people with diabetes), and primary care providers (PCPs) in the four most populous cities in the United States.
Method: An online survey was conducted 5–13 September 2024 in New York City, Los Angeles, Chicago, and Houston. Respondents included a sample of 5,408 adults, including 1,000 adults self-reporting having diabetes and 800 PCPs, weighted to n = 4,000 (1,000 per city) reflective of the cities' populations in terms of age, gender, ethnicity, and educational background. Awareness of MASLD was assessed with the item "Have you ever heard of metabolic dysfunction-associated steatotic liver disease (MASLD)?," reported as descriptive statistics evaluated with Chi-square tests. A regression model assessed awareness of MASLD with age, gender, ethnicity, education and health utilization factors (reporting ever had a blood test to assess liver enzymes and annual primary care visits). Odds ratios were reported with 95% confidence intervals (CI) at alpha = 0.05.
Results: Among the general population, 18.7% had heard of MASLD, ranging from 16.2% in Houston to 20.2% in Chicago. Among adults with diabetes, 37.8% were aware of MASLD. Of PCPs 54.7% reported having heard of MASLD. Age was negatively associated with MASLD awareness, with only 9.7% of those aged ≥60 aware. Individuals with higher education levels were significantly more likely to have heard of MASLD, with 45.7% of those holding post-graduate degrees reporting awareness ($p < 0.001$). Those who had ever had a blood test to assess liver enzymes were 4.4 [CI: 3.39–5.65] times more likely, and those who reported annual primary care visits were 2.0 [CI: 1.26–3.03] times more likely to have heard of MASLD ($p < 0.005$). Ethnicity and city of residency were not significant factors for awareness.
Conclusion: In the four U.S. cities studied, awareness of MASLD was low overall as well as among people with diabetes and PCPs, highlighting the need for targeted health literacy initiatives, including at the city level, to raise MASLD awareness and prevention efforts. Focused initiatives can support individuals in making informed health decisions, reinforcing the importance of prevention among at-risk populations and their caregivers.

THU-030

Risk factor awareness for liver disease in four United States cities

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Background and aims: Liver diseases pose a significant public health burden, yet awareness of their risk factors remains limited. This study evaluates awareness of key risk factors for liver disease among the general population in the four most populous U.S. cities.
Method: An online survey was conducted 5–13 September 2024 in New York City, Los Angeles, Chicago, and Houston to assess knowledge of liver disease risk factors in a sample of 5,408 adults, including 1,000 individuals with self-reported diabetes and 800 PCPs, weighted to 4,000 adults (1,000 per city) reflective of the cities' populations in terms of age, gender, ethnicity, and educational background. A risk factor awareness index was created based on responses to questions about the association of five specific dietary and lifestyle factors (high-calorie diets, high-cholesterol foods, ultra-processed foods, sedentary lifestyle, and alcohol consumption) with liver disease. Each factor was assigned a score of 1 if the respondent was aware of the association, resulting in a total score ranging from 0 to 5, which was then transformed to a 0 to 100 scale. Ordered logistic regression analysis was performed on the index with age, education, ethnicity, diabetes status, and primary care provider status.
Results: Chicago had the highest awareness of risk factors score (47.0), followed by Houston (43.9), Los Angeles (43.3), and New York City (42.0). Primary care providers were over twice (odds ratio (OR) = 2.09, $p < 0.001$) as likely to demonstrate higher awareness of the five risk factors. Higher educational attainment strongly correlated with increased awareness (OR = 1.50, $p < 0.001$). A significant positive association was observed between age and awareness (OR = 1.07, p = 0.026), with older respondents demonstrating greater awareness.
Conclusion: This study highlights an overall low awareness of risk factors for liver disease in major U.S. cities, underscoring the importance of raising awareness to support preventive health measures. Age and education were key determinants of awareness, with older and more educated individuals demonstrating greater knowledge of liver disease risk factors. These findings emphasize the need for targeted educational interventions to increase awareness, particularly among younger and less-educated populations.

THU-031

MASLD impacts quality of life and work productivity

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent cause of chronic liver disease.

Data on quality of life (QoL), work productivity, and absenteeism in early-stage steatotic MASLD are scarce. This study aimed to investigate the influence of steatosis on general and mental health, as well as productivity among patients in primary care and a diabetic population with low fibrosis prevalence.
Method: The study comprised three prospective cohort studies conducted from 2019 to 2023 across primary care centers in Belgium and the Netherlands and a hospital endocrinology department in Belgium. Fibrosis (liver stiffness) was defined by a cutoff value of above 12 kPa, and steatosis by a cutoff value of >275 dB/m, both measured using the Transient Elastography and Controlled Attenuation Parameter (CAP) with FibroScan® (Echosens, France). Participants completed questionnaires measuring anxiety (General Anxiety Disorder (GAD)-7), depression (Patient Health Questionnaire (PHQ)-9), work productivity, absenteeism, and presenteeism (Workers Productivity and Activity Impairment (WPAI), and general health (Short-Health Form (SF-36)). Data were analysed using Mann-Whitney U-test and Spearman correlation.
Results: Out of 870 screened participants, 619 (71.1%) were eligible, with 311 (69.2%) completing the questionnaires. Steatosis and advanced fibrosis were present in 142 (45.7%) and 15 (4.7%) of participants, respectively. Steatotic individuals had a significantly higher median BMI (30.5 kg/m² vs. 25.5 kg/m², $p < 0.001$) and increased liver stiffness (5.7 kPa vs. 4.6 kPa, $p < 0.001$) compared to those without. No significant differences were found between steatotic and non-steatotic individuals for depression (PHQ-9, $p = 0.955$) or anxiety (GAD-7, $p = 0.557$). However, absenteeism was more prevalent in the steatosis group (WPAI, $p = 0.016$). People with steatosis had significantly lower general health scores (SF-36, $p < 0.001$) and physical functioning (SF-36, $p = 0.024$) compared to those without. Correlation analysis revealed that higher CAP values were negatively associated with physical functioning ($r = -0.193$, $p < 0.001$), energy/fatigue (SF-36, $r = -0.112$, $p = 0.049$), and general health ($r = -0.235$, $p < 0.001$) in the total cohort but not in the steatotic and non-steatotic groups.
Conclusion: Steatosis negatively impacts general health and work productivity but does not appear to affect anxiety or depression in this cohort study.

THU-033
The "Traffic Light System" – a radiology-led pathway for hepatocellular carcinoma surveillance in patients with liver cirrhosis
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Background and aims: Patients with liver cirrhosis are at increased risk of developing hepatocellular carcinoma (HCC). An effective HCC surveillance program enhances early diagnosis but there is currently no framework for implementation in the United Kingdom. Six-monthly ultrasound scans (USS) are recommended but the processes of interpreting reports and re-booking scans can be time-consuming and risks patients being lost to follow-up. We developed a radiology-led pathway using our "Traffic Light System" (TLS), aimed at creating a safe and effective process that minimises clinician involvement and improves patient experience. We aimed to a) assess the safety of the TLS by identifying patients where no follow-up USS occurred without a decision to stop surveillance; b) determine the number of patients diagnosed with HCC through the TLS; and c) evaluate the effectiveness of the diagnostic imaging pathway once an alert was issued.
Method: A protocol and USS report templates were developed following consultations among sonographers, radiologists, and hepatologists. The TLS defines criteria for green, amber and red pathways (we added grey for non-diagnostic). 'Green' indicates no changes on USS, prompting the sonographer to inform the patient about the good news and agree on the next date in six months (radiology staff requesting USS). 'Red' indicates concern for possible cancer (e.g. new focal liver lesion): the sonographer completes an MRI safety questionnaire with the patient and requests an MRI liver (within 14 days) and notifies the 'cancer co-ordinator' and hepatologist. If the MRI supports HCC, the radiology team requests the staging CT scan (within 14 days). 'Amber' indicates 'something has changed', e.g. evidence of liver disease progression, or other incidental finding, and the hepatologist is notified urgently. 'Grey' indicates 'non-diagnostic USS', e.g. limited views of the liver; sonographer notifies the hepatology team. We included all patients with liver cirrhosis enrolled in the HCC surveillance program at our hospital from 01/03/2021 to 28/02/2022. Booked USS appointments were tracked until 01/03/2024.
Results: 220 patients were included. 3 patients (1.4%) were lost to follow-up: one due to radiology process error and two due to hepatology not restarting the TLS after an amber warning. Focal liver lesions were identified in 18 patients (8.1%), all of whom progressed to MRI scan. HCC was diagnosed in 9 patients (4.0%), with a median time between USS and MRI of 11 days. During the 3-year period, 16 patients (7.3%) died, with 9 (56%) deaths attributed to end-stage liver disease.
Conclusion: We developed a safe and efficient method for managing 6-monthly USS liver surveillance (HCC screening), with enhanced patient experience and reduced process steps (time). We believe the TLS has the potential for wider adoption within the National Health System (NHS) and further afield.

FRIDAY 09 MAY

FRI-003
Changing prevalence and risk factors of metabolic dysfunction associated steatotic liver disease in Taiwan
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Background and aims: Metabolic dysfunction associated steatotic liver disease (MASLD) is the most growing etiology of liver disease worldwide. MASLD is currently the leading cause of hepatocellular carcinoma and liver transplantation in many countries. Herein, we aim to investigate the changing prevalence and risk factors of MASLD in Taiwan.
Method: This study utilized data from two large cohorts in Taiwan including the Taiwan Biobank (TWB) and the MJ Health Management Institution cohort (MJ cohort) from 1996 to 2022. The diagnosis of steatotic liver disease (SLD) was made by abdominal ultrasound or hepatic steatosis index >36 or fatty liver index >30. MASLD was defined as SLD with at least one of the 5 cardiometabolic risk factors, excluding hepatitis C viral infection and alcoholism. Personal data including regions of residence, income and biochemistry data were analyzed as their association with MASLD.
Results: A total of 729,061 participants (including 149,687 from TWB and 579,374 from MJ cohort) were enrolled. The mean age was 42.2 ± 13.5 years old and 45.5% of the participants were male. The proportions of hepatitis B, C viral infection and alcoholism were 12.4%, 0.8%, and 3.8%. The prevalences of SLD, MASLD were 34.2%, and 31.2%. The Eastern and central region of Taiwan had the highest and lowest prevalence of MASLD. We found the risk factors of developing

MASLD were old age, male gender, high or no working income, and living in the Southern and Eastern regions of Taiwan. Meanwhile, we found the increased prevalence of MASLD over time, particularly among participants of younger age, and male gender. And there were also increasing prevalence of having cardiometabolic risk factors over time, especially in the overweight and pre-diabetes/type 2 diabetes.
Conclusion: We identified the changing prevalence and risk factors of MASLD in Taiwan which will further help making the national strategies in the prevention and managements of MASLD.

FRI-004

Association between metabolic syndrome and hepatocellular carcinoma in Mongolia: Prevalence and risk factors across different populations

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Background and aims: Metabolic Syndrome (MetS) is a cluster of risk factors increasing the likelihood of cardiovascular diseases and type 2 diabetes. Hepatocellular carcinoma (HCC), the most prevalent form of liver cancer, is a leading cause of cancer-related mortality in Mongolia, with viral hepatitis being a key factor. The high prevalence of both MetS and HCC in Mongolia represents a significant public health issue. This study aims to assess the prevalence of MetS in a high-risk HCC population in Mongolia and investigate the potential association between MetS and HCC.
Method: This analysis used data from 940 subjects enrolled in the DETECT-HCC study between September 15, 2023, and September 23, 2024. HCC diagnosis was confirmed by contrast-enhanced MRI (CE-MRI). MetS was assessed using the Asian-modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. Hepatitis infection status was evaluated using qHBsAg and qAnti-HCV tests on a HISCL5000 analyzer, while HBV-DNA and HCV-RNA loads were measured with Cepheid GeneXpert. Cirrhosis was assessed using Fibrocan 630 (Echosens) and CTP score. Statistical analysis was conducted using R software.
Results: The prevalence of MetS in the HCC group (n = 366) was 28.7%, compared to 20.4% in the non-HCC group (n = 574), with a significant association between MetS and cohort status ($X^2 = 3.93$, $p = 0.047$). In the HCC cohort, 210 were male (mean age 59.6) and 156 were female (mean age 64.47). Among them, 174 had HBV/HDV co-infection, 25 had HBV mono-infection, 62 had active HCV infection, 66 had undetected HCV, and 35 had non-viral hepatitis. The highest prevalence of MetS was observed in the non-viral hepatitis group (48.6%), followed by the undetected HCV group (39.4%), detected HCV group (35.4%), mono-HBV group (24%), and HBV/HDV superinfection group (18.9%). After excluding subjects with alcohol abuse and liver cirrhosis, the adjusted prevalence rates were 25.7%, 29.2%, 30.6%, 15.5%, and 12.5%, respectively. Additionally, subjects from Ulaanbaatar's Ger District and Nomads showed higher glucose levels (8.5 mmol/L and 8.7 mmol/L, respectively) compared to those living in apartments (6.8 mmol/L). This trend was consistent across all five MetS risk factors, suggesting a higher overall risk for MetS in these groups.
Conclusion: This study highlights a significant association between MetS and HCC, with a higher prevalence of MetS in the HCC cohort. These findings suggest that MetS may contribute to the risk of HCC, underscoring the need for targeted prevention strategies. Additionally, subjects in Ulaanbaatar's Ger District and Nomads appear to face a higher risk for MetS, likely due to lifestyle, socioeconomic, and environmental factors. Further research is needed to explore the mechanisms linking MetS and HCC and to refine prevention strategies.

FRI-005

Metabolic dysfunction-associated steatotic liver disease as the leading cause of hepatocellular carcinoma in mexican cirrhotic patients: a perspective consistent with trends observed in europe

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Background and aims: Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related mortality, often linked to chronic liver diseases such as hepatitis B (HBV) and C (HCV) infections, alcohol-related liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD). Although cirrhosis is a major precursor of HCC, it can also develop in non-cirrhotic livers, particularly in MASLD and HBV cases. The increasing prevalence of obesity and metabolic disorders has changed the etiology of HCC, especially in Western countries. In Mexico, HCC reflects a complex mix of traditional and emerging risk factors, including viral hepatitis and MASLD. This study evaluates the prevalence and etiologies of HCC, focusing on key risk factors in Mexican patients with liver cirrhosis.
Method: A multicenter retrospective study was conducted across 13 health centers in Mexico from 2018 to June 2024. Clinical records of adults with liver cirrhosis were reviewed to identify cases of HCC, assessing prevalence, etiologies, and clinical characteristics. Sociodemographic, clinical, imaging, and biochemical data were analyzed, with a focus on regional variations.

Results: The study included a total of 2,182 patients diagnosed with liver cirrhosis, with a mean age of 61 ± 12 years. Of these, 53.8% (n = 1,175) were female and 46.1% (n = 1,007) were male. Of the 2,182 patients, 8.8% (n = 194) developed HCC. The prevalence of HCC was higher in women (55.1%, n = 107) and in older age groups. Patients aged 60 years or older accounted for 78.3% (n = 152) of all HCC cases. Among women, the majority of HCC cases were observed between the ages of 70 and 79 years (39.2%, n = 42), while in men, the peak prevalence was observed between the ages of 60 and 69 years (39%, n = 34). Geographic analysis revealed notable variations in the prevalence of HCC in the different regions of Mexico. Central region showed the highest prevalence of HCC (10.4%), while southern region had a prevalence of 4.1%, and southern region had the lowest prevalence at 3.8% ($p < 0.001$). The overall distribution of HCC etiologies showed that the main cause was MASLD, with 39.1% (n = 76) of cases, followed by HCV infection, with 33% (n = 64), and ALD, with 18.6% (n = 36), while less common etiologies such as autoimmune hepatitis, primary biliary cholangitis, and VHB together accounted for 7.2% (n = 14) of cases.
Conclusion: This study highlights the significant burden of HCC in patients with liver cirrhosis in Mexico, with notable demographic and regional variations. The findings demonstrate a higher prevalence of HCC in women and older age groups. These results are consistent with changes observed worldwide, especially in European countries, where MASLD has become a predominant cause of HCC, in particular among women. The parallels between Mexico and Europe emphasize the growing impact of metabolic disorders in HCC and underscore the importance of global strategies to address this changing etiological landscape.

FRI-006

Reference blood-based biomarkers SteatoTest-2 (ST2) and NashTest-2 (NT2) permit assessment of the prevalence of steatosis and MASH in large general population of UK-Biobank (UKB), stratified by cardiometabolic risk factors (CRF) and alcohol consumption (AC)

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Background and aims: There are no widely validated biomarkers of liver steatosis and MASH inflammation available in the UKB. MRI-PDFF is only available in a 10-percent-subset. Available UKB blood biomarkers do not allow direct calculation of ST2 nor NT2. The aim was to construct proxies with very high correlation to allow assessment of the stratified prevalence of these diseases in general population.
Method: Using the princeps cohort with CRN-7-tier biopsies (n = 1,081), ST2-proxy and NT2-proxy were built using the markers available in the UKB (Bilirubin, GGT, ALT, AST, Apo-A1, Triglycerides (TG), Total-Cholesterol(TC)), both adjusted by age and gender. Performance was estimated with Pearson-correlation and difference of AUCs. ST2-proxy and NT2-proxy were then applied into the UKB (n = 343,064), pre-determined cut-offs were applied to estimate steatosis (S0: <5%, S1: 5–33%, S2S3: >33%) and MASH inflammation; and prevalence were assessed stratified by CRF (BMI, Diabetes, Hypertension, high TG and low HDL) and AC.
Results: NT2-proxy and ST2-proxy had high correlations ($R^2 = 0.99$ and 0.91, respectively) in the princeps cohort and AUCs were not different (0.79[%95CI = 0.77–0.82] vs. 0.79[0.77–0.82] p-difference = 0.66 and 0.76[0.70–0.81] vs. 0.77[0.72–0.83] p-difference = 0.24, respectively). When applied in the UKB, significant steatosis prevalence was 14.1% overall, from 0.3–0.5% for subjects with 0 CRF, 1.6–1.8% for 1 CRF, 6.4–7.9% for 2 CRF, 18.4–25.3% for 3 CRF and 47.2–57.3% for 4–5 CRF. MASH prevalence was 24% overall, from 1.7–2% for subjects with 0 CRF, 5.8–6.5% for 1 CRF, 15.5–20.9% for 2 CRF, 32.3–48% for 3 CRF and 56.7–72.7% for 4–5 CRF. For both, the more severe AC had the highest prevalence.
Conclusion: Presence of validated biomarkers ST2 and NT2 in the UKB permit assessment of steatosis and MASH in large population like UKB, allowing other applications.

FRI-007

An algorithm based on the liver risk score to identify subjects at-risk for advanced liver disease in the general population

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Background and aims: Screening for advanced hepatic fibrosis in the general population may help to identify patients at risk for negative hepatic outcomes. However, the ideal non-invasive marker in terms of accessibility and accuracy is yet to be developed. Current guidelines (EASL 2021) recommend using the low exclusion threshold of the FIB-4 score (< 1.3) as a primary screening tool in patients at risk for metabolic-dysfunction associated steatotic liver disease (MASLD), but the low specificity may result in a large number of potentially false-positive results requiring specialist referral and costs. Recently, the liver risk score (LRS) has been suggested to more accurately identify patients at-risk. The aim of this study was to evaluate the prevalence of individuals at-risk for advanced liver fibrosis in the general population of the Paris region according to FIB-4 and LRS.
Method: "Cerbafib" was a prospective cohort derived from a collaboration with laboratories throughout the Paris region to evaluate the prevalence of advanced liver disease in the general population.
Results: Between January and April 2023, 179 865 patients were included in the cohort. The mean age was 52 years and 45% were men. FIB-4 identified 55 376 (31%) patients requiring specialist referral (> = 1.3) and 4 002 patients (2.2%) with suspected advanced fibrosis. LRS identified 38 175 (21%) patients with estimated liver stiffness > = 6 kPa, 1 933 patients (1%) > = 10 kPa and 35 (0.02%) patients > = 15 kPa. There was a significant but poor correlation between the two tests ($r = 0.45$, $p < 0.01$). Among patients with a FIB-4 score above 1.3, 61% have an LRS corresponding to a minimal risk of liver fibrosis. In return, 24% of the minimal risk patients according to LRS have a FIB-4 score above 1.3.
Conclusion: The Liver Risk Score is a practical tool to identify a population in need of further hepatologic evaluation. Its use as a mass screening test in the general population at risk for MASLD may help to more accurately identify those at risk for advanced liver disease. The well-established FIB-4 test only partially identifies this subgroup and may generate more false positives and increase the need for confirmatory resources and costs. We suggest an adapted new screening algorithm using the LRS.

FRI-008

Prevalence of steatotic liver disease and steatohepatitis in a population of healthy workers

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Background and aims: Steatotic Liver Disease (SLD) may silently evolve into Steatohepatitis (SH). In clinical practice, elevation of liver enzymes (LE) is used as a surrogate marker of liver inflammation.

Screening of liver disease is gaining attention and novel strategies need to be found. We aimed to study the prevalence and associated factors of SLD and SH in a population of healthy workers.
Method: 780 healthy workers were prospectively enrolled during yearly health checkups (from January to September 2024) at Bridgestone factory (Bilbao, Spain). Ultrasound, anthropometric and biochemical data were collected. 335 patients with all available data were further analysed. Patients were divided into the following groups: no steatosis and normal LE (Healthy), steatosis and normal LE (SLD), steatosis and elevated LE (SH), no steatosis and elevated LE (Hepatitis).
Results: The Healthy Group accounted for half of the patients (57%), while the remaining patients were divided into the other three groups (SLD 20%; SH 11%; Hepatitis 12%). The analysis of variance showed differences in age, BMI, HDL, triglycerides, glucose and haemoglobin. At post-hoc analysis only BMI increased significantly between Healthy (25.10 [23.15, 27.16]), SLD (26.87 [24.97, 30.05]) and SH Groups (30.38 [27.59, 33.18]). Multivariate logistic regression for risk factors for SLD showed: BMI (aOR 1.21 [1.11, 1.31], $p < 0.001$), and hypertension (aOR 2.19 [1.10, 4.37], $p = 0.026$). The only significant risk factor for SH after adjustment was BMI (aOR 1.31 [1.18, 1.48], $p < 0.001$).
Conclusion: The inclusion of liver ultrasound and transaminases in healthy workers' checkups can be effective in identifying patients with metabolic liver disease.

FRI-009

External validation of Dallas steatosis index (DSI) in the diagnosis of steatotic liver disease (SLD) in thai population

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Background and aims: Steatotic liver disease (SLD) is a global health concern, associated with long-term liver and extrahepatic complications. The Fatty Liver Index (FLI) is the most widely accepted scoring system for identifying patients with SLD at the population level. However, FLI includes waist circumference and gamma-glutamyl transferase (GGT), which are not routinely measured in clinical practice. The Dallas Steatosis Index (DSI), which incorporates more routinely available variables, has recently been developed to detect SLD in the U.S. population. This study aims to validate the DSI for diagnosing SLD in Thai population.
Method: A cross-sectional study was conducted from 2019 to 2023 at a tertiary care hospital in Southern Thailand. The study included individuals aged ≥18 years old who participated in health check-up programs that involved abdominal ultrasound (USG) and blood tests. SLD was diagnosed when liver steatosis was identified on the USG report. The exclusion criteria were those with positive HBsAg and/or HCV Ab, missing data on variables for calculating DSI (Age, Sex, ALT, Triglycerides [TG], BMI, fasting blood sugar [FBS], Diabetes, and Hypertension status). For ethnicity, which is one of the variables in DSI, all participants were categorized as Asian. The performance of DSI in diagnosing SLD was evaluated using areas under the receiver operating characteristics curve (AUROC), and sensitivity and specificity at the given cutoff were evaluated.
Results: A total of 5987 individuals were eligible and included in the study. The prevalence of SLD diagnosed by ultrasound was 45.2% in the entire cohort. As expected, individuals with SLD were more likely to be older, predominantly male, and had higher waist circumference, BMI, TG, FBS, LDL, AST, ALT, and platelet levels compared to those without SLD. Additionally, they had a significantly higher proportion of concomitant diabetes, hypertension, dyslipidemia, and cardiovascular disease. DSI was calculated using the published formula (https://dsi.wustl.edu/) and presented as predictive probabilities. DSI showed a very good performance in diagnosing SLD with an AUROC of 0.830 (95%CI: 0.820–0.841). At the given cutoff of 0.2 and 0.5 as the low and high cutoffs for the diagnosis of SLD, DSI <0.2 showed a sensitivity of 86% and NPV of 84.4% for ruling out SLD, and at the DSI >0.5, the specificity and PPV were 92.5% and 83.97% to ascertain SLD status, respectively.
Conclusion: This is the first external validation of DSI in Asian population. The DSI demonstrated satisfactory performance in the diagnosis of SLD with an AUROC of 0.83 and may be considered as an alternative to FLI for the diagnosis of SLD at the population level particularly in settings where ultrasonography, transient elastography, or other imaging modalities are not feasible. Nonetheless, further studies comparing the diagnostic accuracy of DSI and FLI are still needed.

FRI-010

Economic evaluation of biomarker-base surveillance for hepatocellular carcinoma in thai patients with compensated liver cirrhosis

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Background and aims: Hepatocellular carcinoma (HCC) is the leading cause of cancer-related death in Thailand. However, most Thai patients at high risk of HCC lack access to routine surveillance programs. This study used ultrasound- or biomarker-based screening approaches to assess the cost-utility analysis of routine HCC surveillance in patients with compensated liver cirrhosis (CLC).
Method: The model utilized a Markov-style microsimulation framework to simulate outcomes from alternative HCC surveillance methods for Thai patients. The model was designed to represent Thai patients and healthcare as accurately as possible, and novel Thai patient data was used to estimate treatment and survival associated with screening. Outcomes included diagnostic performance, total costs, and overall health expressed as quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) was assessed according to the Thai willingness-to-pay threshold (฿160,000 = USD 4,660).
Results: Results suggest that routine HCC surveillance is likely cost-effective in Thai patients with CLC. Among the biomarker-based approaches, GAAD score, which combined gender, age, alpha-fetoprotein (AFP), and des-gamma carboxyprothrombin (DCP), was the most cost-effective due to its high detection of HCC while resulting in relatively few false positive diagnoses. Compared to no routine surveillance, GAAD surveillance was cost-effective (ICER: ฿154,372). Compared to ultrasound plus AFP – the recommended standard of care – GAAD was dominant, resulting in better overall health at a lower cost.
Conclusion: Bi-annual routine HCC surveillance is cost-effective for the Thai healthcare system when used for patients with CLC. Among biomarker-based approaches, GAAD appears to be the most cost-effective and could maximize the benefits of HCC surveillance in high-risk patients.

FRI-011

What is known about the relationship between food insecurity and metabolic dysfunction-associated steatotic liver disease? A systematic review

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) has risen in prevalence in parallel with obesity over the past decade reaching epidemic proportions. With limited pharmacological options, a prudent diet is the first line of treatment to mitigate an unfavourable prognosis leading potentially to cirrhosis and irreparable liver damage. Little is known on the relationship between limited or uncertain access to nutritious food as is experienced during food insecurity and liver health. This review aimed to summarise and synthesise quantitative data on the relationship between food insecurity and MASLD.
Method: A systematic review was conducted across four databases: MEDLINE (Ovid platform), Embase, Web of Science and CINAHL, up to 9th April 2024. Any design of observational study whose participants were adults or children over 2 years of age, with food security status assessed via a validated tool, and MASLD defined by clinical diagnosis or estimated by robust diagnostic criteria were included. All studies were quality assessed using Joanna Briggs Institute tools. Narrative synthesis was conducted as the clinical heterogeneity of the studies precluded meta-analysis.
Results: Thirteen full text studies and nine abstracts were included. All data on food insecurity and MASLD were cross-sectional regardless of study design. Seven of the ten studies with relevant data reported that food insecure individuals had an increased odds of MASLD compared to those who were food secure, reported increases ranged from 38% to 237% ($p < 0.05$). Studies reported a prevalence of food insecurity in those with MASLD ranging from 9%–57%. In all but one small study this was consistently higher than comparable reported levels of food insecurity amongst the general population. Prevalence of MASLD amongst food insecure participants varied from 17%–54%, with higher rates seen in studies comprised of Hispanic participants.
Conclusion: These results indicate that public health programmes to facilitate food and nutrition security in communities in need, coupled with screening for food insecurity in clinical settings are critical to ensure health equity and prevent unnecessary disease progression in MASLD patients. The review highlights the paucity of data examining food insecurity and its relationship with hepatic health in the context of cardiometabolic disease, indicating that further cross-speciality prospective longitudinal research is warranted in this area.

FRI-012

Unveiling the burden of cirrhosis among Ontario, Canada's refugee population

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Background and aims: Liver disease is on the rise, contributing to high mortality and healthcare costs. Refugees face additional barriers to healthcare, leading to delayed diagnoses of conditions like cirrhosis, which can arise from chronic diseases like HBV, HCV, and ALD. Despite this, little is known about cirrhosis in refugee populations. This study investigates the incidence and etiology of cirrhosis among refugees in Ontario compared to other immigrant populations. Previous research has identified the growing burden of cirrhosis worldwide, and a recent paper by our research group has defined the incidence of cirrhosis among recent immigrants and refugees to Ontario, however, this project is the first to specifically identify the unique health burdens of refugee populations. Understanding these factors can help inform targeted screening, prevention, and treatment efforts, ultimately reducing the impact on the healthcare system and improving outcomes for vulnerable populations.
Method: This population-based cohort study made use of routinely collected healthcare data housed in various ICES databases. Using a validated algorithm, individuals with cirrhosis were identified, stratified by etiology, and linked to other datasets using unique encoded identifiers. These data were separated by immigration status to compare recent immigrants and refugees to one another. Frequencies and proportions were used to describe categorical variables, and medians and IQRs were used to describe continuous variables. Rate ratios were calculated using a Poisson regression, at a significance of $p < 0.05$.
Results: From 2000 to 2017, 22,469 immigrants with incident cirrhosis were identified (4,403 refugees, 18,066 non-refugee immigrants). Within the refugee population, 35% were female with a median age at cirrhosis diagnosis of 49 years (IQR 40–58), and 73% lived in neighborhoods of the lowest/second lowest income quintiles. Within the non-refugee immigrants, 43% were female, with a median age of diagnosis of 50 years old (IQR 40–63), and 56% live in neighborhoods of the lowest/second lowest income quintiles. Incidence rates of cirrhosis increased over time, both between the two groups (RR 1.342 (CI 1.298–1.387); $p < 0.001$) and also when examining year over year increase within each group (RR 1.034 (CI 1.031–1.037, non-immigrant refugees); RR 1.040 (CI 1.034–1.046, refugees); $p < 0.001$). Non-refugee immigrants exhibited a lower incidence rate of cirrhosis. MASLD-cirrhosis had the highest increase in incidence rate over time.
Conclusion: This study is the first to examine cirrhosis among refugees in Ontario, revealing a 1.37-fold higher rate among refugees compared to immigrants, along with an overall increase in the incidence of cirrhosis for both populations. Continued research will refine our understanding of cirrhosis epidemiology and contribute to improved public health outcomes.

FRI-013

Age-related trends in FIB-4 scores among MASLD risk groups: insights from primary care data

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Background and aims: The Fibrosis-4 index (FIB-4) is a valuable screening tool for fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD). Guidelines emphasize its use in identifying high-risk MASLD patients who may benefit from treatment. Given the prevalence of diabetes, dyslipidemia, or hypertension—common MASLD risk factors—among middle-aged and elderly individuals visiting family doctors, we examined the distribution and characteristics of FIB-4 among this demographic.
Method: We analyzed FIB-4 score from clinical tests ordered by family doctors at the Kumamoto City Medical Association Inspection Center from August to October 2024. Key variables—FIB-4 score, aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, and platelet counts—were stratified by age group. High-risk cases of advanced fibrosis were defined as FIB-4 > 2.67, and the relationship between high-risk judgement and the components of the FIB-4 formula was analyzed.
Results: Among 63,728 cases, the largest age group was the 70 s (21.0%), with 57.3% aged 60 or older. FIB-4 scores increased with age and platelet counts decreased ($P < 0.05$). ALT levels decreased after the 40 s ($P < 0.05$). High-risk judged patients accounted for 12.5%,

with age-specific rates of 0.6% (40 s), 1.6% (50 s), 4.4% (60 s), 14.2% (70 s), 34.6% (80 s), and 54.0% (90+). For those in their 80 s, the rates of high-risk judgment, platelet count ≤150,000, and ALT > 30 were 14.6% and 6.9%, respectively. ROC analysis showed platelet count had the highest AUROC for identifying high-risk cases across all ages (0.906), and the AUROC for age decreased in the elderly (all ages: 0.870, 80 years and over: 0.631). For 80 and older, AUROC was highest for 1/platelet count (0.888) and AST/$\sqrt{}$ALT (0.785).
Conclusion: The age group that most frequently undergoes blood tests at their family doctor corresponds to the peak age of first occurrence of metabolism-associated liver cancer in our data, suggesting that screening methods for liver fibrosis at family doctors is an important issue. The significant rise in high-risk judgment in patients aged 80+ suggests aging and declining platelet counts and ALT levels may increase false positives. Of the factors involved in calculating FIB-4, platelet count had the greatest impact on screening for cases suspected of having severe fibrosis in all age groups. When using FIB-4 for screening, age-specific adjustments, including the incorporation of platelet count, may reduce over-diagnosis in elderly patients.

FRI-014
Impact of COVID-19 pandemic on racial/ethnic disparities in liver transplant waitlist outcomes among U.S. adults with end-stage liver disease
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Background and aims: In the U.S., end-stage liver disease (ESLD) disproportionately affects vulnerable populations, including racial/ethnic minorities. Existing racial/ethnic disparities in access to liver transplantation (LT) may have been exacerbated by the COVID-19 pandemic. Whether these pandemic-related disparities persist 4 years following the COVID-19 pandemic is not clear. We aim to evaluate racial/ethnic disparities in receipt of LT and LT waitlist mortality among U.S. adults with ESLD before, during, and following onset of the COVID-19 pandemic.
Method: Adults (≥18 years old) with ESLD without hepatocellular carcinoma who were listed for LT from 3/1/2018–2/29/2024 were evaluated using the United Network for Organ Sharing registry data. Probabilities of receiving LT and waitlist removal (death or too sick) within 1 year of listing were evaluated using competing-risks adjusted Cox proportional hazards models across three periods: Era 1 (3/1/2018–2/29/2020), Era 2 (3/1/2020–2/28/2022), and Era 3 (3/1/2022–2/29/2024).
Results: We identified 49,949 adults with ESLD awaiting LT from 2018–2024. During Era 1, significantly lower probability of LT within 1 year was observed among Hispanics (vs. non-Hispanic whites [NHW]) (55% vs. 59%; aHR 0.88, 95% CI 0.79–0.98). The disparity in LT receipt among Hispanics (vs. NHW) worsened in Era 2 (54% vs. 63%; aHR 0.77, 95% CI 0.70–0.85). While this inequity improved in Era 3, lower probability of LT among Hispanics (vs. NHW) remained (65% vs. 69%; aHR 0.90, 95% CI 0.82–0.97). Although Hispanics (vs. NHW) were more likely to be removed from the LT waitlist due to death or sickness within 1 year, the risk of removal did not significantly change during the pandemic (Era 1: aHR 1.30, 95% CI 1.02–1.65; Era 2: aHR 1.25, 95% CI 1.03–1.52). While there was no significant difference in LT waitlist removal among Asians (vs. NHW) in Era 1 or 2, Asians were significantly more likely to be removed from the waitlist in Era 3 (aHR 1.53, 95% CI 1.04–2.25, all $p < 0.05$).
Conclusion: Racial/ethnic disparities in LT waitlist outcomes were exacerbated during the COVID-19 pandemic, especially for Hispanics who had greater risk of waitlist removal and lower probability of LT. Asians also had disproportionately greater risk of waitlist removal compared to NHW. Better understanding and addressing modifiable barriers to equitable LT care is needed to address the persisting disparities that remain following the COVID-19 pandemic.

FRI-019
Patient safety, cross-sectoral quality of care, cost efficiency, and interprofessional competence: a comparison of the interprofessional training wards A-STAR with conventional hepatology-focused wards at Regensburg university hospital
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Background and aims: Effective interprofessional collaboration is crucial in modern medical practice. Since the establishment of interprofessional training wards (IPSTAs) in 1996, these wards have been designed to improve teamwork and communication across different professional boundaries. This study conducted at Regensburg University Hospital examines and compares patient outcomes, cost-effectiveness, quality of cross-sectoral care, and satisfaction levels among patients, families, and caregivers between the interprofessional training ward A-STAR in Regensburg and traditional hospital wards.
Method: The study was conducted from October 2019 to October 2024. Anonymized and standardized questionnaires were utilized to evaluate patient outcomes, cost efficiency, and satisfaction. This included the Collaboration and Satisfaction About Care Decisions (CSACD) and the Family Satisfaction in the Intensive Care Unit (FS-ICU) assessments. Both general practitioners and patients were surveyed regarding the quality of trans-sectoral transfers.
Results: The analysis included data from 1,514 patients treated on the A-STAR ward and 5,847 patients from conventional wards. The clinical outcomes, such as discharges against medical advice, complication-related readmissions, and mortality rates, showed no significant differences between the two groups. However, the A-STAR ward demonstrated greater cost efficiency, characterized by lower material costs and higher DRG revenue per case. Patient, family, and caregiver satisfaction was notably high in the interprofessional wards. Patients in the A-STAR ward required significantly fewer medication adjustments by follow-up physicians (0% compared to 12.63%; $p = 0.035$). They also reported more frequent health improvements and experienced significantly fewer new symptoms after discharge (3.03% compared to 22.45%; $p = 0.011$).
Conclusion: IPSTAs, such as A-STAR, provide patient care that is comparable to conventional wards while improving the training quality for healthcare professionals. The findings indicate that these wards are cost-effective and have a positive impact on patient and family satisfaction, as well as on the overall quality of care across different sectors. Incorporating these training wards into medical education could enhance patient safety and promote stronger collaboration among healthcare teams.

FRI-021

Differential liver-related mortality among native hawaiian/pacific islander (NHPI) and asian subpopulations: a national cohort study

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Background and aims: Globally, over 30 million Asians live in North America and Europe, encompassing over 20 origin groups. Asians are often aggregated in health surveillance registries, which can mask health differences among subpopulations. In the United States (US), a recent modification to race categories on death certificates enables the disaggregation of Native Hawaiian/Pacific Islanders (NHPIs) from Asians. This study compares liver-related mortality between NHPI and Asian adults.
Method: We analysed mortality data among adults aged ≥25 years from the US National Vital Statistics System between 2018–2022. Following established definitions, NHPI was defined as individuals with NHPI listed as their race on death certificates, whether as a single race or in combination with other race groups. Similarly, Asians included individuals with single or multi-race listings. Validated international classification of diseases 10th revision (ICD-10) codes for the underlying cause of death were used to categorize deaths as attributable to liver disease. Age-standardized mortality rates per 100,000 and rate ratios were used to compare NHPI and Asian adults.
Results: From 2018 to 2022, there were 699 and 8,592 liver-related deaths among NHPI and Asian adults, respectively. A higher proportion of liver-related deaths occurred among NHPI adults under the age of 65 compared to Asian adults (NHPI: 62.9% vs. Asian: 46.0%). The liver disease-related age-standardized mortality rate for NHPI adults was 15.8 (95% CI: 14.6–17.0) deaths per 100,000 adults, which was 1.4 (95% CI: 1.4–1.5) times higher than that of Asian adults (11.7 deaths per 100,000; 95% CI: 11.4–11.9). The liver disease-related age-standardized mortality rate for Black and White adults was 18.3 (95% CI: 18.1–18.6) and 25.5 (95% CI: 25.4–25.6) deaths per 100,000 adults, respectively. In terms of etiology, alcohol-related liver disease had an age-standardized mortality rate of 5.0 (95% CI: 4.4–5.7) deaths per 100,000 adults for NHPI adults compared to 2.9 (95% CI: 2.7–3.0) deaths per 100,000 adults for Asian adults, and non-alcohol-related liver disease had an age-standardized mortality rate of 10.7 (95% CI: 9.7–11.7) deaths per 100,000 adults for NHPI adults compared to 8.8 (95% CI: 8.6–9.0) deaths per 100,000 adults for Asian adults.
Conclusion: NHPIs have higher mortality rates from liver diseases compared to Asians, especially among younger adults and for alcohol-related liver disease, a disparity previously masked by aggregation of NHPI within Asian populations for mortality surveillance. This national study underscores the importance of carefully considering how Asian populations are categorized in national health surveillance registries to better inform targeted global public health strategies across the world.

FRI-022

Ultra-processed foods significantly increase liver and metabolic injury among younger adults, lessons from the liver screening program SIRIUS

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Background and aims: Ultra-processed foods (UPF) have been linked to a plethora of diseases, including metabolic syndrome and metabolic dysfunction-associated steatotic liver disease. However, the link may be biased since metabolic burden increases with age while UPF consumption tends to decrease. We explored data from the liver screening program SIRIUS for age-dependent links between UPFs, liver injury and its excess burden.
Method: The point-of-care SIRIUS project operated in Slovakia since 2022 and visited more than 30 sites. Free-of-charge screening for liver disease is offered to local community-dwelling adults. Inclusion criteria were age >18 y, excluded were cases with a history of chronic liver disease or incapacitating severe systemic diseases. The screening procedure included questionnaires on medical history, AUDIT-C, quality of life, basic anthropometric measurements, blood drop analysis for aminotransferases and blood lipids, and liver stiffness and CAP (Fibroscan by Echosense). The consumption of UPFs was evaluated using the 24-hour dietary recall questionnaire.
Results: 4319 cases were included in the analysis with a median age of 53.2, 40.8% of males, 75.3% with abdominal obesity, 6.6% with a history of diabetes, 9.5% with ALT > 1.5 times the upper limit of normal, 47.7 and 47.3% with liver steatosis based on FLI > 60 or CAP > 248, and 5.2% of liver stiffness >10 kPa. The median quantity of UPFs consumed was 2 (range 0–20). In participants younger than 46 years comprising the lower three age deciles, individuals consuming UPF quantities in the 5th quintile (median 6.2 items) had significantly ($p < 0.05$) higher fatty liver index (+27.7%), CAP value (+5,3%), ALT (+41.4%), and waist circumference (+4.8%) compared to the 1st quintile (median 0.7 items). The difference has not been observed for liver stiffness and in older participants.
Conclusion: Evidence from the liver screening program SIRIUS shows that younger individuals are more susceptible to the adverse effects of ultra-processed foods having a 5 to 40% excess burden on the liver and metabolic health.

FRI-023

Prevalence of MASLD and its association with the consumption of sugar sweetened beverages among a non-communicable disease cohort in the rural district of Iringa, Tanzania

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Background and aims: The global health community has increasingly shifted its focus toward non-communicable diseases (NCDs), recognizing them as a critical public health emergency, particularly pronounced in low and lower middle-income countries. The prevalence, associated factors, and consequences of MASLD in the African continent, particularly in Sub-Saharan Africa (SSA), remain poorly understood. Indeed, no SSA studies were included in the latest major literature review and meta-analysis on the global epidemiology of MASLD. Tanzania, like many other SSA countries, is undergoing a demographic and epidemiological transition, leading to a marked increase in the burden of NCDs. The primary aim of this study was to estimate the prevalence of MASLD among an NCDs population in rural Tanzania. The secondary objective was to investigate whether the consumption of sugar sweetened beverages (SSB) is associated with MASLD.
Method: This study entailed a retrospective analysis of a prospectively collected cohort of consecutive patients attending the NCDs

outpatient clinic of Tosamaganga Hospital, from August 2022 to March 2023. Detailed sociodemographic, clinical, laboratory, and abdominal ultrasound data were collected for all participants. The Beverage Intake Questionnaire (BEVQ-15) was administered to evaluate their everyday drinking behaviors; and for each item, the average daily intake in fluid ounces (fl-oz), and calories (kcal) were calculated.

Results: Of 183 patients enrolled in the cohort, 128/183 (70%) were female. The mean age was 58 ± 13.7 years and mean BMI was 28 ± 6.67 Kg/m^2. Hypertension affected 141 individuals (77.0%), diabetes affected 77 (42.1%), and both conditions co-occurred in 35 patients (19.1%). SLD was found in 88/183 (48%) patients; with 39/88 (44.3%) of moderate or severe steatosis. MASLD was identified in all steatotic patients. Overall, on average the participants drank a mean of 12.6 fl-oz of SSB (throght sodas). MASLD patients drank an average of 22.4 fl-oz of SSB per day. Multivariable analysis revealed that BMI and daily SSB consumption (fl-oz) exhibited significant associations with MASLD, with respective OR of 1.16 (95% CI: 1.06–1.28, p = 0.002) and 1.19 (95% CI: 1.12–1.27, p < 0.001).

Conclusion: This study unveils a considerable prevalence of MASLD among the rural Tanzanian NCDs population, affecting nearly half (48%) of all patients studied. Timely identification of MASLD, facilitated by straightforward diagnostic means, holds pivotal importance for patient management and the dissemination of vital lifestyle modification guidance. Furthermore, our study, one of the pioneering efforts to demonstrate a significant association between SSB consumption and MASLD in an African context, underscores the imperative to heighten awareness regarding the risks posed by SSB consumption among NCDs patients and potentially the wider population.

FRI-024

Living with liver disease: patient and carer experiences in the United Kingdom

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Background and aims: To understand and assess differences in patient experience and satisfaction with liver care, insights were gathered from patients across the UK. These insights provide a foundation for improving patient outcomes and standardising care practices across the UK and provide a framework for similar projects in other countries.

Method: An online survey was distributed through multiple channels, including the British Liver Trust's newsletter, support networks and social media. Clinicians assisted shared the survey with patients at appointments or through email. The survey was conducted twice, in 2019 and 2024. Survey respondents' satisfaction with their care was graded on a scale from 0 to 100 where 100 indicated complete satisfaction. Data were analysed in R.

Results: 1465 responses were received in 2019 and 2425 responses in 2024. People with liver disease made up the majority of responses (3209, 82.5%), and 645 respondents described themselves as carers or family members of people with liver disease. Most people experienced symptoms prior to their diagnosis of liver disease. The most common symptom was abdominal pain or swelling (59%). Itching was common (24%) especially amongst people with PBC (49%). Approximately one third felt their disease was diagnosed at an early stage (34%), and another third felt their disease was diagnosed at a late stage (30%). Late diagnoses were most common in people with cholangiocarcinoma (50%), hepatitis C (43%) and ArLD (37%). Respondents' experience of the initial identification of possible liver disease was mixed: 48% were referred or admitted to hospital and 22% were offered further testing, but 24% felt their condition was dismissed. Nearly one in five respondents waited for more than 12 months for specialist referral, and 10% reported not being referred at all. A majority of respondents felt their condition had been explained properly (43%) but the information given was usually inadequate: 53% were given too little information and 22% were given no information at all. Most people (91%) sought further information mainly from online sources. In the 2024 survey 22.5% of respondents felt that there was stigma associated with a diagnosis of liver disease. Over the two iterations of the survey in 2019 and 2024, satisfaction with care fell from a median of 63 to 52 out of 100. In addition, there were small reductions in the number of people whose condition was diagnosed early (29% to 26%) and an increase in those diagnosed late (21% to 24%).

Conclusion: Timely diagnosis, referral and providing patients with a good understanding of their disease are all critical for effective management. However, many patients are experiencing delays and are not receiving the information or support that they require once diagnosed. The perception of the quality of care received has fallen over the last five years. The voice of patients and carers is essential to improve liver services.

FRI-025

Readily available indices of liver fibrosis and insulin resistance associated with cancer and cardiovascular disease outcomes

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Background and aims: Liver fibrosis and insulin resistance are known drivers of cancer and cardiovascular disease (CVD) outcomes through metabolic dysfunction and inflammation. However, gold standard measurements, e.g., imaging and hyperinsulinemic-euglycemic clamp test, are often costly and impractical in large population-based studies or resource-constrained settings, making surrogate markers appealing alternatives. We aimed to evaluate the prospective associations of commonly used liver fibrosis (Fibrosis-4, FIB-4) and insulin resistance measurement (triglyceride glucose index, TyG) with cancer and CVD risk.

Method: We developed a prospective cohort based on data from the Harvard Mass General Brigham Biobank. We excluded those with cancer or CVD diagnosis at baseline and without biomarker data and integrated data on demographics and lifestyles (analysis sample: N = 66,015 for cancer and 62,747 for CVD). FIB-4 was derived using age, aspartate aminotransferase, alanine aminotransferase, and platelet count, with a cutoff of 1.3. TyG was derived using fasting blood glucose and triglyceride, with a cutoff of 8.8. Health outcomes were collected via electric medical records. We used Cox models to estimate hazard ratios (HRs) [95% confidence intervals (CIs)] for disease outcomes adjusting for potential confounding factors including demographics and lifestyles factors.

Results: With a median follow-up of 14.6 y for cancer and 6.5 y for CVD analyses, we identified 25,407 cancer and 46,488 CVD outcomes. A higher FIB-4 index was associated with elevated risk of digestive cancers (1.13 [1.04–1.22]), liver cancer (2.34 [1.94–2.82]), hepatocellular carcinoma (3.92 [3.10–4.95]), intrahepatic cholangiocarcinoma (1.64 [1.12–2.39]), leukemia (1.90 [1.67–2.17]), and non-Hodgkin lymphoma (1.37 [1.23–1.53]). TyG index was positively associated with pancreatic cancer (1.19 [1.02–1.39]), lung cancer (1.14 [1.04–1.24]), kidney cancer (1.35 [1.20–1.53]), bladder cancer (1.20 [1.07–1.36]), leukemia (1.22 [1.09–1.37]), and non-Hodgkin lymphoma (1.16 [1.06–1.27]). For CVD, higher FIB-4 index was associated with all types of CVD outcomes except for the hypertension with a HR ranged

from 1.11 [1.04–1.19] for ischemic stroke to 1.36 [1.24–1.49] for hemorrhagic stroke. Similarly, TyG index was associated with higher risk of all types of CVD outcomes with a HR ranged from 1.06 [1.02–1.10] for atrial fibrillation to 1.51 [1.43–1.59] for myocardial infarction. Those associations remained essentially unchanged in sensitivity analyses including excluding cases that occurred in the first two years of follow-up.
Conclusion: Liver fibrosis and insulin resistance, as assessed by readily available measures such as the FIB-4 and TyG index, are associated with elevated risks of specific cancers and most CVD outcomes. Further studies in other populations are needed to confirm our findings.

FRI-026
Metabolic dysfunction-associated steatohepatitis (MASH) prevalence in germany – results from a claims analysis
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Background and aims: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) that can lead to severe complications, including liver cirrhosis and hepatocellular carcinoma. These conditions impose a significant burden on both patients and healthcare systems. An estimated 4% of the German population is affected by MASH as of 2016 with an increasing global prevalence of the disease. Despite its rising prevalence, MASH often remains underdiagnosed due to patients being asymptomatic and the invasive nature of liver biopsy which is required for the confirmatory diagnosis. This results in a lack of appropriate follow-up and management for many patients. This study aimed to estimate the administrative incidence and prevalence of MASH in Germany, as well as to characterize these patients in terms of age and gender.
Method: A retrospective analysis was conducted using statutory health insurance claims data from the InGef research database. The study period spanned from January 1st, 2020, to December 31st, 2022. Prevalence and incidence figures were analyzed for the year 2022, identifying MASH patients by International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification (ICD-10-GM) diagnosis code K75.8 "Other specified inflammatory liver diseases [Nonalcoholic steatohepatitis NASH]." For inclusion, this diagnosis had to be recorded at least once in the inpatient sector (as primary or secondary discharge diagnosis) or at least twice in different quarters in the outpatient setting. Incident patients were defined as those with a diagnosis-free period of two years. Patients with evidence of alcohol use disorder or alcohol-associated liver disease were excluded.
Results: In 2022, 3,719 prevalent MASH patients in the InGef research database were identified, which corresponds to an administrative one-year-prevalence rate of 103.03 patients per 100,000 individuals, or 0.10%. The incidence rate was 15.71 patients per 100,000 individuals, equivalent to 0.02%. The average age of prevalent patients was 59.9 years, with 49.3% being female, while incident patients were slightly younger, averaging 55.7 years of age.
Conclusion: The results of this study suggest that significant underdiagnosis of MASH exists within the German healthcare system.

FRI-027
Metabolic dysfunction-associated steatohepatitis as a risk factor for hepatocellular carcinoma mortality
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Background and aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. Metabolic dysfunction-associated steatohepatitis (MASH), the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD), has become one of the fastest growing risk factors of HCC in the US. While studies suggest that individuals with MASLD are at a higher risk of HCC mortality, evidence regarding the relationship between MASH and HCC mortality death is limited. In this analysis, we aim to add to the existing evidence base by assessing the differential risk of HCC-related death among MASH and non-MASH patients within a competing events framework.
Method: A retrospective cohort study including HCC patients diagnosed from 2015–2020 was conducted using SEER-Medicare data. The 12-month period prior to HCC diagnosis date (index date) was used for sample selection, covariate measurement, and to determine MASH status using the K75.81 diagnosis code. Patients presenting with MASH and other liver diseases (e.g., viral hepatitis) were excluded due to an inability to identify proximate HCC cause. The study period consisted of the time from a patient's index date through first of the following events: HCC death, non-HCC death, a censoring event, or loss to follow-up. Cause-specific (CS) hazard models were fitted to evaluate the relationship between MASH, HCC death, and the competing risk of non-HCC death. Results from a separate Fine-Gray (FG) subdistribution hazard model were used to assess the extent to which differential non-HCC death rates may be driving these results. All models adjusted for year of HCC diagnosis, age at HCC diagnosis, sex, race/ethnicity, cirrhosis status, HCC stage at diagnosis, and Charlson Comorbidity Index. Model assumptions were tested via residual analysis.
Results: Of the 6,301 HCC patients included in the final sample, 313 (5%) had a prior MASH diagnosis and 5,988 (95%) did not. The majority of patients (68.1%) died within 5 years of their HCC diagnosis, with 76% of these deaths attributable to HCC. CS model results indicate that the risk of HCC mortality was 23% higher in MASH patients over the follow-up period (adjusted CS hazard ratio [HR]: 1.23, 95% confidence interval (CI): 1.05–1.44). The minimal difference between HRs from the CS model for HCC death and FG model (adjusted FG HR: 1.17, 95% CI: 1.00–1.38) indicate that the impact of non-HCC death as a competing event is small.
Conclusion: In this analysis, clinically rich SEER-Medicare data were combined with competing risks survival analysis to generate additional insight into the relationship between MASH and HCC death. Results suggesting that MASH patients are at a higher risk of HCC death highlight the importance of expanded surveillance and effective treatment in reducing HCC mortality in this population.

FRI-028
Shortfalls and obstacles in sexual function assessment by healthcare providers in patients with liver disease and liver transplantation
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Background and aims: Sexual function (SF) is an important patient reported outcome which is often neglected in patients with liver disease (LD) and liver transplantation (LT). The aim of this study was to identify potential barriers to SF assessment by healthcare providers (HCP).
Method: A 24-item online questionnaire was sent to all HCP who are members of the British Association for the Study of the Liver (BASL), United Kingdom.
Results: A total of 149 responses out of 1,100 potential participants were received (response rate 14%). One participant did not review patients with LD/LT and was excluded. There were more women (57%) compared to men (40%) and other gender groups (3%). The majority were consultant Hepatologists (31%), trainees (22%) and specialist nurses (30%). There were a similar proportion from transplant centres

(44%) and teaching hospitals (43%) with less from district general hospitals (13%). 58% had 1–10 years' experience in managing LD/LT patients and 36% had over 10 years' experience. Almost 40% of HCP were unsure what percentage of their LD patients were experiencing sexual dysfunction (SD) and this increased to 50% when asked about LT recipients. Over half of the HCP reported never or hardly ever discussing SD with their patients despite 61% disagreeing with the statement that "it was not their duty" to discuss SD and 43% felt that all specialists should manage SD. Obstacles for SF assessment included time constraints (65%), lack of knowledge about SD (60%) and having more important clinical priorities than SD (51%). Overall, 29% felt uncomfortable discussing SF with their patients and this increased to 51% when involving patients under 18 years of age. Over 90% disagreed or strongly disagreed that they had received sufficient training about managing SD and would prefer online resources (84%) or medical conferences (53%) to learn about SD. Only 1% reported lack of interest in learning about SD. On multivariate analysis, having knowledge about SF predicted the likelihood of asking about SF (CI −2.79–−0.68, p = 0.001) whereas gender, years of experience, place of work, training received and feeling uncomfortable was not statistically significant.

Conclusion: There is interest and a need to increase resources on SD in patients with LD/LT for HCP with a focus on LT recipients and younger patients. This will ultimately move towards improving quality of life measures in patients with LD/LT.

FRI-029

The global prevalence and mortality of metabolic dysfunction associated steatotic liver disease-related cirrhosis

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Background and aims: Despite its increasing global burden, the prevalence and mortality of MASLD-related cirrhosis among the general population remains incompletely characterized. Our aim was to provide updated estimates of the global prevalence and outcomes of MASLD-related cirrhosis.

Method: A systematic review was conducted by searching PubMed, Ovid MEDLINE, EMBASE, Web of Science, and SCOPUS databases through June 2024, followed by a meta-analysis of the extracted data. Eligible studies focused on MASLD and cirrhosis, with populations categorized into general practice settings (outpatient) and high-risk settings (inpatient or referred for liver biopsy due to clinical indications). Data extraction and quality assessment adhered to PRISMA guidelines. Random-effects models were used to pool prevalence and outcome measures, accounting for between-study heterogeneity.

Results: From 7,924 screened studies, 35 articles encompassing 513,742 MASLD patients met inclusion criteria. The pooled prevalence of cirrhosis was 3.26% (95% CI: 2.47–4.31%) in the general practice and 14.51% (95% CI: 11.22–18.57%) in the high-risk settings. Global regional differences in prevalence among high-risk populations were noted, with North America and Australia showing the highest rates (18.38%; 95% CI: 9.06–33.75%), followed by Europe (10.16%; 95% CI: 5.71–17.44%) and Asia (9.12%; 95% CI: 6.11–13.40%) (p = 0.007). Notably, ICD-based cirrhosis diagnoses yielded higher prevalence estimates (27.43%) as compared to biopsy-confirmed cases (13.24%; p < 0.001).

The pooled all-cause mortality rate among MASLD-cirrhosis patients was 7.91 per 100 person-years (PY) (95% CI: 4.44–13.71). Stratification by severity of cirrhosis revealed mortality rates of 4.85 per 100 PY (95% CI: 3.43–6.80) for MASLD-related compensated cirrhosis and 12.47 per 100 PY (95% CI: 4.44–30.37) for MASLD-related decompensated cirrhosis. Incidence of hepatic decompensation among patients with compensated MASLD-cirrhosis was 7.17 per 100 PY (95% CI: 2.33–12.10). Additionally, in all patients with MASLD-cirrhosis, the incidence of hepatocellular carcinoma incidence was 4.45 per 100 PY (95% CI: 0.55–8.35), and liver transplantation was 1.84 per 100 PY (95% CI: 0.84–2.84).

Conclusion: This systematic review reveals a significant burden of MASLD-related cirrhosis across the globe with some geographic and diagnostic variability.

FRI-030

In patients with metabolic dysfunction-associated steatotic liver disease, sleep disturbance is highly prevalent and associated with a profound impairment of health-related quality of life

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Background and aims: Metabolic dysfunctional-associated steatotic liver disease (MASLD) patients have impaired health-related quality of life and other patient-reported outcomes (PROs) which can be exacerbated by comorbidities, including sleep disorders. Our aim was to assess the prevalence of sleep disturbance and its association with PROs in MASLD.
Method: Patients with MASLD were prospectively enrolled into the Global NAFLD/MASLD Registry™ (GNR). Clinical and PROs (FACIT-F, CLDQ-MASH, and WPAI) data were analyzed by the presence of sleep disturbance (defined as CLDQ-MASH Sleep score of ≤4 on a 1–7 scale).
Results: 5342 MASLD patients from 17 countries in the GNR were included: mean (SD) age 53 (13) years, 48% male and 60% obese, 41% had type 2 diabetes (T2D), 46% hypertension, 43% hyperlipidemia, 15% with advanced fibrosis (by biopsy or FIB-4 or transient elastography), 20% depression, 52% clinically overt fatigue, 32% abdominal pain, and 20% sleep apnea. Prevalence of sleep disturbance among MASLD was 34%. MASLD patients and sleep disturbance were more commonly female (63% vs. 46%), with more components of metabolic syndrome (obesity 65% vs. 57%, T2D 47% vs. 37%, hypertension 54% vs. 42%, hyperlipidemia 51% vs. 39%), non-hepatic comorbidities (anxiety 52% vs. 24%, depression 31% vs. 13%, clinically overt fatigue 60% vs. 48%) and sleep apnea (26% vs. 16%) than those without sleep disturbance (all $p < 0.01$). In logistic regression model, presence of sleep disturbance in MASLD was associated with older age, female sex, history of anxiety, depression, clinically overt fatigue, abdominal pain, smoking, lack of regular exercise, and presence of significant pruritus (all $p < 0.01$). In MASLD patients with sleep disturbance, PRO scores in all domains of CLDQ-MASH and FACIT-F were lower (up to −25% of a score range size), and work productivity impairment was higher (mean [SD] 0.30 [0.33] vs. 0.11 [0.23]) (all $p < 0.0001$). In particular, the presence of sleep disturbance was strongly associated with lower fatigue scores of CLDQ-MASH and FACIT-F (more fatigue) and with lower pruritus scores (more pruritus) of CLDQ-MASH (effect size −17% to −23%, all $p < 0.0001$). In multiple regression analysis, sleep disturbance was independently associated with lower PRO scores in all domains of CLDQ-MASH, FACIT-F, and WPAI (beta up to −15%). Other independent predictors of lower PRO scores in MASLD included age, female sex, comorbidities (metabolic syndrome components, psychiatric disorders, clinically overt fatigue, and sleep apnea), advanced fibrosis, smoking, and lack of regular exercise ($p < 0.05$).
Conclusion: Sleep disturbance is highly prevalent in patients with MASLD. It is associated with fatigue and pruritus, non-hepatic comorbidities, lifestyle factors, and substantial impairment in HRQL and work productivity. Patients with MASLD should be assessed for sleep disturbances and advised accordingly.

FRI-031

Performance of chronic liver disease questionnaire – metabolic dysfunction-associated steatohepatitis (CLDQ-MASH) against non-invasive tests

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Background and aims: Patients with more advanced histologic fibrosis due to metabolic dysfunction-associated steatotic liver disease (MASLD) can experience health-related quality of life (HRQL) impairment. Most HRQL instruments that have been validated in MASLD were evaluated against liver biopsy. However, non-invasive tests (NITs) are increasingly being used in clinical practice and clinical research. Our aim was to assess correlations of NIT scores with HRQL scores using a newly validated HRQL instrument for MASH (Chronic Liver Disease Questionnaire – Metabolic Dysfunction-Associated Steatohepatitis, CLDQ-MASH).
Method: The data from MASLD/MASH patients enrolled in the Global NASH/MASH Registry were used, including NIT scores (FIB-4, Enhanced Liver Function or ELF, liver stiffness measurement (LSM) by transient elastography) and HRQL assessed by the CLDQ-MASH (7 domains) instrument. The NIT cutoff values with the strongest association (the greatest effect size) with the total CLDQ-MASH score were identified.
Results: There were 8504 MASLD patients with NIT and HRQL data included: mean (SD) age 54 (12) years, 45% male, 62% obesity (BMI > 30), 50% type 2 diabetes, FIB-4 score 1.59 (1.25), ELF score 10.0 (1.0), LSM 12.4 (10.2) kPa. All studied NITs were significantly negatively correlated with Activity (correlation coefficient (r) −0.04 to −0.12), Fatigue (r = −0.04 to −0.06), Sleep (r = −0.04 to −0.05), and Systemic symptoms (r = −0.06 to −0.11) domains of CLDQ-MASH; FIB-4 and LSM were additionally correlated with Worry (r = −0.08 to −0.13), and LSM with Digestive symptoms (r = −0.07) domain scores (all $p < 0.01$). For FIB-4, the cutoff with the strongest association with HRQL was 1.60 (34% of the sample met the cutoff); as a result, patients with FIB-4 ≥1.60 had significantly lower HRQL scores in 5/7 domains of CLDQ-MASH including Activity, Fatigue, Sleep, Systemic symptoms, and Worry (mean score impairment up to −0.23 on a 1–7 scale, $p < 0.0001$) while the domains of Digestive symptoms and

Emotional health were not associated with FIB-4 at any cutoff (all p > 0.05). For ELF, the cutoff for the strongest association with HRQL was 10.8 (met by 22%): MASLD patients who met the cutoff had lower scores in all 7 domains of CLDQ-MASH (score impairment up to –0.37, all p < 0.01). For LSM, the cutoff with the greatest effect size for association with HRQL was 26.5 kPa (met by 7%): in patients who met the cutoff, all CLDQ-MASH scores were significantly lower by up to –0.57 (all p < 0.01).
Conclusion: NIT scores in MASLD correlate negatively with HRQL as assessed by CLDQ-MASH. This indicates that higher NIT scores consistent with higher disease severity correlate with more HRQL impairment. The NIT cutoffs commonly used for the diagnosis of advanced fibrosis return the strongest association with HRQL impairment in MASLD. This suggests that CLDQ-MASH can be used in conjunction with NITs in clinical research in MASH/MASLD.

Public Health – Viral Hepatitis

TOP-001-YI
Community-based screening of viral hepatitis infections among high risk migrant and refugee populations in Greece, Italy and Spain: 2-year results of the VH-COMSAVAC project
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Background and aims: Migrants and refugees from countries with intermediate or high incidence and prevalence of hepatitis B and C virus (HBV and HCV) are at higher risk of acquiring these infections. This study aimed to increase HBV and HCV testing, HBV vaccination, and linkage-to-care among migrants and refugees living in Europe and report the latest epidemiological data.
Method: From 11/2022–11/2024, the VH-COMSAVAC study was implemented in Greece, Italy and Spain. Decentralised screening for HBV and HCV was offered in community and faith-based spaces, non-governmental organisations, and prisons. Simplified diagnostic tools, including HBsAg and anti-HCV rapid diagnostic tests were used, and expedited referral pathways were established to refer positive participants to collaborating tertiary hospitals. Intercultural mediators and community health workers supported recruitment and screening interventions to enable language and cultural appropriateness.
Results: Among 1,704 participants screened across the three countries, overall HBsAg and anti-HCV prevalence were both 3.4%. The highest HBsAg prevalence was observed in Spain (6.1%), which was higher than in Greece (2.2%) and Italy (2.1%). Anti-HCV prevalence was highest in Greece (5.9%) followed by Italy (2.3%). Participants were mostly male (74.2%), with a median age of 38 years (IQR = 30–48), and 51.9% were recently arrived migrants (≤5 years in country). 28.3% of participants were from sub-Saharan Africa, followed by Eastern Europe (17.8%), and Central and South America (13.9%). Most HBsAg+ participants (71.4%) were sub-Saharan African, mainly from Ghana and Senegal. 48.3% of anti-HCV+ participants were from Eastern Europe. Georgia, Pakistan and Egypt contributed to the highest HCV burden with an anti-HCV prevalence of 51.4%, 13.8%, and 7.0%, respectively. Among positive participants, 63.6% were successfully linked to care in Spain (N = 21/33), 47.5% in Greece (N = 29/61), and 12.5% in Italy (N = 2/14). Most of those not yet linked are facing legal barriers to access care.
Conclusion: The migrants and refugees in this study had high levels of viral hepatitis. Decentralized and simplified screening for viral hepatitis can successfully enhance diagnosis of HBV and HCV among migrants and refugees across Europe when provided in a culturally and linguistically appropriate manner. Legal barriers hindering individuals from accessing healthcare services must be addressed to ensure access throughout the cascade of care.

TOP-002-YI
Disparities in hepatocellular carcinoma screening and in its detection rates in individuals with hepatitis B or C and cirrhosis in Canada
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Background and aims: Hepatocellular carcinoma (HCC) is a major global and Canadian cause of mortality. Regular HCC screening improves early detection and survival, especially among individuals with liver cirrhosis due to chronic hepatitis B (HBV) or C (HCV). Despite the benefits, disparities in HCC screening and their impact on post-diagnosis outcomes are underexplored. We assessed HCC screening disparities and detection among individuals with HBV or HCV in British Columbia, Canada.
Method: Using the BC Hepatitis Testers Cohort, we included individuals with HBV or HCV diagnosed with cirrhosis from 1990–2020. Screening was defined as >1 liver or abdominal ultrasound; HCC diagnosis required matching topography and histology codes. Logistic regression identified factors associated with screening and HCC detection.
Results: Among 117,524 individuals with chronic HBV (n = 42,259), HCV (n = 69,117), or HBV/HCV co-infection (n = 6,148), 13,995 had cirrhosis (HCV: 10,246; HBV: 2,221; HBV/HCV: 1,528). Median age at cirrhosis diagnosis was 56 years (Q1-Q3: 49–63); 68.1% were male, and 59.7% had decompensated cirrhosis. Over half of the cohort underwent at least one HCC screening, including those with HCV mono- or HBV/HCV co-infection. Overall, 15% were diagnosed with HCC, with the highest prevalence among HBV mono-infected individuals (22.7%). In multivariable models, diabetes was positively associated with screening (adjusted odds ratio [aOR]: 1.49–1.62 across groups). South Asian (aOR: 1.49; 95% CI: 1.13–1.95) and other

ethnicities (aOR: 1.75; 95% CI: 1.54–1.99) were more likely to be screened compared to East Asians. Conversely, males, individuals aged ≥45, those with injection drug use history, and decompensated cirrhosis were less likely to be screened. HCC detection was more likely in older individuals (45–54 years), males, and those with decompensated cirrhosis, while injection drug use and non-East Asian ethnicity were associated with lower odds of detection.
Conclusion: Significant disparities in HCC screening and detection exist by age, sex, injection drug use, ethnicity, and liver disease severity among individuals with cirrhosis due to HBV and HCV. Targeted interventions are needed to address these disparities, particularly for middle-aged males and those with advanced liver disease. Future research should explore barriers to screening in high-risk groups and evaluate strategies to improve surveillance and outcomes.

TOP-015

Emergency department opt out testing for HBV and HCV in London with integrated linkage to care: an effective initiative to diagnose hepatitis or work in progress?

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Background and aims: Widespread opportunistic screening is critical to eliminating HBV and HCV. From April 2022, in areas of high (>5/1000) HIV prevalence, NHS England launched 'opt-out' testing for HIV, HBV and HCV in 34 emergency departments (EDs) with integrated linkage to care. We report on the first 2 years, focusing on 28 EDs in London, an urban metropolis with a diverse population of 9.7 million with over 40% of residents born outside of the UK.
Method: Adults attending ED who were having blood tests were offered opt-out screening for HBV and HCV (HBV surface antigen (HBsAg) and HCV antibody (HCV Ab), with reflex RNA if Ab positive). Information was displayed using posters in EDs and BBV screening performed unless the individual opted out. Results management was directed through hepatitis services with engagement and contact to individuals with a new or unlinked positive result. Linkage to care (LTC) was recorded if there was ≥1 attendance at hepatitis services. Aggregated, anonymised data was reported monthly by sites; LTC is underestimated as it does not take into account clinical exclusions, attendance at a service other than the notifying one, or that individuals may have been tested in more than one ED.
Results: By 2 years, triple BBV testing in London was live in 28 EDs. Screening for HBV and HCV was undertaken for a median of 18 months. There were 3.3 million ED attendances with 1.9 million having blood tests. 1,157,321 HBsAg and 1,171,253 HCV Ab tests were performed; testing uptake was 68% [IQR 48–77% between sites] for HBV and 69% [IQR 51–81%] for HCV. HBV: There were 9115 positive HBsAg tests: HBsAg positivity was 0.77% [IQR 0.57–0.94%]). Care status of screen positive cases, after excluding duplicates, was: 2866/7971 (48%) new diagnoses, 586 (10%) previously diagnosed but not in care and 2538 (42%) in care. LTC was 57% [IQR 31–75%]. HCV: There were 11831 positive HCV Ab tests: HCV Ab positivity was 0.98% [IQR 0.76–1.26%]. In those with current or past infection (HCV Ab+) only 13% [IQR 9–20%] of RNA tests were positive. Among RNA+ cases: 874/1289 (76% [IQR 59–87%]) were new diagnoses, 164 (9% [IQR 2–15%]) were previously diagnosed but not in care and 274 (8% [IQR 6–27%]) were in care. LTC was 68% [IQR 49–83%] for new diagnoses and 29% [IQR 2–69%] for people lost to care. Sites reported that 18% [IQR 10–26%] and 15% [IQR 0–26%] of new/ unlinked HBV and HCV RNA+ cases were 'uncontactable'. When this occurred, inclusion health partners (community peers, outreach and primary care providers) were engaged.
Conclusion: Opt-out ED BBV testing in London, a capital city with an ethnically diverse population, is effective and acceptable in diagnosing people living with HBV and HCV, with large cohorts of infected individuals identified. Low RNA+ rates in HCV exposed people indicates significant progress towards elimination. LTC was variable. Capacity building to deliver responsive clinical pathways, peer support and specialist management is critical to ensure optimal outcomes at an individual and population health level.

WEDNESDAY 07 MAY

TOP-016

Genetic determinants of hepatitis B surface antibody disappearance in Taiwan's vaccinated generations: a genome-wide association study

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Background and aims: Hepatitis B (HB), caused by HBV, affects 257 million people globally and causes 1.1 million deaths annually due to complications like cirrhosis and HCC. Chronic hepatitis B (CHB), defined as persistent HBsAg for over six months, remains a key public health concern. Taiwan's universal HBV vaccination program for newborns, launched in 1986, reduced the HBsAg positivity rate from 9.8% pre-vaccination to 0.64% after 35 years, significantly lowering HBV carrier rates and HCC incidence. However, studies show 60% of vaccinated individuals have anti-HBs levels below the protective threshold 15–18 years post-vaccination, raising concerns about increased HBV susceptibility. The mechanisms underlying anti-HBs decline remain unclear. This study investigates genetic factors associated with anti-HBs decline to develop risk prediction models and personalized HBV prevention strategies.
Method: The study utilized data from the Taiwan Biobank, including 6,255 participants born after July 1, 1986, under Taiwan's universal

vaccination program. Individuals born before this date or testing positive for anti-HBc were excluded. A genome-wide association study (GWAS) was conducted to explore genetic factors influencing anti-HBs seronegativity. Rigorous quality control (QC) procedures using PLINK software included sex-genotype concordance checks, thresholds for SNP call rates, heterozygosity evaluation, and kinship filtering to exclude related individuals. At the SNP level, QC involved filtering based on minimum allele frequency, SNP call rates, and Hardy-Weinberg equilibrium testing. Significant SNPs identified through GWAS were mapped to gene regions, and logistic regression analysis with Bonferroni correction was applied to control for false positives.

Results: Seventy-five SNPs were significantly associated with anti-HBs seronegativity ($p < 5 \times 10^{-8}$), with 73 SNPs clustered in the HLA-DPB1 region and 2 in COL11A2. Analysis of specific HLA-DPB1 allele combinations, such as HLA-DPB1 05:01/05:01 and HLA-DPB1 02:02/02:02, revealed significant associations. Logistic regression models adjusted for age and sex showed that individuals with the HLA-DPB1 05:01/05:01 allele combination had a higher risk of anti-HBs seronegativity compared to those with other combinations (OR = 1.27, 95% CI = 1.09–1.47, p = 0.002). Conversely, individuals with the HLA-DPB1 05:01/02:02 combination had a reduced risk of anti-HBs seronegativity (OR = 0.73, 95% CI = 0.58–0.92, p = 0.008).

Conclusion: HLA-DPB1 variation significantly influences anti-HBs seronegativity in individuals vaccinated against HBV. The HLA-DPB1 05:01/05:01 allele combination increased the risk of anti-HBs disappearance, while HLA-DPB1 02:02/02:02 was protective. These findings underscore the role of genetic variation in determining long-term immune responses to HBV vaccination and provide a foundation for personalized vaccination strategies and improved HBV prevention.

WED-003

One-pot assay based on CRISPR/Cas13a technology for HEV RNA point-of-care testing

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Background and aims: Hepatitis E virus (HEV) poses a serious threat to both public health and animal food safety, thereby highlighting the demands for rapid, sensitive, and easy-to-use detection. This study aimed to develop a One-Pot assay using CRISPR/Cas13a for detecting HEV RNA, suitable for point-of-care testing (POCT) in resource-limited settings.

Method: CRISPR/Cas13a combined with reverse transcription polymerase chain reaction (RT-PCR) and reverse transcription recombinase-aided amplification (RT-RAA) was applied to a One-Pot assay device. Additionally, a large cohort of HEV-infected patient (154) and animal (104) specimens was utilized for validation.

Results: The RT-PCR/RT-RAA+CRISPR/Cas13a assays for HEV RNA detection (genotypes: HEV-1, HEV-3, and HEV-4) were established, optimized, and validated, achieving a limit of detection (LoD) of 1 copy/μL and 100% specificity. In the application validation for HEV infection, the positive rates of the RT-PCR+CRISPR and RT-RAA +CRISPR assays were 98.6% and 89.6% for patients, and 96.6% and 88.8% for animals, respectively, which were superior to those of RT-qPCR. Furthermore, sample rapid lysis, reagent lyophilization, and the One-Pot device were integrated to construct a One-Pot assay with a LoD of 102 copies/μL. Despite slight decreases in sensitivity, the One-Pot assay significantly reduces the assay time to 35 minutes, making it easy to perform, minimizing contamination, and meeting the requirements for screening.

Conclusion: We developed a One-Pot assay of HEV RNA using the CRISPR/Cas13a which effectively realizes a POCT test and maximizes the impetus for POCT implementation and shows potential as a valuable tool for detecting and monitoring HEV infection.

WED-004

Global burden of liver cancer related to viral hepatitis attributable to high body mass index from 1990 to 2021

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Background and aims: Liver cancer is a prominent contributor to global cancer mortality, with primary etiologies including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Metabolic risk factors, including high body mass index (BMI), has been associated with an increased risk of liver cancer and is gaining recognition in the context of its global impact. This study aims to estimate the global burden of liver cancer due to hepatitis B or hepatitis C attributable to high BMI.

Method: Data on the number and rate of deaths and disability-adjusted life years (DALYs) of liver cancer due to hepatitis B or C attributable to high BMI were extracted from the Global Burden of Disease (GBD) 2021. Age-standardized rates (ASR) of deaths and disability-adjusted life years (DALYs) were analysed across various demographics, including sex, age groups, and socio-demographic index (SDI) levels. The estimated annual percentage change (EAPC) in deaths and DALYs was calculated to identify trends over time.

Results: The overall ASR of deaths due to hepatitis B has decreased from 2.5 (95% CI 2.154–2.916) in 1990 to 2.089 (95% CI 1.721–2.551) in 2021, with an EAPC of –0.65 (95% CI –0.789–0.511), and for hepatitis C from 1.699 (95% CI 1.466–1.986) to 1.739 (95% CI 1.489–1.994) with an EAPC of –0.084 (95% CI –0.247–0.080). However, the ASR of deaths attributable to high BMI has shown an alarming increase. For hepatitis B, the ASR of deaths rose from 0.081 (95% CI 0.032–0.131) in 1990 to 0.18 (95% CI 0.069–0.309) in 2021, with an EAPC of 2.598 (95% CI 2.506–2.691). For hepatitis C, the ASR of deaths increased from 0.101 (95% CI 0.041–0.169) to 0.2 (95% CI 0.084–0.337), with an EAPC of 2.2 (95% CI 2.091–2.309). Additionally, ASR of DALYs for hepatitis B and C have also increased, with DALYs for hepatitis B rising from 2.639 (95% CI 1.023–4.235) to 5.74 (95% CI 2.204–9.840) and for hepatitis C from 2.346 (95% CI 0.941–3.982) to 4.461 (95% CI 1.860–7.620), both showing EAPCs of 2.489 (95% CI 2.388–2.590) and 2.101 (95% CI 1.986–2.217) respectively. Male exhibits higher EAPC of deaths and DALYs than female. When stratified by age, the crude rate of deaths and DALYs are higher in the 50–69 and 70+ age groups, which are also increasing annually. However, the EAPC is notably higher in the 15–49 age group. In terms of SDI, the ASRs of deaths and DALYs attributable to high BMI is highest in the high-middle SDI group for hepatitis B, and in the high SDI groups for hepatitis C. Nevertheless, the middle SDI group exhibits the highest EAPC for both hepatitis B and C.

Conclusion: Despite the global decline in both mortality and DALYs for liver cancer due to hepatitis B and C, there is a contrasting increase in the burden attributable to high BMI. This upward trend is particularly evident among male, in countries with middle SDI, and within the 15–49 age group.

WED-005

Current hepatitis D virus infection prevalence in persons with human immunodeficiency virus and hepatitis B virus across Europe

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Background and aims: People with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are at increased risk of also having hepatitis D virus (HDV) infection given the shared transmission pathways. However, much of the current epidemiological literature on HDV in those with HIV/HBV are based on decades-worth of data and there is no clear understanding of the current prevalence of HDV in this patient population. We aimed to determine the HDV screening rate and estimate the prevalence of HDV infection of people with HIV/HBV who are currently in care in Europe.
Method: Data from several clinical cohorts across Europe (i.e., the Netherlands, Germany, Switzerland, Spain, Italy, United Kingdom, and Poland) of people with a confirmed HIV diagnosis were used. We included those who were ever hepatitis B surface antigen positive, aged ≥18 years, and actively in care on December 31, 2023. We assessed HDV testing rates in the total cohort. In addition, we calculated the prevalence of individuals who ever had an anti-HDV positive serology (i.e., past/current infection) and the prevalence of individuals whose last HDV RNA result was positive (i.e., active infection). We also provided prevalences by key population, based on HIV transmission [i.e., men who have sex with men (MSM), heterosexual/other, and people who inject(ed) drugs (PWID)].
Results: Of 3176 persons with HIV/HBV included, anti-HDV antibody results were available in 2027 (63.8%). Of them, 263 had past/current HDV infection (13.0%, 95% CI = 11.5–14.5). This prevalence ranged from 4.5% in the Netherlands to 22.2% in Poland. Among the 263 individuals with an anti-HDV positive result, 174 had been tested for HDV RNA and of them, 88 had active HDV infection (50.6%, 95% CI = 42.9–58.2%). The prevalence of active HDV infection was comparable across countries. The majority of past/current infections were observed in PWID (n = 127/289; 48.3%) followed by heterosexual/other (n = 84/868; 31.9%) and MSM (n = 52/870; 19.8%). Similarly, most of active infections were observed in PWID (n = 38/80; 43.2%) compared to heterosexual/other (n = 28/60; 31.8%) and MSM (n = 22/34; 25.0%).
Conclusion: In Europe, roughly one in eight individuals with HIV/HBV who are actively in care have evidence of past/current HDV infection. A smaller percentage of individuals had active HDV infection, representing 88 individuals likely needing treatment. Nevertheless, these results come from a setting where HDV RNA testing needs to be increased.

WED-006
Liver stiffness and AST-to-platelet ratio index (APRI) predict all-cause mortality in untreated people living with hepatitis B across Africa: a multi-centre cohort analysis in the hepatitis B in Africa collaborative network (HEPSANET)

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Background and aims: The African region has the highest global prevalence of hepatitis B, yet longitudinal data for people living with hepatitis B (PLWHB) on the continent are scarce. There is a need for improved data on the prognostic value of liver stiffness measurement (LSM) and low-cost biomarkers such as APRI, which were developed in non-African populations, for making treatment decisions. We aimed to evaluate the relationship between pre-treatment LSM and APRI and overall mortality among untreated PLWHB in HEPSANET, an Africa-wide cohort collaboration.
Method: We included treatment-naïve PLWHB aged ≥12 years who had a pre-therapy evaluation with transient elastography and/or APRI, and longitudinal outcome data. We excluded PLWHB with HIV, hepatitis C or D co-infection and those who developed hepatocellular carcinoma within 180 days of enrolment, and for APRI, those with AST > 200 U/L. For 10 PLWHB with an unknown date of death, we imputed survival time using multiple imputation. We used a Cox proportional hazards model for all-cause mortality with a restricted cubic spline with 5 knots for LSM and APRI. We right-censored patients 180 days after their last visit if designated lost to follow up, or at commencement of HBV treatment.
Results: Across 12 sites in 9 African countries, we included 3,803 treatment-naive PLWHB with a total of 12,629 person-years of follow up (PYFU) with a baseline LSM, and 3,860 PLWHB with 12,613 PYFU with a baseline APRI score. Median age was 33 years [IQR 27, 41] and 60% were male. Pre-therapy LSM was <7, 7–12 and >12 kPa in 79%, 15% and 7%, respectively; APRI was <0.5, 0.5–0.9, 1.0–1.4 and ≥1.5 in 79%, 13%, 3% and 5%, respectively. LSM and APRI were non-linearly associated with mortality, and increasing incidence of mortality was observed when LSM exceeded 7 kPa and APRI exceeded 0.3. Relative to LSM of 4 kPa, hazard ratios for mortality after a median follow up of 2.8 years (IQR 0.7, 5.8) at 7, 10, 15, 20 and 30 kPa were 1.6 [95% CI 1.2–2.2], 9.4 [6.6–13.4], 26.4 [16.3–43.0], 33.4 [21.0–53.2] and 51.5 [33.5–79.2]. Relative to APRI of 0.3, APRI scores of 0.5, 1.0 and 2.0 were associated with hazard ratios for mortality after a median 2.6 years [0.6–5.7] of follow up, of 3.4 [2.9–4.3], 8.2 [5.9–11.5] and 8.5 [6.1–12.0], respectively.
Conclusion: This analysis shows a strong and non-linear association between mortality and both LSM and APRI in PLWHB in Africa. This finding may support the expansion of antiviral therapy for PLWHB with LSM > 7 kPa or APRI > 0.5, as recently recommended by the World Health Organization 2024 guidelines.

WED-007
Implementation of a multicenter reflex testing program for hepatitis D detection of and registration of positive cases in Catalonia

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Background and aims: In Spain, the prevalence of HBsAg is 0.22%, with a 7.7% rate of HDV coinfection. Previous research involving small cohorts has shown that introducing reflex testing for hepatitis D in HBsAg-positive cases leads to an increase in absolute diagnoses. This project aims to establish and implement a reflex screening program for hepatitis D in all HBsAg-positive samples across the public healthcare centers of the Catalan Health Institute (Institut Català de la Salut, ICS). Additionally, a registry of positive cases will be created to evaluate their clinical characteristics and treatment indications.
Method: A multicenter prospective study was conducted, including all HBsAg+ samples analyzed at the seven ICS laboratories (covering more than 95% of the Catalan population). A double reflex testing for anti-HDV and HDV RNA was performed. Demographic, epidemiological, clinical, laboratory data, and patient linkage to care status for all anti-HDV positive patients were recorded on a digital platform.
Results: From 1/Jan to 31/Oct of 2024, 220,242 HBsAg determinations were performed, identifying 5,333 HBsAg+ samples. Anti-HDV antibodies were tested in 4,810 samples (90%), of which 185 (3.8%) were positive after removing duplicates. Of the 185 anti-HDV positive cases, 63 (35%) were also positive for HDV RNA. The program allowed testing for 2,223 HBsAg+ samples (46%) that had not been previously tested for HDV, detecting 56 new anti-HDV+ and 9 new HDV RNA+ subjects. Of the 53 currently registered HDV RNA+ patients, 65% were male, with a median age of 53 years (range 42–59). Thirty-nine percent were Spanish, and 38% reported risk factors. Thirty-eight percent had elevated ALT levels, 51% had liver cirrhosis, 8% had a history of hepatic decompensation, and 6% had hepatocellular carcinoma. A total of 26 patients had previously received treatment with PegIFN without response. Currently, 25 (47%) patients have started treatment with Bulevirtide. Those treated had more advanced fibrosis (≥F3: 84% vs 50%, p = 0.01), a higher frequency of prior PegIFN treatment (80% vs 21%, p < 0.001), and a higher frequency of previously known HDV diagnosis (96% vs 82%, p = 0.195) compared to untreated patients. The reasons for not receiving treatment included refusal due to fibrosis stage <F2 (36%), no prior PegIFN treatment (21%), limitations in drug administration (14%), or other reasons (29%).
Conclusion: This regional program has enabled the testing for hepatitis D in 46% of HBsAg-positive samples for the first time. Half of the patients with hepatitis D are now receiving Bulevirtide, particularly those with advanced fibrosis and those who failed to prior PegIFN treatment. This ongoing screening and monitoring program, integrated into the public healthcare system, will help determine the prevalence, characteristics, and treatment response to Bulevirtide in patients with hepatitis D.

WED-008-YI
Micro-elimination of hepatitis C utilizing hepatitis C virus self-testing in a district prison of northern India: a demonstration project

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Background and aims: Incarcerated populations have a high prevalence of Hepatitis C virus (HCV) infection and face significant barriers to testing and treatment. This demonstration project evaluated the feasibility of using Hepatitis C virus self-testing (HCVST) to achieve micro-elimination of HCV in a district prison in Northern India.
Method: A micro-elimination project, was conducted at Haridwar Jail, Uttarakhand, among 1150 inmates (55 female) from August to October 2024. Participants were offered HCVST. Those with reactive results received reflex HCV RNA testing and fibrosis assessment using vibration-controlled transient elastography (VCTE). All those with active HCV infection were linked to on-site care and initiated on direct-acting antiviral (DAA) therapy under national viral hepatitis control program (NVHCP). A total of 111 inmates were enrolled to evaluate the usability and acceptability of HCVST kits.
Results: Participants (n-1150, 55 females) ranged in age from 18 to 90 years (mean age = 34.8 ± 14.4 years), with 43% under 30 years old. Most were literate (74%) and 40% were unmarried. Two-thirds (66.6%) belonged to lower socioeconomic classes. Reported risk behaviors included history of surgery (2.5%), dental procedures (5.9%), razor sharing (68%), tattooing (1.3%), needle sharing (3.1%), intravenous drug use (3.9%), and unsafe sex (26%). Intravenous drug use (odds ratio 37, 95% confidence interval (CI) 17–77), tattooing (odds ratio 6.5, 95% CI 1.7–23.9), and needle sharing (odds ratio 45, 95% CI 20–99) were significantly associated with HCV infection. HCVST identified 72 (6.3%) individuals with anti-HCV antibodies. Of these, 41 (56.9%) had active HCV infection (HCV RNA positive) with a median HCV RNA level of 30,245 IU/ml (range 262–625463). Four of the 41 HCV RNA positive individuals had liver stiffness measurement >12 kPa, indicating significant liver fibrosis. All 41 individuals with active HCV infection initiated DAA treatment. Overall usability of the HCVST kits was 70%, with sample collection being the most challenging step (98% required assistance).
Conclusion: This project demonstrates the feasibility of utilizing HCVST to screen for HCV infection and link inmates to care within a correctional setting. By implementing a comprehensive micro-elimination strategy, including readily accessible testing, treatment, and support services, significant progress can be made towards eliminating HCV in this high-risk population and contributing to national elimination goals.

WED-009
Return to Care (R2C) - the missing link in hepatitis C elimination

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Background and aims: The UK is committed to eliminating the Hepatitis C virus (HCV) by 2030. The landscape of HCV detection and treatment has been transformed by the advent of highly effective and well tolerated oral treatments, but large numbers of people remain infected and not engaged with treatment and care. A previous national HCV re-engagement exercise, led by UKHSA, identified over 50,000 untreated patients in England but had limited success, with 71% of cases remaining unresolved. This presentation describes a new, highly effective peer-led outreach model developed by Find&Treat (a pan-London NHS inclusion health outreach service) to identify, contact, and engage 'lost to follow-up' (LFU) patients.
Method: Return 2 Care (R2C) was established in response to rising LFU referrals, driven by expanded opportunistic bloodborne viral disease testing in prisons and emergency departments, as well as improved surveillance and information systems identifying untreated patients. The programme employs peers who use digital searches, direct collaboration with NHS and allied providers, and intelligence-led street outreach to identify, contact, and engage patients. These efforts facilitate retesting, treatment, and holistic support. This study examines the first 1,000 patients referred to the service.
Results: Of the 1,000 patients referred, 84 (8.4%) had died, 682 (68.2%) were successfully identified, contacted, and engaged (ICE), while 234 (23.4%) remain uncontacted. Of the ICE'd cohort (682), 364 (53.4%) were engaged directly by peers, 257 (37.7%) through NHS and third-sector services, and 61 (8.9%) via prison healthcare. Among these, 404 (59.2%) were confirmed as previously treated, 199 (29.2%) have initiated or completed treatment, 39 (5.7%) are pending assessment for treatment, 35 (5.1%) achieved spontaneous viral clearance, and 5 (0.7%) experienced treatment failure and remain under review. Despite an extremely high level of social complexity (59% were homeless, 10% incarcerated, and 28% actively using heroin and crack cocaine) 72% of those requiring treatment have been treated or cured.
Conclusion: This study highlights the effectiveness of a peer-led model in reengaging untreated HCV-positive patients with care and treatment. This approach represents a critical component of HCV elimination strategies and can be scaled internationally to address both retrospective and future LFU cases.

WED-010
Complex multiple morbidity and social vulnerability among hep C patients with delays accessing care

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Background and aims: Multiple studies have highlighted an association between chronic Hepatitis C viral (HCV) infection and chronic renal disease, mental illness, and neurological disorders, but evidence on other common long-term chronic diseases, social vulnerability and especially on multiple morbidity is lacking. Understanding the factors that complicate accessing care for HCV patients is essential to better tailor services that can meet their needs. Find&Treat are a peer led pan-London NHS inclusion health outreach service who receive referrals for HCV patients in need of locating and engaging with treatment and care. We characterised the health status of a large cohort (200) of HCV patients who experienced significant challenges and delays accessing Hep C treatment to better understand the burden of complex comorbidity and social vulnerability and inform their ongoing care needs during and post HCV treatment.
Method: We linked a representative sample of 200 HCV patients referred for reengagement with care to the London Care Record, a secure NHS platform that combines data from both primary care practices and hospitals across London. This resource provides a comprehensive health care record for patients that can be viewed by medical practitioners across the capital to speed up communication and improve care. Data on key diagnoses, health care access and social vulnerabilities were collated to characterise the burden of complex comorbidity and multiple morbidity.
Results: The majority were UK born (71%) and male (73%), and the overall mean age was 54 (Range 24–78). 52% had a diagnosis of anxiety/depression, 20% schizophrenia/psychosis, 11% diabetic or pre-diabetic, 17% had a cardiovascular diagnosis and 42% had chronic obstructive respiratory disease. 2% were HIV coinfected, 56% had an ulcer, wound, abscess and/or cellulitis and 23% had a history of serious head injury. 11% of patients had one recorded comorbidity and 38% had over 5 comorbidities. 75% reported ongoing drug and alcohol dependency and 60% were homeless.
Conclusion: This study reveals a substantial burden of comorbidity, complex multimorbidity, and social vulnerability among HCV patients experiencing delays in accessing care in London. These patients have significant unmet healthcare needs at time of engagement with Hep C treatment services and major ongoing care needs. Further research is needed to better understand the care needs of Hep C patients and to develop HCV treatment models that can improve linkage to care for ongoing health needs post HCV treatment.

WED-011
Treatment for chronic hepatitis C infection in Pakistan – in a high prevalence country treatment initiation is sub-optimal and may impact elimination programs

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Background and aims: Elimination of HCV requires treatment of most infected people. The prevalence of HCV in Pakistan is among the highest in the world (estimated at 6.8%) and current treatment programs with sofosbuvir/daclatasvir are being rolled out nationwide in an effort to eliminate the infection. In this under educated population with limited access to accurate health information the uptake of antiviral therapy may be suboptimal. Here we assess the uptake of therapy, provided at no cost to the patient, in local programs as part of a preliminary elimination program.
Method: HepFreePak is an observational 25,000 person study of the impact of sofosbuvir/daclatasvir treatment in Pakistan that examines, prevalence, incidence over 12 months in uninfected and successfully treated patients and response to current standard of care (sofosbuvir/daclatasvir for 12 weeks in people with an APRI score of <1.5 or 24 weeks in those with an APRI score of >1.5 or other features of cirrhosis). We examined treatment uptake and attendance for SVR12 testing in three different treatment programs: a 'door-to-door' case finding approach (Malir); an urban clinic and community testing events (Karachi) and a community camp based 'test and treat' strategy (Gujranwala). All treatment associated costs were met by the program along with small cash incentives to attend for treatment/testing.
Results: In a 'door-to-door' test and treat strategy in Malir, Karachi 14,612 people were tested, 167 (1.2%) were antibody positive but RNA negative and 930 (6.36%) were HCV RNA positive. 713 (77%) initiated treatment and 633 (89%) attended for SVR12 assessment of whom 89% achieved an SVR12.
In an urban clinic and community testing program in Karachi 2828 people were tested, 199 (7%) were HCV antibody positive and HCV RNA negative and 242 (8.6%) were HCV RNA positive. 227 (94%) initiated treatment and 157 (69% of treated) attended for SVR12 assessment of whom 96% achieved SVR12. In a community-based test

and treat strategy in Gujranwala (Punjab) 3609 people were tested, 127 (3.8%) were antibody positive and HCV RNA negative and 246 (6.8%) were HCV RNA positive. 178 (72%) initiated treatment and 76 (42% of those treated) attended for SVR12 assessment of whom 95% achieved an SVR.
Conclusion: The prevalence of chronic HCV infection remains very high with rates of 6–8%. Despite the availability of free antiviral treatment and incentives to attend for treatment less than 80% commenced treatment and even fewer were able to complete an SVR12 assessment. Information and awareness programs along with appropriate pictorial literature will be required to assist the elimination program in Pakistan.

WED-012

A comparative analysis of carbon footprints: nucleic acid test vs. rapid antigen test for preventing mother-to-child transmission of hepatitis B in the gambia

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Background and aims: Healthcare systems contribute over 4% of global carbon emissions, underscoring the urgent need for measures to mitigate their environmental impact. When selecting between different healthcare strategies, environmental impact should be considered alongside health outcomes and economic costs to guide decision-making. However, only some studies have conducted life cycle assessments (LCA) to estimate the carbon footprint related to healthcare technologies. To date, there is no study comparing the carbon footprint of alternative rapid tests versus conventional reference tests in resource-limited countries. In this study, we estimated and compared the carbon emissions of three testing strategies used to assess eligibility for antiviral prophylaxis in pregnant women with chronic hepatitis B virus (HBV) infection in The Gambia: i) conventional strategy to quantify serum HBV DNA levels using point-of-care real-time PCR (Xpert HBV Viral Load), ii) the innovative strategy to detect hepatitis B core-related antigen with a rapid diagnostic test (HBcrAg-RDT) using capillary blood, and iii) the HBcrAg-RDT strategy using plasma.
Method: We conducted an LCA with field data collection in four healthcare facilities in The Gambia. The data collection included all products and processes involved in each testing strategy. Our functional unit was defined as a single testing visit to determine eligibility for peripartum antiviral prophylaxis during antenatal care in The Gambia. The carbon emissions, expressed as grams of CO2 equivalent (gCO2e), of each testing strategy were calculated and presented with their respective uncertainties.
Results: Across the four study sites, the average CO2e of the Xpert® HBV Viral Load (1519.7 gCO_2e [95% CI, 1323.0–1716.0]) was significantly higher than that of both HBcrAg-RDT using plasma (392.3 gCO2e [95% CI, 342.3–442.3]) and HBcrAg-RDT using capillary blood (253.5 g CO2e [95% CI, 215.1–291.7]). This trend was consistent across all healthcare facilities. The largest contributors to carbon emissions varied with the testing strategy. For the Xpert® HBV Viral Load, the share of emissions was dominated by energy consumption (57.4%), the test (17.8%), and women's travel (12.2%). The high associated energy consumption for Xpert® HBV Viral Load is mainly attributed to air conditioning required during HBV DNA amplification to maintain optimal operating conditions. Furthermore, the analysis of the carbon footprint of testing strategies across healthcare facilities revealed considerable variations mainly attributable to on-site service organization and women's trajectories.
Conclusion: The carbon emissions associated with HBcrAg-RDTs are approximately four to six times lower than those of conventional molecular assays. This underscores the importance of incorporating alternative rapid tests that do not require machines to promote a more sustainable strategy for eliminating HBV mother-to-child transmission in resource-limited settings.

WED-013

Clearing the road for viral hepatitis microelimination in croatian prisons: the Hepatos project

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Background and aims: In Croatian prisons, hepatitis C (HCV) prevalence is notably higher than in the general population. To bridge the gap between diagnosis and treatment, the Croatian Society for Liver Disease - Hepatos launched the Mobile InfoHep Centre (MIHC), a mobile clinic within the prison system. This initiative aimed to demonstrate the feasibility of HCV microelimination through civil society-led linkage-to-care services in collaboration with governmental institutions, public health authorities, and clinical experts.
Method: From June 2021 to April 2024, the project engaged experts from the Croatian Gastroenterological Society and the Public Health Institute, with financial backing from the Ministry of Justice. The Hepatos MIHC provided linkage-to-care services, including on-site liver exams using FibroScan®, consultations, HCV and/or HIV testing, and referrals to specialists.
Results: Hepatos conducted 18 outreach activities across 10 prisons, engaging 537 male and 62 female prisoners, mean age 42.3 ± 11.9 years and delivering 2078 services. The MIHC reached about 5% of the Croatian prison population. Only 8.7% of examined prisoners self-reported previous HCV contact, while 33.7% and 13.7% agreed to HCV and HIV testing, respectively. 41% (83/202) of tested prisoners were anti-HCV positive, and none was HIV positive. All anti-HCV positive prisoners were referred to HCV RNA testing: 19.3% tested negative and 43.4% (36/83) who tested positive were further referred to DAA treatment. For the rest PCR test is pending. 597 prisoners underwent on-site Fibroscan® exam with a median LMS of 5.3 (IQR 2.2, range 1.6.–52.3) kPa, with the following distribution of fibrosis: stage 1) 24.2%, stage 2) 9.7%, stage 3) 4.7% stage 4) 2.5%. A median CAP was 253 (IQR 81, range 100–400) dB/m and 36.9% of prisoners had steatosis with CAP values >276 dB/m. All prisoners with high degrees of fibrosis were referred to specialists. Anti-HCV positive prisoners had significantly higher LMS values (6.2 (IQR 3.8, range 2.8–52.3) kPa) compared to anti-HCV negative prisoners (5.1 (IQR 1.8, range 1.6–27.0) kPa), ($p < 0.001$).
Conclusion: Prisons play a critical role in detecting and treating HCV, particularly for those with limited healthcare access and engaged in risky behaviours. This collaboration among civil society, governmental bodies, and public health agencies showed that Croatia still has a significant HCV burden in prisons, but the joint approach enables to enhance prisoner health literacy and stimulate inmate willingness to undergo testing and treatment. Following governmental recognition

of these efforts, the Ministry of Justice is co-financing continuation of Hepatos program for the following three years (2025–2027) - providing linkage-to-care activities within prisons aiming to get a step closer to microelimination in Croatian prisons.

WED-014

Evaluation of Belgium's progress towards HBV elimination: results from a national serosurvey

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Background and aims: The WHO strives to eliminate HBV by 2030 by reducing the hepatitis B surface antigen (HBsAg) prevalence to ≤0.1% in ≤5-year-olds and achieving at least 90% coverage of 3 doses of HBV vaccine (HepB3). In addition, universal infant HBV vaccination is recommended. This has been implemented in Belgium since 1999, with a catch-up at 12-years of age. In 2021, the vaccine coverage in Belgium was estimated to be 97.1% in 18–24-month-old children. We previously showed that HBsAg positivity alone overestimates the HBV prevalence and hepatitis B core antibody (anti-HBc) confirmatory testing should be performed in low-endemic countries. In this nationwide serosurvey, we evaluated Belgium's progress to reach the WHO elimination targets and assessed the impact of the national vaccination strategy by systematically analyzing HBsAg, anti-HBc and hepatitis B surface antibodies (anti-HBs).
Method: A total of 4968 individual residual serum samples were collected from ambulatory patients at 10 private diagnostic laboratories in Belgium – geographically representing the whole country – during Q2/Q3 2020 (outside COVID-19 lockdown). The number of samples in each laboratory was stratified per region, age group (10-year age bands) and sex. HBsAg, anti-HBs and anti-HBc were analyzed on the Abbott Alinity I. The samples were weighted by comparing sample and population frequencies by sex, 10-year age band and province. Quantifiable anti-HBs titers (limit of quantification (LOQ) = 2 IU/L) were evaluated as a proxy for HBV vaccine uptake, therefore not taking into account natural waning of vaccine-induced antibodies and residual HBV immune memory.
Results: HBsAg was detected in 2/89 (2.2%) samples from children aged ≤5 years. Both samples were anti-HBc negative (<1 S/CO), corresponding to the absence of chronic HBV infection. In our study, 2336 of the 4968 (47.0%) samples were HBsAg and anti-HBc double negative and had a quantifiable anti-HBs titer, indicative of prior HBV vaccination. Weighted analysis estimated a vaccination degree, based on anti-HBs >LOQ, of minimum 47.2% (95% CI 45.5%–48.8%) for the Belgian population. This was significantly higher in the younger age groups. More specifically, the weighted proportion with anti-HBs titers >2 IU/L was significantly higher ($p < 0.001$) in the ≤33-year-olds (71.5%, 95% CI 69.1%–73.7%) compared to the >33-year-olds (31.2%, 95% CI 29.2%–33.2%), which is in line with the Belgian vaccination policy implemented in 1999.
Conclusion: In this population-based nationwide serosurvey, none of the samples of ≤5-year-olds were HBsAg and anti-HBc double positive. At least 71.5% (95% CI 69.1%–73.7%) of the age cohort subject to the universal vaccine program had quantifiable anti-HBs titers. These results reinforce that Belgium is on track to reach the 2030 WHO HBV elimination targets.

WED-019

Direct measurement of incidence and prevalence of Hepatitis C infection using the gold-standard of prospective HCV re-testing of people at risk. A national needs assessment of people who inject drugs and of all people who use addiction services in England

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Background and aims: In England, it is recommended that people who inject drugs (PWID) attending addiction services are tested regularly for hepatitis C virus (HCV) infection following an assessment of infection risk. There is divergent practice as to what constitutes 'risk of infection' and testing frequency. Accurate information on the current prevalence in all people attending addiction services is essential for planning future HCV programs. A proportion of PWID do not attend addiction services. We assessed the needs of these populations by direct measurement of incidence and prevalence.
Method: Prospective HCV antibody (AB) and RNA testing & retesting of people at high risk either in addiction services or outside of structured treatment. Additional variables collected included post-code, age, gender, reason attending services, engagement with structured treatment and awareness of infection. Analyses were conducted using SPSSS 28.
Results: In autumn 2022, 11,020 people were tested for both HCV antibodies and RNA in a period of 6–8 weeks in >200 locations in all English regions. Testing took place in over 150 addiction services as well as the community, needle exchanges, soup kitchens, hostels, and the streets, using trained outreach teams of nurses and people with lived experience to identify people not engaged with structured services. Every living person was offered re-testing in 2023–24, even if relocated or incarcerated. In addiction services, prevalence of chronic HCV infection was significantly different between PWID (10.9%, 95% CI [10.0–11.9%]) and other clients (1.8%, 95% CI [1.4–2.2%]), $p < 0.001$. As expected, prevalence was higher in PWID outside structured treatment compared to those who were engaged with a service in the previous 12 months (15.9%, 95% CI [13.6–18.4%]). Prevalence was significantly higher in people who had been tested previously in the last 12 months in all groups and in all settings, $p < 0.001$. The highest prevalence was in a subgroup or people who had not engaged with treatment in the previous year but who had -nonetheless- been tested for HCV in the previous year by an outreach team (25%, 95% CI [19.4–31.3%]). Testing frequency and age were equally distributed in both gender groups. Virus clearance increased with age and was higher amongst women and people attending services. 6,000 people had a valid follow-up HCV test, and the preliminary annual incidence value based on the paired tests is 1.85 per 100 in all PWID.
Conclusion: This is the first direct measurement of incidence amongst at risk groups in England, with a large initial sample and extensive location coverage. Prevalence is higher with testing frequency, highlighting the programme's robust HCV testing structures and the holistic person-centred approached delivered by multidisciplinary teams inside and outside structured treatment. Incidence figures indicate that this World Health Organisation target has already been reached.

WED-020

Mind the gap - addressing inequitable hepatitis D testing in Wales

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Background and aims: Hepatitis D (HDV) infection only occurs in those with concurrent Hepatitis B (HBV), as HDV lacks the ability to replicate in the absence of co-infection The true prevalence of hepatitis D infection in Wales is unknown. It is important to identify coinfected patients as treatment is now available targeting HDV. EASL, AASLD & NICE all recommend screening for HDV infection. Wales has a population of 3.2 million of whom approximately 3000 have HBV infection. Clinical care of those living with infectious hepatitis is provided by a variety of specialties in six health boards. However, laboratory diagnostic services are centralised and performed at just two sites by one organization, Public Health Wales (PHW). At present HDV Ab testing must be requested by the reviewing clinician. Samples returning a positive HDV Ab result require an additional request for HDV PCR to ascertain whether there is ongoing infection. These processes introduce potential missed/delayed opportunities for diagnoses. We used the PHW laboratory network to identify those with hepatitis B surface antigen (HBsAg) positivity and ascertain what proportion by health board had HDV Ab testing performed. If poor compliance with hepatitis D testing was shown we planned to instigate reflex testing for HDV infection in all those that are HBsAg positive to improve compliance with guidance and identify more patients who may benefit from treatment.
Method: An all-Wales laboratory integrated management system managed by PHW called Datastore was used to extract all HBsAg positive samples that tested positive from 12/01/2015–06/04/24 and all hepatitis D requests in the same period.
Results: 3000 people over 9 years were identified as HBsAg positive. 35% had at least one HDV Ab test performed, leaving 65% of those identified with HBV infection in Wales, never having had HDV screening. Further interrogation of the data demonstrated wide variation in testing by health board. The best performing health board had tested 45% of all HBsAg positive patients compared with one health board only having tested 23.5%. Furthermore, of those that were identified as HDV Ab positive, 28% had no record of going on to have HDV PCR testing performed at any time.
Conclusion: This piece of work has demonstrated the importance of standardized operating procedures in diagnostics to ensure equitable care irrespective of patient location or clinical team specialism. Through this piece of work we have successfully, as of September 2024 bought in reflex testing of all HBsAg positive samples for HDV Ab on at least one occasion. Additionally, we have gone on to ensure reflex HDV PCR testing in all those samples that test positive for HDV Ab. We plan to review our data one year (Sept 2025) from instating this change in practice. By this time, all those that have had a positive HBsAg living in Wales, who are accessing care will have had reflexive HDV Ab testing and HDV PCR testing, where indicated. The availability of bulveritide, highlights the value of prompt, effective HDV testing.

WED-021

Emergency department screening and linkage to care for undiagnosed hepatitis C infection: an effective initiative to reach elimination targets

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Background and aims: NHS England has set a target to eliminate Hepatitis C (HCV) by 2025. As part of elimination efforts, selected emergency departments (ED) have been implementing opt-out blood-borne virus (BBV) testing including HCV since April 2022. We describe how BBV testing in three Southeast London NHS Trusts has helped identify hard-to-reach patients, initiate them on treatment and achieve sustained virologic response (SVR).
Method: Patients seen in EDs in Southeast London with a reactive HCV antibody result and a positive reflex-tested HCV RNA or HCV core antigen between November 2022 to June 2024 were identified. Telephone contact was attempted with all patients and those accepting were offered follow-up and direct-acting antiviral (DAA) treatment. The clinical data and treatment outcomes were collected.
Results: In the 20-month period, 226,517 hepatitis C antibody tests were performed, and 303 unique patients had a positive diagnosis of HCV. 169 (55.8%) were new diagnoses. The median age was 53 years (IQR 43–64) and 207 were male (68.3%). 28 patients (9.2%) were clinically cirrhotic on presentation, 2 patients subsequently died of decompensated liver disease. 4 patients presented with hepatocellular carcinoma (HCC), and all have subsequently died. In addition, 38 patients have also died from non-liver related causes. Of the 303 patients identified, 164 patients (54.1%) have been initiated on treatment with 107 patients having confirmed SVR at time of writing. A further 39 patients have completed treatment awaiting SVR confirmation. 16 patients with confirmed SVR were diagnosed in ED but subsequently completed treatment in other non-hospital settings. It was established that 52 patients (17.2%) had no fixed abode or were in temporary accommodation, of whom 19 patients achieved SVR following an ED diagnosis.
Conclusion: ED screening effectively identifies new diagnoses of HCV infection; indeed 55.8% of HCV diagnoses here were in patients who had not been tested before. Many of these individuals did not have standard risk factors for infection and would not have been covered by other screening programmes. Overall, of those linked into treatment, a high SVR rate is seen. A significant proportion of those diagnosed in ED were individuals without permanent residence but more than a third of these were still successfully linked into treatment and SVR. Barriers remain to linkage after an ED diagnosis; 45% of patients here were not linked and efforts are ongoing to engage with these patients and understand the barriers. Nonetheless, as we work towards elimination, ED testing has been a successful and powerful initiative to diagnose and cure patients with HCV.

WED-022

Automated universal testing for hepatitis B in the emergency department improves screening and characterises the undiagnosed and untreated cohort in an australian setting

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Background and aims: Untreated chronic hepatitis B (HBV) infection causes cirrhosis and hepatocellular carcinoma (HCC), concerning for those with HBV who remain undiagnosed and/or not linked to care. Migrant populations with higher HBV prevalence may encounter

unique barriers to routine health care. This study aimed to evaluate the utility of an automated, universal HBV screening service in the emergency department (ED) setting. Prevalence and characterisation of unmet needs are reported.

Method: SEARCH-3X (Screening of Emergency Admissions at Risk of Chronic Hepatitis-Extension 3) is a novel pilot clinical service which was feasibility tested across 4 four metropolitan EDs in Sydney, Australia. 5000 patients were tested per site. A computer algorithm automatically triggered HBV surface antigen (HBsAg) testing in all biochemistry blood tubes collected as part of routine care in the ED. Data were collected on patient demographics, HBV prevalence and HBV clinical care. South Western Sydney Local Health District Human Research Ethics Committee approval number is 2022/ETH01158.

Results: A total of 19,607 adult patients were tested, of whom 183 (0.9%) were HBsAg positive. Linkage to care has been successful in 175/183 (95.6%). Over half of the HBsAg positive group were male (54.1%). Median age at time of testing was 58.3 years (IQR 47.5–70.0). HBsAg was more likely to be positive in those ≥40 years old (1.1%) compared to those aged 18–39 (0.2%), $p < 0.00001$. Overseas born (OB) patients were more likely to be HBsAg positive than Australian born patients (1.6% vs 0.2%, $p < 0.00001$). Indigenous Australians were more likely to be HBsAg positive compared to non-Indigenous Australians (0.7% vs 0.1%, $p = 0.009$). Prevalence of HBsAg varied greatly according to country of birth; countries with the highest prevalence were Cambodia (8.8%, 19/215), Tonga (6.8%, 8/117), Vietnam (5.6%, 53/940), Sudan (5.5%, 3/55), Malaysia (4.3%, 3/70), China, (4.1%, 25/608), Myanmar (4.0%, 2/50), Thailand (4.0%, 3/76), Jordan (3.9%, 3/77), Hong Kong (3.6%, 2/55) and Cyprus (3.3%, 3/92). The prevalence of HBV in OB patients ranged from 0.6% in younger patients aged 18–24 up to a maximum of 2.5% in those aged 50–59. A new diagnosis of HBV was made in 23.4% (41/175) of patients. HBV monitoring had been conducted in 67.2% (90/134) of those with known HBV within the past 12 months. 50.9% (55/108) of those with known HBV and an indication for HCC surveillance had undergone surveillance within the preceding 12 months. There were no patient complaints and ED throughput was unaffected.

Conclusion: Automated testing for HBsAg in the ED is easy and effective. Universal testing in EDs with a high migrant population detects significant rates of infection, often in patients who were not aware of their HBV diagnosis or whose care was suboptimal. The OB and/or indigenous Australian cohort has higher HBsAg prevalence and appears to be the one to focus on for universal testing.

WED-023

Three-year evaluation of retention in specialist care among migrants and refugees living with HBV in Catalonia following a community-based intervention

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Background and aims: People born in countries with intermediate or high prevalence of HBV are at higher risk of acquiring this infection due, in part, to a scarcity of effective prevention and screening strategies in their countries. Upon migration, these individuals face additional barriers to access and navigate their host health system, delaying their diagnosis and care opportunities, in turn hindering their capacity to be treated and retained in care. This study aims to evaluate the retention in care of migrants and refugees living with HBV, following screening in community-based settings.

Method: From 11/2020 to 12/2023, the HBV-COMSAVA pilot study was implemented in Catalonia, Spain to offer decentralized screening for HBV in 61 screening interventions in community and faith-based spaces. A field team of community workers and nurses used HBsAg rapid diagnostic tests and plasma separation cards (PSCs) to test for HBV. Expedited referral pathways for positive participants to collaborating tertiary hospitals were provided. Data on patient´s baseline, follow-up, and retention in care, including HBV treatment, were collected.

Results: Among 830 people screened; 70 (8.4%) had a HBsAg positive RDT result by rapid point of care test and were referred to a collaborating hospital. Of the 56 (80.0%) participants with a documented first visit with a specialist, 47 had retention in care information available. Of these, seven (14.9%) did not return for additional visits. The majority of HBsAg+ participants were men (85.1%), mean age of 40.9 years and HBeAg negative (95.2%). Most patients were from Ghana (78.7%, N = 37) and Senegal (17.0%, N = 8). The median number of specialist care visits were two (IQR = 2–4), with a mean follow-up time of 14 months. Three (6.4%) people were eligible for antiviral treatment, of which two initiated and adhered to Nucleoside Analogue (NUC) treatment. Median HBV DNA and ALT levels were higher among those with treatment indication than those without, 61,000 UI/mL vs. 287 UI/mL, and 38 U/L vs. 31.5 U/L, respectively. Two (4.3%) participants were identified as false positives for an active HBV infection, and were positive for anti-HBc. Among the remaining, upon finalization of the follow-up period, eleven (23.4%) were still in follow-up care, while 21 (44.7%) were lost to follow-up.

Conclusion: Community-based strategies for screening of viral hepatitis infections were effective in increasing HBV diagnosis among migrants and refugees; however, linkage and retention in care was found to be a major challenge despite expedited referral processes. Additional strategies to enable successful linkage and retention in care must be explored to reduce loss to follow and improve health outcomes.

WED-024

Linking community-based organizations and specialized prescribing pharmacist teams to improve testing and treatment in hard-to-reach hepatitis C-infected groups: the LiveRx experience in Alberta, Canada

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Background and aims: LiveRx is a research project funded through Alberta Innovates with the goal to develop community-focused approaches to address significant hepatitis C (HCV) testing and treatment gaps in underserved populations who do not/cannot access traditional healthcare models in Alberta, Canada, including people who are Indigenous, houseless, use drugs, or live in rural/remote areas. LiveRx leverages the *Alberta Primary Care HCV Testing/Treatment Pathway* (www.albertahealthservices.ca/assets/about/scn/ahs-scn-dh-pathway-hepatitisc.pdf) to enhance links between community-based pharmacies and community-based organizations (CBOs – including health programs and not-for-profit organizations) to identify, test, treat, retain in care, and ultimately cure HCV-infected individuals in their local communities.

Method: Community pharmacists with medication prescribing authorization and an interest to be trained in treating HCV, who worked in pharmacies recognized as providing safe environments for underserved populations were identified through collaborative discussions with CBOs and individuals with lived experience. LiveRx pharmacists received training through tailored HCV e-modules and in-person workshops co-developed by the International Network on Health and Hepatitis in Substance Users (INSHU) and LiveRx for HCV screening (point of care [POCT], diagnosis, direct acting antiviral [DAA] prescribing, and follow-up care). LiveRx staff, hepatologists, and pharmacy consultants provided support for HCV screening and treatment through pharmacist case-finding, referrals and community/peer outreach.
Results: A total of 20 LiveRx pharmacies screened 700 patients for HCV via POCT and 116 individuals (16.6%) were found to be HCV antibody reactive (Ab +ve). Additionally, 38 HCV Ab +ve patients were identified through pharmacy record case-finding. HCV RNA testing was obtained for 103 of these HCV Ab +ve cases, 44 via Dried Blood Spot Testing (DBS) and 59 via phlebotomy, with 61 HCV RNA +ve cases (59.2%) identified. Notably, 14.8% of identified individuals were previously documented to be HCV Ab +ve and 49.6% HCV RNA +ve but were never successfully linked to treatment. DAA therapy was initiated by LiveRx pharmacists for 58 individuals (95.1%) and 51 (87.9%) completed treatment. 33 treated individuals (64.7%) had post-treatment HCV RNA testing for sustained virologic response (SVR), with a 100% SVR rate. Two deaths occurred during treatment, unrelated to HCV treatment.
Conclusion: Collaborations developed through LiveRx between community-based pharmacies and CBOs facilitated high rates of identification and successful linkage to care/ treatment of HCV-infected individuals within groups that are historically very challenging to treat. Wider implementation of similar pharmacist-CBO HCV care models may enhance achieving HCV elimination goals.

WED-025

Engaging hard-to-reach individuals through community-based holistic care health and wellness fairs linked to HCV testing and treatment in Alberta, Canada

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Background and aims: In Alberta, Canada, an implemented primary care hepatitis C (HCV) pathway (www.albertahealthservices.ca/assets/about/scn/ahs-scn-dh-pathway-hepatitisc.pdf) and well-defined screening strategies have increased diagnosis of hepatitis C (HCV). However, linking diagnosed individuals to treatment remains challenging, especially in those with unmet complex healthcare needs related to persistent, social, economic, and systemic structural barriers including lack of connection to traditional healthcare pathways. The LiveRx program was created to address this care gap by exploring alternative ways to better link highly marginalized to HCV testing and treatment.
Method: To do this LiveRx designed/ implemented health and wellness fairs as part of a novel HCV care model co-developed with engaged community-based organizations (CBOs). The goal was to foster connection of attendees to existing but difficult to access support services/programs including housing, addictions, mental health, foot/wound care, diabetes care, cultural support, STI testing/ treatment, vaccination and women's health under one roof, as well as point-of-care (POCT) HCV antibody (Ab) and HCV RNA testing with direct on-site linkage to pharmacist direct acting antiviral (DAA) prescribers for positive cases.
Results: 1591 individuals were engaged through ten health and wellness events conducted in 7 small and large communities across Alberta, Canada between January 2023-October 2024 (9 of 10 occurred in 2024). A total of 224 organizations/ programs were engaged across the 10 events. 1054 (66%) of attendees underwent POCT HCV Ab testing and 139 (13%) were HCV Ab +ve (69 [49%] were previously known to be HCV Ab +ve but had not been linked to treatment); 113 (81%) had HCV RNA testing and 38 (33%) were RNA +ve. Of these 38 individuals 36 were linked to post-test counselling and a pharmacist DAA prescriber at the event. 10 of these 36 (28%) initiated DAA treatment with 6 completing therapy and 2 having a documented SVR to date.
Conclusion: Health and wellness fairs are an effective strategy to engage individuals from underserved populations in an inclusive, non-stigmatizing, and culturally appropriate venue that removes barriers to access to healthcare services, filling an unmet public health need. Bundling HCV testing/ treatment access with other priority health and wellness services led to high HCV testing rates (66%) and identified significant HCV Ab (13%) and RNA (33% of Ab +ve cases) positivity rates. 95% of HCV RNA +ve cases were linked to a DAA prescribing LiveRx pharmacist at the event, and ~30% have started therapy.

WED-026

Development of a predictive model using artificial intelligence (AI) for the detection of hepatitis C based on real-world data from the population health database (BPS) of Andalusia, Spain

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Background and aims: The 2016–2021 WHO strategy aimed to significantly reduce hepatitis C as a public health threat by achieving a 90% reduction in new infections, a 65% reduction in hepatitis C-related deaths, and treating 80% of detected cases by 2030. Reaching vulnerable populations remains challenging, and age-based screening has been controversial. In the AI era, developing predictive models can aid clinicians in identifying hepatitis C cases, optimizing the effort required for successful screening.
Method: Using real-life data from the Andalusian Health Population Database (BPS), containing electronic medical records of over 15 million patients, we trained a predictive AI model to identify undiagnosed hepatitis C cases. Several machine learning methods were evaluated, with XGBoost (eXtreme Gradient Boosting) proving the most accurate. The model was trained using 6,078 patients diagnosed with hepatitis C from 2017 to 2022, alongside a control group of 121,560 individuals with similar characteristics who tested negative for hepatitis C.
Results: The model successfully identified 84% of all hepatitis C patients with a sensitivity of 0.15, despite class imbalance simulating a real-world scenario. This significantly outperformed the conventional detection strategy, which achieved a sensitivity of only 0.007. The model selected various informative variables for prediction, including different hepatitis C analytical tests and comorbidities, listed in the table. The developed model identified one case for every six individuals selected, whereas the conventional risk group strategy required evaluating 143 people to find one case.
Conclusion: The developed predictor constitutes a cost-effective and highly accurate screening model using already available patient data in the healthcare system, clearly outperforming conventional risk

group-based or age-based screening. This model could aid early detection and potentially boost regional efforts aimed at eliminating hepatitis C.

WED-027-YI

Changes in hepatitis C virus screening and treatment rates in pregnant individuals before and after implementation of universal screening guidelines compared to hepatitis B virus screening during the same time frame

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Background and aims: Hepatitis C virus (HCV) incidence has doubled since 2013 among individuals of reproductive age. In contrast, Hepatitis B virus (HBV) rates have remained stable. As a result, HCV screening recommendations have changed drastically. In Aug 2017, the Society of Maternal Fetal Medicine (sMFM) recommended HCV screening for high-risk pregnancies, followed by universal screening in March 2020 by the United States Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) in May 2021. Universal HCV screening improved detection, but not linkage to care within a year postpartum. HBV screening was recommended by the USPSTF in 1996 and supported in the recent 2023 ACOG guidelines. This study aims to assess adherence to universal HCV and HBV screening during pregnancy and its impact on postpartum treatment.
Method: Retrospective analysis of pregnant adult patients who received their first prenatal visit at two centers within our institution between Jan 1, 2013–Oct 1, 2023. HCV screening was defined as HCV-antibody (Ab) testing, and HBV screening was defined as HBV-surface antigen (HBsAg) testing. HCV-Ab, HBsAg, and HCV/HBV viral loads were extracted from electronic medical records. Patients were grouped into 3 screening phases (SP): SP 1 – before risk screening (Jan 1, 2013–Aug 1, 2017), SP 2 – after sMFM risk screening but before ACOG universal screening (Aug 2, 2017–May 1, 2021), and SP 3 – after ACOG universal screening (May 2, 2021–Oct 1, 2023). For patients with positive HCV-Ab/HCV viral load or HBsAg, charts were reviewed to assess linkage to care and treatment within 1-year postpartum.
Results: Of 31,927 patients, 6,713 (21%) had HCV-Ab testing. 1% (111/11,414) in SP1, 16.6% (2,085/12,594) in SP2, and 57% (4,517/7,919) in SP3. 40 were HCV-Ab positive (0.6%), with 35 (87.5%) undergoing HCV RNA testing; 5 of which were positive. All 5 were linked to an HCV provider, but none received treatment within 1-year postpartum; 1 was treated after that period. For HBV screening, 28,759/31,927 (90.1%) patients had HBsAg ordered. Screening rates were 84% (9,587/11,414) in SP1, 92.7% (11,671/12,594) in SP2, and 94.7% (7,501/7,919) in SP3. Only 60.2% of patients who had testing ordered completed screening. Of those, 49.2% (4,715/9,587) in SP1, 66.9% (7,813/11,671) in SP2, and 63.7% (4,779/7,501) in SP3 were screened. In total, 23 patients tested positive for HBsAg, two of whom had known HBV and were already under hepatology care. Of the remaining 21, 15 were appropriately linked to care.
Conclusion: HCV and HBV screening increased with each screening phase, though both remain suboptimal. While patients with positive HCV viral loads were linked to care, treatment initiation was rare. In contrast, HBV screening recommendations were high, but many patients did not complete testing, and nearly 30% of those with positive HBV results were not linked to care.

WED-028

Hepatitis B surface antigen clearance rate achieved with pegylated interferon-alpha therapy in different chronic hepatitis B virus infection populations: a systematic review and meta-analysis

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Background and aims: The clearance or seroconversion of hepatitis B surface antigen (HBsAg) serves as a critical marker of functional cure in patients with chronic hepatitis B (CHB). HBsAg clearance can significantly reduce the risk of CHB progressing to end-stage liver disease. Currently, Pegylated interferon- alpha (PegIFNα)-based therapy is recognized as the most effective approach to enhance HBsAg clearance in CHB patients. HBsAg clearance rates may differernt among different natural course of infection, treatment and special patient populations. This study aims to thoroughly analyze HBsAg clearance and seroconversion rates in different chronic hepatitis B virus (HBV) infection treated with PegIFNα, accounting for multiple influencing factors.
Method: We conducted a systematic review and meta-analysis, searching PubMed, Embase, Web of Science, and the Cochrane Library up to December 6, 2023, for studies on HBsAg clearance or seroconversion in HBV treated with PegIFNα, excluding co-infections. Independent quality assessment, data appraisal, and extraction were performed by trained reviewers. We systematically analyzed and summarized demographic characteristics, HBsAg clearance, and seroconversion rates across chronic HBV populations, exploring heterogeneity through subgroup analyses and meta-regression. This study protocol was registered with PROSPERO, CRD42024604070.
Results: Out Of 4867 screened, 121 studies met the inclusion criteria, with 115 of these included in the meta-analyses. The overall rate of HBsAg clearance following PegIFNα-based therapy in chronic HBV infection was 16% (95% CI 13%–20%). Notably, there were differences in the efficacy among different HBV infected populations. The HBsAg clearance rate at the end of PegIFNα-based treatment in treatment-naive CHB patients, Nucleos(t)ide analogues (NAs)-treated CHB patients, inactive HBsAg carriers and children with CHB were 5% (95% CI 4%–7%), 21% (95% CI 16%–26%), 57% (95% CI 48%–65%), and 22% (95% CI 10%–37%), respectively. Subgroup and meta-regression analysis identified that the year of publication, study design, sample size, HBeAg status, treatment strategy, treatment duration, and follow-up duration were key factors influencing HBsAg loss and seroconversion.
Conclusion: Different populations with chronic HBV infection exhibit varying potentials for HBsAg clearance following PegIFNα treatment. These notable differences underscore the complexity of managing chronic HBV infection and the need for personalized treatment strategies tailored to each group's unique characteristics and circumstances.

WED-029

Patient-reported outcomes measuring an individual's overall self-rated health after long-term treatment with bulevirtide 2 mg for chronic hepatitis delta in the phase 3 MYR301 trial

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Background and aims: Chronic hepatitis delta (CHD), the most severe form of viral hepatitis, leads to worse patient physical and psychologic quality of life compared with chronic hepatitis B. Patients with CHD who received 48 weeks (W) of bulevirtide (BLV) 2 mg monotherapy reported greater improvements in their perceived health status compared with patients who received no treatment. This study reports an exploratory analysis of EQ-5D visual analogue scale (EQ VAS) outcomes at 144W of BLV 2 mg treatment among patients with CHD in an ongoing clinical investigation.
Method: Patients in this study (n = 150) were enrolled in MYR301 (NCT03852719), a Phase 3, randomised (1:1:1), multicentre, open-label, parallel-group trial. Treatment groups received either BLV 2 mg once daily (QD; n = 49) or BLV 10 mg QD (n = 50) for 144W, or delayed treatment for 48W followed by BLV 10 mg QD for 96W. This study focuses on BLV 2 mg, which is approved by the European Medicines Agency (and other agencies in non-European countries). Patients completed the EQ VAS on their own at key time points, including baseline (BL), 24W, 48W, 96W, and 144W. High scores on the EQ VAS (range, 0–100) reflect the patients' best perceived imaginable health state. Mean (95% confidence interval [CI]) scores and least squares mean (LSM) changes from BL are reported; changes from BL where the 95% CI included 0 were considered not statistically significant. Subgroup analyses of patients by cirrhosis status at BL are also reported.
Results: Patient characteristics and mean EQ VAS scores (range, 72.0–73.9) were similar between treatment groups at BL. By 144W, 12 patients dropped out of the study, with no discontinuations due to study treatment. For patients who received BLV 2 mg (n = 44 at W144), the mean (95% CI) EQ VAS score at W144 was 85.5 (81.14–89.91); LSM (95% CI) score improvement from BL to W144 was 12.1 (7.32–16.87) and was considered statistically significant. LSM (95% CI) EQ VAS score improvement from BL reported at W144 of BLV 2 mg treatment was greater than the LSM improvement from BL to W48 and W96. Among patients with cirrhosis, LSM (95% CI) EQ VAS score improvement from BL to W144 (12.5 [5.32–19.61]; n = 21) was considered significant and was greater than the LSM improvement from BL to W48 and W96. Likewise, for patients without cirrhosis, LSM (95% CI) EQ VAS score improvement from BL to W144 (11.8 [5.20–18.39]; n = 23) was considered significant and was greater than corresponding scores at W48 and W96.
Conclusion: Patients with CHD with and without cirrhosis who were treated with BLV 2 mg for up to 144W reported improvements in their perceived health state compared with BL. These improvements were greater than perceptions reported at both 48W and 96W of treatment, demonstrating the long-term benefits of BLV monotherapy.

WED-030

Trends in the effect of direct acting antivirals on mortality in people diagnosed with hepatitis C in England using routine surveillance data

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Background and aims: With fewer side-effects and higher cure rates, direct acting antivirals (DAAs) transformed the clinical management and epidemiology of hepatitis C virus (HCV) infection. We aimed to compare mortality between treated and untreated individuals diagnosed with HCV and to describe trends in adult life expectancy (LE) between these populations.
Method: Data come from routine surveillance of HCV in England, and cause of death information from the UK Office for National Statistics. Individuals contributed person-time to the analyses from their fifteenth birthday or their earliest HCV diagnosis date, whichever was later. Individuals were classified as treated six months after their most recent treatment date. Estimates of adult LE were computed using continuous-time survival analysis as the area under the Kaplan-Meier survival curve. The analysis was split into two four-year periods (2015–18 and 2019–22). 2015–2018 represents the early DAA era when treatment prioritized advanced liver disease. The four-year period reduced the influence of mortality changes in any single year and combined sufficient data to stratify analyses, allowing us to decompose total LE difference due to treatment into contributions from mortality differences in five-year age groups. Age group contributions were calculated using the Arriaga method. Using cause-specific mortality fractions, we estimated the cause contributions to treatment differences in adult LE for each age group. Analyses were performed separately for each period.
Results: Between 2015 and 2022, 93,024 adults diagnosed with HCV were included in the analyses. They contributed 322,397.8 untreated and 200,564.1 treated person-years of observation. In 2015–18, there were 5,812 deaths resulting in a crude death rate of 22.4 (21.2–23.6) per 1000 person-years among untreated females, 27.5 (26.7–28.4) among untreated males, 16.7 (14.3–19.4) among treated females and 24.3 (22.4–26.4) among treated males. In 2019–22, there were 7,486 deaths resulting in a crude death rate of 25.6 (24.1–27.2) among untreated females, 30.0 (28.9–31.2) among untreated males, 17.9 (16.7–19.1) among treated females and 24.9 (24.1–25.9) among treated males. These differences translated into 8.5 years LE advantage for treated females and 8.9 years for treated males in 2015–18. This contracted in 2019–22 for both sexes to 6.7 and 5.2, respectively. This contraction was explained by a reduction in mortality rates between 25–65 years for the untreated population and reduced differences in mortality from liver related causes between the treated and untreated.
Conclusion: LE was higher for treated compared to untreated individuals. The effects of treatment on mortality shrunk between the two periods studied, but LE remained significantly higher for the treated. We hypothesize that the early prioritization of individuals with advanced cirrhosis resulted in a relatively healthier untreated population in 2019–2022 compared to 2015–2018.

WED-031

Healthcare resource use (HCRU) and cost impact of potential drug-drug interactions (DDIs) among HCV patients receiving Direct-Acting Antivirals (DAAs) concomitantly with antipsychotic drugs in the US

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Background and aims: Scarce information exists in the US regarding the use of Direct-Acting Agents (DAA) concomitantly with antipsychotic drugs in HCV patients. We explored the use of antipsychotic drugs in a US claims database concomitantly with the use of any of the two pangenotypic DAAs, sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (GLE/PIB), evaluating the risk of associated

DDIs, quality of the prescriptions based on the DDI risk, and the related healthcare resource use and costs.
Method: A retrospective cohort study was conducted using IQVIA PharMetrics Plus claims database from July 2015 to June 2023 for HCV patients treated with SOF/VEL or GLE/PIB concomitantly with antipsychotic drugs. We assessed the quality of prescriptions by evaluating the risk of DDIs using the Liverpool DDI tracker (https://www.hep-druginteractions.org/) and calculating the proportion of patients prescribed DDI-related comedications (DDIRC) classified as clinically significant. All-cause HCRU and costs (per patient per month (PPPM)) were assessed over a 6-month follow-up period starting from the initiation of DAA therapy. These outcomes were compared between SOF/VEL and GLE/PIB cohorts, created using 1:1 propensity score matching without replacement. Mean costs were analyzed using Generalized Gamma regression.
Results: Patients on antipsychotics represented 3.7% (420/11,324) of the total HCV cohort, 3.9% (267/6,784) treated with SOF/VEL and 3.4% (153/4,540) with GLE/PIB. 95% patients received only one antipsychotic during the DAA therapy, but 5% (23) received >1 (14 in SOF/VEL and 9 in GLE/PIB), indicating multi-DDI risk. Among the 267 SOF/VEL patients, DDI risk was present in 39 patients (14.6%; 1.5% for clinically significant DDIs (CSDDI) and 13.1% for weak DDIs (WDDI). For the 153 GLE/PIB patients, 100% were on DDI risk (83.7% for CSDDI and 19% for WDDI). The matched SOF/VEL and GLE/PIB cohorts concomitantly receiving antipsychotics, each comprised 142 patients. All matched patients incurred HCRU, with the majority attributed to pharmacy visits (242 patients) and outpatient visits (22 SOF/VEL patients and 26 GLE/PIB patients). All-cause costs PPPM were lower for SOF/VEL patients ($39) compared to GLE/PIB patients ($69); however, the difference was not statistically significant (P = 0.07). In contrast, when examining specific components of healthcare costs, patients prescribed SOF/VEL had significantly lower mean all-cause outpatient costs PPPM ($7) compared GLE/PIB ($29).
Conclusion: Despite the extended recognition of the use of the Liverpool HEP DDI tracker by all HCV treatment guidelines, this analysis of the DAAs based on the DDI risk demonstrates importance of safety monitoring of patients and the need for individualized medicine to ensure an appropriate DAA is used in patients with polypharmacy. Additionally, compared to GLE/PIB, SOF/VEL presents lower DDI risk and lower outpatient costs in the HCV patients receiving DAA treatment concomitantly with antipsychotic drugs.

WED-033
Treatment persistence, discontinuation, and health care cost among chronic hepatitis B (CHB) patients initiating antiviral treatment

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Background and aims: Nucleos(t)ide analogues are recommended as first-line monotherapy for patients with CHB. Little is known about treatment pattens and cost in a real world setting. This study describes CHB-related health care cost, persistence, discontinuation, switch, restart in treatment (TX)-naïve patients.
Method: This was a retrospective study using claims from the Optum Research Database for commercial and Medicare Advantage enrollees. TX-naïve CHB patients initiating tenofovir alafenamide fumarate (TAF), entecavir (ETV), or tenofovir disoproxil fumarate (TDF) between 01Nov2016 and 30Nov2022 were identified. Persistence was the time to discontinuation (therapy gap >30 days), switch, or end of follow-up. Adherence was the proportion of days covered (PDC) during the variable length follow-up. CHB-related cost included claims with a diagnosis of CHB and fills for CHB medications. Descriptives, Kaplan-Meier (KM), Cox PH and GLM models adjusting for demographics, clinical characteristics, and baseline cost and utilization were conducted overall and among patients ≥65.
Results: Of CHB patients identified (N = 14,935), 4067 treated adults and had 6 months baseline and follow-up enrollment. A total of 1384 TX-naïve patients met inclusion criteria. On index 338(24%) patients initiated TAF, 477(35%) ETV, and 567(41%) TDF. Age was ≥65 for 89 (26.3%) TAF, 146(30.6%) ETV, and 127(22.4%) TDF patients. From KM analysis, median persistence (months) was longest for TAF (23.3), followed by ETV (11.5) and TDF (9.2). Among patients 65+, median persistence was 38.0 (TAF), 9.0 (ETV) and 6.9 (TDF). Mean PDC was highest for TAF (0.75) followed by ETV (0.62) and TDF (0.54). Persistence was more likely to end due to discontinuation vs. switching; TAF: 49% vs. 7.4%; ETV: 60% vs. 3.6%; TDF: 64% vs. 7.6%. After discontinuation, most patients (56%-60%) restarted the index therapy. Compared to TAF, adjusting for covariates, the rate of discontinuation/switch was higher for ETV (HR = 1.34, p < 0.01) and TDF (HR = 1.62, p < 0.01). CHB-related medical cost were similar between the cohorts with costs 1% greater for ETV (Cost Ratio [CR] = 1.01, p = 0.98) and 28% lower for TDF (CR = 0.72, p = 0.14). Among patients ≥65, medical costs were 10% greater for ETV (CR = 1.10, p = 0.81) and 26% lower for TDF (CR = 0.74, p = 0.43). Pharmacy costs were lower for ETV (CR = 0.21, p < 0.01) and TDF (CR = 0.20, p < 0.01) compared to TAF overall and among patients ≥65 (ETV: CR = 0.13, p < 0.01; TDF CR = 0.17, p < 0.01).
Conclusion: Despite having greater pharmacy costs, TAF was found to have higher adherence, longer persistence, and similar medical cost versus ETV and TDF, especially among patients 65+ years old. These findings have clinical implications for patient engagement, therapy selection, and achieving long-term treatment success and should be considered when formulary decisions and exclusions are implemented as they may impact patient outcomes.

WED-034
Prevalence of HBV and HCV among migrants in EU-27: the impact of the ukrainian refugee crisis

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Background and aims: In countries with relatively low baseline burdens of hepatitis B and C viruses (HBV, HCV) but high levels of migration, the burden of viral hepatitis can be greatly impacted by migration. The screening and linkage to care of migrants requires different methods and sensitivities than a broad-based program. We aimed to estimate the prevalence of HBV and HCV among migrants in EU-27 countries in 2020. To consider recent trends, the Ukrainian refugee situation was also analyzed. These data can provide policy makers with guidance of which migrant communities are most in need.
Method: Using the United Nations 2020 migrant stock data, we were able to estimate the migrant population for each EU-27 country by five-year age and sex cohorts by country of origin. These five-year age and sex distributions were then cross-multiplied by five-year age and sex prevalence estimates in the country-of-origin models maintained by the Polaris Observatory. The total number of refugees from Ukraine recorded in-country was combined with the age and sex distribution of Ukrainian refugees undergoing health screening. These data were then multiplied the by the age- and sex-specific prevalence in the Ukrainian country models and added to the 2020 totals.
Results: In 2020, we estimate that there were 1.47 million (UI: 887,000–2.2 million) migrants living with HBV and 563,000 (UI: 395,000–879,000) living with viremic HCV in EU-27, corresponding to migrant prevalences of 2.68% (UI: 1.6–4.1%) and 1.02% (UI: 0.7–1.6%) respectively. The highest prevalence of HBV among migrants, 5.5%, was estimated to be in Portugal, but the largest absolute number of migrants living with HBV was in Germany, 399,000. For HCV, the highest prevalence among migrants, 1.98%, was estimated to be in

Lithuania, while the largest absolute number of migrants living with HCV was in Germany, 181,000. There was great heterogeneity in the leading country of origin for HBV and HCV prevalence in EU-27. Four counties had Syria as the country of origin with the most absolute number of migrants living with HBV and four countries had the Russian Federation as the country of origin with the most absolute number of migrants living with HCV. We estimate that the Ukrainian refugee situation resulted in an additional 37,800 people living with HBV and an additional 68,800 people living with HCV in EU-27 compared to the 2020 analysis. While these migrants only represent 3% and 12% increases relative to the 2020 HBV and HCV baseline estimates at the EU-27 level, respectively, they have a large impact on the HCV prevalence in certain countries.
Conclusion: Using the most detailed data — the 2020 UN estimates — and combining it with the impact of the Ukrainian refugee crisis would result in an estimated 1.5 million (UI: 910,800–2.3 million) migrants living with HBV, and 632,000 (UI: 451,000–969,300) migrants living with viremic HCV infection in EU-27.

WED-035

A National web self-testing portal for hepatitis C: an empowering solution with good uptake and linkage to care - preliminary data

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Background and aims: The advent of direct-acting antivirals (DAA) has changed the landscape of Hepatitis C virus (HCV) management. With curative treatments, the emphasis has changed to identifying the remaining obstacles/gaps in the HCV care cascade to achieve WHO elimination metrics. To deliver these by 2030, and the UK target of 2025, the HCV National Elimination Program in England has introduced a remote diagnostics tool (Preventx), alongside a media campaign, in order 'to bridge the gap' between individuals living with HCV and improve linkage to care. This strategy focuses on self-testing and patient empowerment. We report real world data of HCV of this self-testing tool as a component of the NHS England elimination strategy.
Method: We reviewed data from the national initiative of patient self-referral and self-testing for HCV. Individuals requested testing kits online, fingerpick blood samples were collected at home, returned freepost with results then delivered via text message. Positive results were then automatically linked to Operational Delivery Networks (ODNs). We cross referenced to our local (Southeast London and Kent [SEL+K]) HCV database to identify whether positive HCV test were truly new cases.
Results: Over a period of 16 months 77,791 tests were requested, 52,513 (67.5%) were returned for HCV testing. In the 730 tests (0.94%) which were antibody positive, 93 confirmatory tests were invalid and in the 637 with a confirmatory test only 145 (22.7%) were viraemic. Engagement was lower in London with 84 requests per 100000 population, compared 134 nationally and 117 in SEL+K. However, prevalence of HCV RNA positivity was 0.55% in London, 0.31% nationally, and 0.26% in SEL+K. Within our region of SEL+K there were 37 HCV Ab positive results. 29 patients were HCV RNA negative and 8 HCV RNA positive. Cross-referenced with our local registry showed that only 6 (21.7%) of the HCV RNA negative and only 1 (12.5%) of the HCV RNA positive patients had been previously identified. This suggests that the majority of positive test were new self-diagnoses. The majority of these RNA positive cases were male with median age of 48.1 years. Linkage to care is excellent with all HCV RNA positive individuals in appropriate care and commencing treatment.
Conclusion: Self-testing for HCV via a web portal was an acceptable initiative for testing with impressive test return rates. Initial data supports patient empowerment, and self-testing is key in identifying individuals with HCV and linking to treatment. We also demonstrate that the total numbers of new or previously not identified HCV RNA positive cases was relatively low, reflecting the success of the national HCV elimination program.

WED-036

The impact of cardio-metabolic risk factors on liver-related diseases and mortality after hepatitis C virus eradication: insights from a multi-center taiwanese cohort

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Background and aims: Chronic hepatitis C (CHC) patients frequently present with steatotic liver disease (SLD) and cardiometabolic risk factors (CMRFs). The long-term risk of major liver-related (LR) diseases and mortality following sustained virological response (SVR) remains unclear. This study aimed to evaluate the impact of CMRF grade and CMRF items on LR risks and all-cause mortality in SLD patients post HCV eradication.
Method: This study utilized nationwide multi-center registry cohorts in Taiwan, including an interferon-based cohort (T-COACH) and a direct-acting antivirals cohort (TACR). SLD was identified via ultrasonography and a hepatic steatosis index (HSI) > 36. Metabolic dysfunction-associated steatotic liver disease (MASLD) was defined as SLD with at least one of five CMRFs. Competing risks of death and liver transplant were considered to analyze the LR incidence using Gray's cumulative incidence method and Cox subdistribution hazards. Cox regression was used to analyze the all-cause mortality.
Results: Among 10,589 CHC patients, achieving SVR with SLD, 323 (3.1%) developed major liver-related diseases (HCC or decompensated liver cirrhosis) over a median follow-up of 3.8 years. Overall, MASLD patients did not exhibit a higher LR incidence or all-cause mortality compared than simple SLD patients. After adjusted for age, FIB-4 and eGFR, hazard ratios indicated that having at least three CMRF significantly increased LR risk (aHR = 1.83 for CMRF grade $\geq$3). Hypertension and diabetes was the two major CMRF increasing LR risk (aHR for hypertension = 1.65, P = 0.001; aHR for diabetes = 1.53, P = 0.011; aHR for both = 2.03, P < 0.001). Additionally, having more than three CMRFs, or having hypertension or diabetes significantly increased all-cause mortality with a 2.8-fold higher risk in patients with both hypertension and diabetes compared to these without these risk factors.
Conclusion: Targeted management of liver-related diseases and mortality is crucial for CHC patients with MASLD post-SVR, particularly for those with more than three CMRFs or with combined hypertension and diabetes.

WED-037

Hepatitis C knowledge and perceptions among Singapore's LGBTQ + Individuals: barriers and opportunities for outreach

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Background and aims: Singapore has a low general population prevalence of chronic Hepatitis C Virus (HCV) at 0.3–0.5%. The lesbian, gay, bisexual, transgender & queer (LGBTQ+) community may face higher HCV infection risks. This study examines the knowledge and perceptions of HCV within the LGBTQ+ community. We hope to use these results to inform and optimise targeted outreach and prevention programs effectively.
Method: Ethical approval (NHG DSRB Ref: 2023/00882) was obtained for this study. Participants were recruited via social media and Pinkdot Pride event on 29 June 2024. An anonymous online questionnaire assessed HCV knowledge and treatment attitudes as well as comparing responses across different LGBTQ+ groups to identify gaps to form targeted interventions.
Results: We recruited 95 participants with an estimated average age of 32.4, most having tertiary education (80%). The majority were male (56.8%), followed by female (29.5%), non-binary (5.3%), transmasculine (3.2%), transfeminine (3.2%), and others (2.1%). Sexual orientations included gay (45.3%), bisexual (17.9%), heterosexual (12.6%), lesbian (9.5%), others (9.5%), and asexual (5.3%). Overall, the awareness of HCV transmission through needles (89.5%) and sex (87.4%) was high but lower for tattoos (57.9%), with misconceptions about transmission via utensils (9.5%) and toilets (5.3%). Most participants would consider HCV testing (87.4%), preferring point-of-care testing over blood draws (64.2% vs. 35.8%). While 84.2% expressed willingness to seek treatment if a cure exists, cost (50.5%) was the top barrier, followed by side effects (40%) and stigma (8.4%). Stigma concerns included those from family and friends (66.3%), workplace (54.7%), public (37.9%), and healthcare workers (32.6%). Among the 47 gay, bisexual men, and transmasculine (GBT) participants, knowledge about HCV was higher compared to the non-GBT group. The GBT group was more likely to have heard of HCV (61.7% vs. 31.3%, $p < 0.05$), recognise it as an infectious disease (78.7% vs. 47.9%, $p < 0.05$), know it is curable (38.3% vs. 16.7%, $p < 0.05$), and identify oral medications as treatment (29.8% vs. 8.3%, $p < 0.05$). However, fewer GBT participants knew HCV could be diagnosed via body fluid investigations (27.7% vs. 54.2%, $p < 0.05$). These findings highlight critical areas for targeted education and intervention.
Conclusion: Among a predominantly LGBTQ+ population, gay, bisexual men, and transmasculine participants demonstrated greater HCV awareness, including its infectious nature and curability. Despite openness to testing and treatment, cost and stigma were significant barriers. These findings highlight the need for tailored outreach programs addressing financial and stigma-related concerns to support Hepatitis C elimination efforts within this community.

WED-038

The impact of COVID-19 outbreak from February to June 2022 on chronic hepatitis B patient management in Shanghai: a cross-sectional study

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Background and aims: The COVID-19 pandemic has posed significant challenges for individuals with chronic diseases, particularly those with chronic hepatitis B (CHB). These patients face interruptions in their ongoing antiviral treatment and regular follow-up, which can lead to HBV breakthrough and missed diagnosis of early-stage hepatocellular carcinoma (HCC). Our study highlights the impact of the COVID-19 pandemic on patients with CHB, as well as the responses of these individuals facing the health crisis during the special lockdown period in Shanghai, China, from February 28 to June 1, 2022.
Method: CHB outpatients in the Infectious Diseases Department of Shanghai Ruijin Hospital were invited to complete a structured questionnaire about the continuity of antiviral treatment and HCC surveillance during the pandemic, either online via the WeChat app or through a face-to-face interview. Descriptive statistics and logistic regression analysis were used for statistical analysis.
Results: A total of 487 respondents, receiving nucleos(t)ide analogs (NAs), interferon, or no antiviral treatment, were enrolled in our analysis. Among those taking antivirals, drug interruption occurred in 13.4% (58/434) of those on NAs and 57.8% (26/45) of those on interferon-based treatment. Telemedicine outpatient services of public hospitals (43.5%) was their main source of accessing NAs during the lockdown phase. Logistic regression analysis showed that interferon-based treatment and age were independently associated with drug interruption (OR = 8.346, 95% CI: 4.253–16.377, $p < 0.001$; OR = 0.968, 95% CI: 0.945–0.992, $p = 0.010$). Of all respondents, 71.3% reported delayed medical needs (accessing antivirals and outpatient reviews), with movement restrictions being the primary reason (88.5%) for the delays. After the lockdown was lifted, 3.7% of respondents were found to have developed hepatocellular carcinoma (HCC), 4.1% had abnormal liver function tests, 5.1% experienced HBV-DNA rebound, and 9.2% had not performed any outpatient reviews so far. Additionally, 48.4% of respondents had an interval of more than six months between two liver ultrasounds, with the COVID-19 pandemic being the leading reason (34.7%) for delayed HCC surveillance.
Conclusion: The COVID-19 outbreak negatively impacted the CHB outpatients care during the lockdown. Younger age and interferon-based antiviral treatment were identified as factors influencing the interruption of ongoing treatment, while sex, residential location, and comorbidities showed no significant correlation with treatment disruption. Measures like telemedicine services need to be implemented to meet the medical needs of patients with chronic diseases during future pandemics of emerging infectious diseases.

WED-039

A comparative study on liver disease severity and comorbidity profile in patients with chronic hepatitis B virus infection and hepatitis B virus/hepatitis D virus co-infection: a korean nationwide study

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Background and aims: This study aimed to describe and compare the baseline characteristics, comorbidities, liver disease severity, and antiviral treatment history for chronic hepatitis B virus (HBV) infection in patients with HBV/hepatitis D virus (HDV) co-infection and those with chronic HBV infection in Korea from 2014 to 2018.
Method: This nationwide retrospective cohort study analyzed claims data from the Korea Health Insurance Review and Assessment Service database between 2013 and 2019. Eligible patients were adults (≥18 years) with ≥1 inpatient or outpatient claims related to chronic

hepatitis B (CHB) (ICD-10 code B17.0, B18.0, and B18.1) between 2014 and 2018. Patients with hepatitis C-related claims were excluded. Patients with HBV/HDV co-infection were identified based on ≥1 claim for an HDV antibody test followed by ≥1 HDV-related claim, while patients with chronic HBV infection were identified as having no HDV-related claims, regardless of any HDV antibody test claims. Comorbidities and liver-related diseases were assessed based on claims during the 12 months prior to the index date, defined as the date of the first observed HBV-related claim for patients with chronic HBV infection or HDV-related claim after HDV antibody test for patients with HBV/HDV co-infection during the identification period.
Results: Among 590,102 eligible patients, 589,349 (99.87%) had chronic HBV infection and 753 (0.13%) had HBV/HDV co-infection. The mean (standard deviation) age of patients with chronic HBV infection and HBV/HDV co-infection was 50.0 (13.3) years and 51.2 (11.7) years, respectively. Patients were predominantly aged 51–60 years (28.8% of chronic HBV infection patients and 38.5% of HBV/HDV co-infection patients), males (56.1% and 66.8%) and visited hospitals in Seoul (25.7% and 50.6%). Patients with HBV/HDV co-infection had significantly greater comorbidity burden than patients with chronic HBV infection: 91.6% vs. 74.0% had any Charlson Comorbidity Index (CCI) comorbidity, 63.2% vs. 27.7% had CCI score ≥3, 34.4% vs. 26.8% had hypertension, and 34.0% vs. 17.7% had diabetes (all $p < 0.0001$). Patients with HBV/HDV co-infection had significantly higher rates of liver-related complications than those with chronic HBV infection: compensated cirrhosis (47.0% vs. 11.2%), decompensated cirrhosis (42.0% vs. 3.4%), and hepatocellular carcinoma (36.3% vs. 5.6%) (all $p < 0.0001$). A higher proportion of patients with HBV/HDV co-infection was on antiviral therapy for CHB than patients with chronic HBV infection (63.1% vs. 23.1%, $p < 0.0001$).
Conclusion: Patients with HBV/HDV co-infection had a greater burden of comorbidities and liver-related complications than those with chronic HBV infection. Early identification, accurate diagnosis, and proper management of HBV/HDV co-infection among CHB patients are crucial to prevent liver disease progression.

WED-040

Trends and cross-country inequalities in the global burden of acute hepatitis A, 1990–2021: a population-based study

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Background and aims: Acute Hepatitis A (AHA) poses a significant global public health challenge and is targeted for elimination by the Sustainable Development Goals 2030. A thorough global analysis is essential for directing effective prevention and control strategies for AHA. This study evaluates the burden at the global, regional, and national levels.
Method: Data from the Global Burden of Disease (GBD) from 1990 to 2021 were leveraged to analyze trends in AHA incidence and disability-adjusted life years (DALYs). A comprehensive assessment was conducted using joint point regression, decomposition, health inequality, and Bayesian forecasting analysis.
Results: The GBD estimates for global AHA incidence and DALYs in 2021 were 160,860,121.69 (95% UIs: 170,430,684.15 to 152,201,084.97) and 1,817,363.17 (95% UIs: 2,792,339.01 to 1,275,384.28), respectively, with age-standardized rates (ASRs) of 2,273.72 (95% UIs: 2,403.76 to 2,150.13) and 24.95 (95% UIs: 39.12 to 17.32) per 100,000. The GBD regional analysis reveals that South Asia had the highest incidence and DALYs cases in 2021, with Eastern sub-Saharan Africa and South Asia exhibiting the highest ASRs. From 1990 to 2021, there was a general decline in global AHA incidence and DALYs, with a more pronounced decrease in DALYs, despite significant disparities across different Socio-demographic Index (SDI) regions, countries, and regions. Decomposition analysis indicates that population growth and epidemiological changes are the primary drivers of the global AHA DALYs burden, with epidemiological control largely offsetting the burden due to population changes. The relative inequality index suggests that countries with lower SDI levels disproportionately bear the AHA burden, although inequalities related to SDI have been narrowing over time. The incidence gap between the highest and lowest SDI countries decreased from −1992 in 1990 to −1242 in 2021, and the DALYs gap reduced from −78 to −15. Projections for 2030 are promising, with a continued downward trend in AHA ASRs and numbers of incidence and DALYs.
Conclusion: This indicates that significant strides have been made in AHA prevention and control over the past three decades through vaccination and health policy implementation, while further comprehensive policies and preventive measures are necessary to effectively achieve the goal of eliminating viral hepatitis.

SATURDAY 10 MAY

SAT-003

A global survey of practice patterns in the management of hepatitis C virus (HCV)-related fibrosis

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Background and aims: Despite availability of curative treatment, there are disparities in HCV-related outcomes. We assessed global clinical practices related to HCV-fibrosis assessment in clinical practice.
Method: An online 7-item global survey (September-November 2024) developed by the Global Liver Council was developed to assess fibrosis assessment (pre- and post- treatment) and screening for hepatocellular carcinoma (HCC).
Results: Healthcare providers from 48 countries completed 361 surveys [59% male, 33% aged 35–44 years old, 87% MD, 32% ≥20 in practice years; 44% hepatology (Hep), 21% Gastroenterology (GI), 12% infectious disease (ID), 23% primary care providers (PCP); 67% practiced in academic health institution, 79% located in an urban setting, 66% reported <10% of their practice involved individuals with history of injection drug use]. Comparing clinical practices between Hep/GI (n = 236) and ID/PCP (n = 125), Hep/GI were in practice longer (>20 years: 39% vs. 18%); practiced in academic institutions (74% vs. 55%), urban settings (84% vs. 69%) but were less likely to see patients with intravenous drug use (73% vs. 54% see <10%) (all $p < 0.01$). Hep/GI were more likely to self-report "superior" HCV knowledge (52% vs. 18%), comfortable treating HCV patients (88% vs. 42%), treating >200

patients (57% vs 19%), using direct acting antivirals (96% vs. 49%) (all p < 0.01). Hep/GI more frequently followed AASLD (35%) and EASL (25%) guidelines; ID/PCP followed WHO guidelines (20%) or did not know (21%). Across global regions, transient elastography (TE) for fibrosis screening was most commonly used North America providers (69% before treatment, 85% after treatment vs. 49% and 72%, respectively, in other regions). Hep/GI compared to ID/PCP reported more frequently screening for fibrosis or cirrhosis prior to starting HCV treatment (99% vs. 78% at least sometimes, 77% vs. 42% always, p < 0.01) with TE (63% vs. 27%); ID/PCP used imaging or FIB-4 score (28% each) (p < 0.05). Hep/GI more frequently screened for fibrosis and cirrhosis after treatment (95% vs. 70% at least sometimes, 45% vs 23% always), using TE (82%); ID/PCP used TE or imaging (54% each) (p < 0.05). In screening for HCC after achieving SVR, 43% Hep/GI only screened if pre-treatment fibrosis of ≥F3 was present, 19% only with cirrhosis- 38% would screen all patients; 19% and 18% of ID/PCP would screen for HCC for those with ≥F3 and cirrhosis, respectively, while 28% would screen all post-SVR patients. Both groups (≥60% each) reported would not stop screening for HCC among HCV with advanced fibrosis or cirrhosis even for evidence of fibrosis regression after SVR- most commonly would consider stopping screening for HCC at a fibrosis level of F2 (36%).

Conclusion: There are variations in HCV screening and management among practitioners. Educational efforts on HCV treatment and follow-up are warranted and may help address HCV outcome disparities.

SAT-004

Emergency department opt-out testing for hepatitis B: a 2-year multicentre study of outcomes across 7 sites

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Background and aims: Opt-out testing for blood-borne viruses (BBV) in adults attending emergency departments (ED) in London is now being rolled out across England. Single-centre reports have identified large numbers of hepatitis B virus (HBV) infected patients who are not in care. Patient and disease characteristics and rates of engagement have not been studied across a large representative cohort.

Method: We undertook a multicentre retrospective study of HBsAg+ patients across 7 ED testing hospitals from North and South London between April 2022 and April 2024. Recruitment was for a minimum of 12 months with a 6 month follow-up period before censor. Patient and disease characteristics were compared with those referred by standard routes (e.g. primary, secondary and antenatal care – "non-ED").

Results: A total of 339627 HBsAg tests were performed at the study sites representing 29% of all tests performed in the program in this period. A total of 1097 HBsAg+ patients were identified after exclusion of 142 false positives on re-testing. 117 patients were not contactable by phone or post. Of the 980 contacted, 286 were already under follow-up and 694 were not under care. Of these, 544 were new to service and 150 were lost to follow-up. 674/694 (98%) were successfully engaged for a full clinical assessment. In the ED cohort, 12.4% had an LSM > 7.4 kPa, 15.5% had a CAP score >300 and 7.7% had a viral load >20000. 13.9% were commenced on nucleotide therapy. 3 new cases of HCC and 4 new cases of HDV infection were identified. A Cox regression multivariate analysis of time from result notification to assessment was performed. Covariates included age, gender, ethnicity, harmful alcohol use, fibrosis stage, viral load, English-speaking status and diagnosis at an ED in a hospital with a dedicated viral hepatitis service. Only the latter significantly improved time to assessment (HR 1.533, 95% CI 1.281–1.834, p < 0.001). The ED cohort was significantly older than those referred by non-ED routes (mean age = 5 0.3 vs 47, p < 0.001), had lower viral loads (mean = 3.8 M vs 15.8 M, p = 0.004) and higher CAP scores (mean = 245 vs 236, p = 0.019, all two-tailed t-tests). ED testing resulted in a 109% increase in hepatitis B assessments in the study period.

Conclusion: ED testing is more than doubling numbers of patients entering hepatitis B services. Excellent rates of engagement can be achieved and delays are attributable to service differences rather than patient factors. Significant proportions have disease that would benefit from liver cancer surveillance and/or viral suppression. Further resources will be needed so that this rapidly expanding cohort can benefit from longitudinal care without detriment to those already under follow-up.

SAT-005

From screening to treatment: the impact of opportunistic hepatitis screening in emergency departments on hepatitis C prevalence

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Background and aims: Most viral hepatitis screening programs in Emergency Departments (ED) have focused on Hepatitis C (HCV), and the reported results are short-term (1–2 years). The aim of this study was to assess the medium-term impact of a systematic and opportunistic viral hepatitis screening program (B, C, and D) in the ED.

Method: A prospective viral hepatitis screening study was conducted from January 2020 to July 2024. HBsAg and anti-HCV antibodies were tested in adults attending the ED who required a blood test. Reflex testing for HBV-DNA and anti-HDV for performed in case of HBsAg + and HCV-RNA in case of anti-HCV+. To maximize cost-effectiveness, after analyzing data from the first three years, an age-based screening strategy was implemented, excluding patients over 80 years old due to the low prevalence of HBV (<0.3%) and the low rate of HCV cases considered suitable for treatment (15%). To assess the effectiveness of the screening, the prevalence of HCV RNA and HBsAg in patients ≤80 years old was compared between the first (Jan/20–Dec/20) and last year (Aug/23–Jul/24) of screening. All patients were individually evaluated by a clinician and referred to outpatient consultations when deemed appropriate.

Results: During the 4.5 years of the program, 35,553 patients were screened. Of these, 200 (0.56%) had detectable HCV RNA, 216 (0.61%) were HBsAg positive, and 8 were anti-HDV positive (3.7% of HBsAg+ cases). 81% of patients with HCV and 57% of patients with HBV were

born in Spain. Only 40% of patients with detectable HCV RNA and 13% of those with HBsAg+ reported risk factors for viral hepatitis. The prevalence of HCV RNA detectable in patients ≤80 years old in 2020 was 0.45% (22/4922) while in the last year, was 0.23% (25/10807) ($p < 0.001$). However, no significant differences were found in the prevalence of HBsAg between the first (0.57%; 28/4922) and last year (0.52%; 56/10807) ($p = 0.6$).

Half of the patients with detectable HCV RNA (n = 98), were considered eligible for linkage, and 88 (90%) were treated and cured. Of the 216 HBV cases, 144 were not linked to care, 119 (83%) were considered candidates for linkage, 103 (87%) attended the outpatient clinics, and 16 started treatment.

Conclusion: Maintaining an opportunistic viral hepatitis screening program in the ED for more than 4 years enabled the detection and linkage to care of a significant number of patients with Hepatitis B and C, most of whom did not report risk factors. This strategy had a significant impact on decreasing the prevalence of Hepatitis C among patients attending the Emergency Department. Screening in emergency settings is an effective tool for the elimination of viral hepatitis as a public health threat.

SAT-006

Emergency department blood-borne virus screening and the revealed burden of hepatitis B-driven liver disease

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Background and aims: Opt-out blood-borne virus (BBV) testing for HIV, Hepatitis B (HBV) and Hepatitis C (HCV) infection has been carried out in selected emergency departments (ED) across England since April 2022. Here we describe patients with newly diagnosed chronic HBV from ED testing at two large NHS Trusts in Southeast London in the first 20 months of testing.

Method: Patients with reactive hepatitis B surface antigen (HBsAg) results from ED were contacted and their hospital and GP records were analysed to establish if this was a new or a known diagnosis. Clinical data and details on linkage to care were collected for all new diagnoses made between November 2022 to June 2024.

Results: In the 20-month period, 1188 patients were reactive for HBsAg. Of these, 353 patients had a new HBV diagnosis. 13 patients presented with clinically overt cirrhosis and 3 had hepatocellular carcinoma (HCC) diagnosed during the admission. 254 new patients (71.9%) were subsequently contactable and accepted a first appointment; 202 attended this first appointment, including 169 having transient elastography (Fibroscan) assessment. Of the patients who had a Fibroscan assessment, 19 (11.2%) had liver stiffness measurements (LSM) of 7–11 kPa and 9 (5.3%) had a LSM of >11 kPa. In addition, 61 patients have a calculated APRI score of 0.5–1.0 and 26 patients a score of >1.0.

44 patients have been initiated on nucleos(t)ide analogue treatment since diagnosis. However, based on the World Health Organisation (WHO) 2024 guidance (APRI >0.5 or HBV DNA >2000 IU/mL and ALT above upper limit of normal) 123 (34.8%) of the newly diagnosed patients meet criteria for initiating treatment. Furthermore 138 patients (39.1%) warrant HCC surveillance based on EASL guidelines; a significant proportion of this cohort being Black Afro-Caribbean males over the age of 40.

74 patients seen in one ED with known chronic HBV but lost to specialist follow up (LTFU) were identified and analysed. 53 patients (71.6%) were re-linked to care, 26 patients (35.1%) meet the WHO 2024 treatment criteria, and 32 (43.2%) patients require HCC surveillance.

Conclusion: Patients with Hepatitis B identified through ED testing represent a significant burden of clinical disease. In the first 20 months of ED testing in Southeast London, 34.8% of those newly diagnosed potentially meet treatment criteria and 39.1% require surveillance for HCC. ED testing is also an opportunity to re-engage LTFU patients, with success in one centre as reported here. Resource is now required as a priority to meet this increase in demand on specialist services in a long-term sustainable manner and novel models of care need to be considered.

SAT-007

National hepatitis C virus (HCV) screening pilot using rapid HCV antibody tests in Kazakhstan

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Background and aims: Hepatitis C virus (HCV) infection continues to pose a major public health challenge in Kazakhstan, affecting an estimated 398,000 individuals. Despite the availability of free testing and treatment, fewer than 10% of cases were diagnosed by 2021. Current screening programs target only high-risk groups, such as pregnant women and surgical patients, leaving many undiagnosed. This gap undermines Kazakhstan's progress toward the World Health Organization's (WHO) 2030 elimination target. This pilot evaluated the effectiveness of large-scale general adult population screening in urban and rural polyclinics. The findings aim to inform the development of a national program to improve diagnosis, treatment, and public health outcomes to meet WHO elimination goals.

Method: Convenience sampling was employed to recruit adults attending polyclinics in five regions: East Kazakhstan, Abay, Turkistan, Karaganda, and Shymkent City. A total of 99,200 individuals were screened for anti-HCV antibodies using rapid diagnostic tests, with data recorded in an electronic registry. Prevalence was analyzed by age, sex, birth region, and clinic region. Poisson regression identified factors contributing to variability in HCV prevalence.

Results: Overall HCV prevalence, adjusted for age and sex, was estimated to be 0.59% (95% CI: 0.55–0.65%). Males had higher prevalence (1.22% (1.10–1.34%)) than females (0.30%, (0.26–0.34%)). Prevalence peaked at 0.99% for those aged 45–49. Regionally, Aktobe exhibited the highest prevalence at 4.68% (0.82–14.2%). Among clinic regions, Shymkent had the lowest statistically significant prevalence of 0.43% (0.31–0.61%). Regression analyses found higher HCV rates in individuals born in Aktobe and tested in Turkistan ($p < 0.001$). Younger age groups showed significantly lower rates compare to those aged 35–39 ($p < 0.01$).

Conclusion: This pilot program demonstrated the feasibility of large-scale HCV screening and identified significant variability in prevalence by age, sex, and geography. Males, individuals aged 45–49, and those from the Aktobe region showed elevated prevalence, highlighting the need for targeted interventions. However, expanding the program to populous regions like Almaty, in addition to high-risk groups, is critical for a comprehensive assessment of HCV prevalence.

Development of a national screening strategy will be essential for Kazakhstan to meet WHO elimination targets and reduce the public health burden of HCV.

SAT-008

Population-based hepatitis C screening and elimination program in Lithuania: 26-month results

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Background and aims: The Lithuanian HCV screening programme started in May 2022. General practitioners (GPs) received special promoting fee for serological HCV antibody testing: 1. For people born between 1945 and 1994 (once in a lifetime) and 2. For people who inject drugs (PWID) or HIV-positive people (annual HCV testing). This initiative is the first in Central and Eastern Europe. The aim of this study was to assess the results of the first 26 months of the programme and the different scenarios for achieving the WHO 2030 targets.
Method: GPs invited people to perform a serum blood test for HCV antibodies. Anti-HCV positive patients were referred to a gastroenterologist or infectologist for HCV RNA testing, and if result was positive, direct-acting antiviral (DAA) therapy was prescribed. Information about patients was obtained from the database of the National Health Insurance Fund. The Markov disease progression model elaborated by the CDA Foundation was used to assess HCV elimination progress. The data from the 2022–2023 screening were used as inputs Three scenarios were developed: the 'Base' scenario - return to pre-screening program level in 2023 and 2 scenarios with different extents of treatment.
Results: At the beginning of 2022, about 1.8 million people born in 1945–1994 lived in Lithuania. Between May 5, 2022 and June 30, 2024 from this population 1264527 people (69.7%) were tested for HCV antibodies. Positive test results were found in 1.25% of cases. In the risk group, 10670 PWID and HIV+ people were screened, of whom 29.6% were seropositive. Seropositive patients were referred to specialists and viremia was detected in 58,6%. During 26-month (May 2022–June 2024) period 3 times more HCV patients were treated with DAA than during the same period (Aug 2020–April 2022) before starting of the program (5881 vs 1921). Treatment delay for 48.9% of HCV patients was related to organizational problems (fibrosis limitations for treatment were canceled only on April, 2024; delay for patients' referral from GP to specialists). The Markov disease progression model to assess HCV elimination progress showed the following scenarios: Scenario 1: if the same number of patients are treated as before the screening, the WHO targets will not be reached. Scenario 2: treating 70% of infected patients will meet most but not all WHO targets. Scenario 3: by treating all infected patients by 2030, the WHO target will be met by saving 150 lives and preventing 90 new cases of decompensated cirrhosis and 120 cases of hepatocellular carcinoma.
Conclusion: Our data show that in European country with moderate HCV seroprevalence, a population-based screening program can be feasible, screening near 70% (more than 1,2 million) of the population born between 1945 and 1994 during the first 26 months of the program. With no restrictions on DAA treatment, we hope that the WHO 2030 targets can be achieved in Lithuania, but it is essential to ensure that all seropositive patients who have been screened by a GP are consulted and treated by specialists.

SAT-009

Risk of advanced liver disease among individuals with hepatitis B virus infection with low-level viremia compared to individuals with no evidence of hepatitis B virus infection

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Background and aims: Current medical society treatment guidelines for hepatitis B virus (HBV) infection do not recommend antiviral therapy for individual with low-level viremia (LLV: defined as HBV DNA ≤2,000 IU/mL) unless cirrhosis has been diagnosed; however, the association between LLV and advanced liver disease is unclear. In this study we examine United States (US) administrative claims and laboratory result data to describe the characteristics of individuals with LLV compared to those with no evidence of HBV, and to evaluate the risk of advanced liver disease events (including compensated and decompensated cirrhosis (CC, DC), hepatocellular carcinoma (HCC), liver transplant (LTx) and a composite outcome of any of these events) in these two groups.
Method: Adults (age ≥18 years) with chronic HBV (defined as ≥2 positive HBV surface antigen (HBsAg) or HBV DNA at least 6 months apart) and low-level viremia (LLV, defined as HBV DNA ≤2,000 IU/mL) were identified from October 2016 – June 2024 using the Optum Clinformatics® Data Mart, a large US administrative claims database of individuals covered by commercial and Medicare Advantage insurance. Individuals with evidence of CC, DC, HCC, LTx, HIV, concurrent hepatitis C or D, or those who had <365 dates of continuous enrollment prior to index or had evidence of nucleot(s)ide analogue (NA) treatment in the six months prior to index were excluded. Index date was defined as the date of the first laboratory results for HBV DNA ≤2,000 that met all inclusion criteria. Chronic HBV patients with LLV were matched to adults with no evidence of chronic HBV on age at index, sex, race, and baseline comorbidities, and differences in the risk (per 100 person-years) of CC, DC, HCC, and composite outcome of aforementioned endpoints were compared between propensity score (PS)-matched groups using Cox proportional hazards models.
Results: After 1:1 PS-matching, we identified N = 4,236 individuals for each cohort (HBV LLV and uninfected controls). When compared to individuals with no evidence of HBV, those with HBV LLV had a significant increased risk of all examined outcomes: CC (HR: 14.24 (6.95–29.18)), DC (HR: 1.90 (1.26–2.86)), HCC (HR: 9.79 (3.90–24.57)), and the composite outcome (HR: 4.83 (3.48–6.71)). Similar results were observed for all outcomes in a subgroup analysis that compared uninfected controls to individuals with HBV LLV with no evidence of NA treatment or recorded HBV DNA > 2,000 at any point during the follow up period (73.6% of the original cohort; N = 3,121). Additional analyses examining the risk of HBV DNA > 2,000 IU/mL with evidence of NA treatment vs. HBV DNA ≤2,000 IU/mL with no evidence of treatment were also conducted.
Conclusion: In this analysis of US claims data including Medicare and laboratory results, individuals with HBV DNA ≤2,000 had a significant increased risk of advanced liver disease events relative to those with no evidence of HBV. These results support the conduct of additional

studies to determine whether starting antiviral therapy in people with hepatitis B virus and low-level viremia prevents advanced liver disease.

SAT-010

Peer-led mass testing in prisons to support hepatitis C elimination

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Background and aims: People in criminal justice systems (CJS) face high rates of hepatitis C as well as high levels of loss to follow up. High Intensity Test and Treat interventions (HITTs) have operated across English prisons since 2019 to screen whole prison populations for hepatitis C (HCV). Delivered collaboratively by NGO The Hepatitis C Trust (HCT), the Prison service, Prison Healthcare, and local community hepatitis C healthcare teams, HITTs enable a prison to 'micro-eliminate' HCV. Funding for additional testing, incentives, clinical and custodial staff time to facilitate the activity was provided by NHS England. HITTs aim to improve understanding of HCV among staff and residents, address stigma, diagnose and rapidly treat HCV within the existing prison population, and increase rates of testing at reception for all new residents. We report early programme evaluation findings.
Method: HCT plan HITTs with prison Governors, conducting site visits and delivering peer-led HCV awareness sessions for prison residents and staff. Taking a wing-based approach and working in teams comprising of a nurse, prison officer, and a peer (someone with lived experience of CJS and HCV testing), teams go cell to cell testing for HCV antibodies (AB). Prisoners testing AB+ access point of care testing using Xpert® HCV Viral Load Fingerstick (Cepheid, CA). Positive cases are referred to the specialist BBV nurse and access a rapid treatment pathway, starting treatment within 2–14 days.
Results: In five years, 54,080 of 58,606 prison residents (92%) were tested through 82 HITTs. HITTs have identified 3,992 people (7.4%) with HCV antibodies, including 49% of residents in one prison. 611 have been referred for treatment, 522 (85%) started treatment, of these 478 (78%) initiating treatment in prison. Ongoing analysis of pre- and post-HITT data in 2024 indicates that reception testing increases by an average of 10% with each HITT. Qualitative feedback indicates high acceptability for prison residents.
Conclusion: HITTs play a key role in raising awareness of HCV in English prisons among prisoners, healthcare professionals and prison staff. This strengthens both the immediate prison-level response to hepatitis C, and ongoing HCV screening and treatment. This is an innovative and consistently effective approach to eliminating hepatitis C among people in prisons.

SAT-011-YI

Survival and inactivation of hepatitis A virus on inanimate surfaces

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Background and aims: Hepatitis A virus (HAV) causes an estimated 159 million infections annually with most of them attributed to fecal-oral transmission through contaminated drinking water or food. Limited data regarding its surface stability and sensitivity to chemical disinfectants are available. The aim of the study was to establish an HAV-based carrier assay to evaluate its surface stability and the virucidal activity of various surface disinfectants.
Method: An efficient cell culture system based on the cytopathic HAV strain HAVcyt/HB1.1 and FRhK-4 cells was utilized. Steel-disc carriers were inoculated with HAV particles and incubated at room temperature and the remaining viral titers were assessed over a period of 50 days. Environmental data regarding temperature and humidity were monitored over the course of the experiment. Furthermore, HAV resistance against different disinfection agents with varying concentrations and exposure times was evaluated according to the manufacturer's guidelines.
Results: Infectious virus was recoverable for up to 40 days, with a half-life of 18.63 days, and changes in temperature and humidity throughout the experiment seemed to have minimal impact on its stability. All alcohol-based disinfectants (Bacillol, Antifect and Meliseptol) were found to be ineffective in significantly reducing viral titers. Virucidal effects could also not be observed for peracetic acid-based disinfectants and hydrogen-peroxide. Only two aldehyde-based products were able to inactivate HAV under the detection limit.
Conclusion: Overall, HAV displayed a high degree of stability against a wide range of surface disinfectants. Of the nine surface disinfectants tested, only two demonstrated a reduction in viral titer below the lower limit of detection, which were based on aldehyde. These findings have strong implications for the recommendation of evidence-based hygiene guidelines to reduce HAV transmission.

SAT-012

Evaluating and aiding hepatitis C elimination efforts through natural language processing (Cogstack): analysis of electronic health records including diagnosis, demographics and outcomes

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Background and aims: Hepatitis C virus (HCV) remains a significant global health challenge, affecting over 50 million individuals worldwide, leading to substantial morbidity and mortality, including cirrhosis and hepatocellular carcinoma (HCC). The WHO aims to eliminate HCV by 2030, emphasising comprehensive screening, early diagnosis, and effective treatment. Despite these goals, barriers to patient identification and treatment access persist. Our aim was to evaluate the clinical impact of current screening and elimination strategies for HCV, leveraging natural language processing (NLP) tools by improving patient identification and assessing survival rate.
Method: This retrospective cohort study analysed electronic health records (EHRs) of HCV-RNA +ve patients between 2014–2023 at King's College Hospital, London. Data extraction and collation were performed using CogStack, an NLP tool for processing clinical text. Data were collected on new HCV diagnoses, including Ab+ve and RNA +ve cases, and patient demographics. Five and 10-year survival rates were assessed. Statistical analyses identified trends and factors influencing HCV incidence and clinical outcomes.
Results: A total of 2,199 HCV RNA-positive patients were identified through the CogStack platform. From these, 61.9% of patients had postcode data available and were from the catchment areas: Lewisham (23.4%), Lambeth (34.7%), Southwark (29.9%), and Bromley (12.0%). The cohort had a male predominance, with 63% male and 37% female patients and a mean age of 49 years (range: 17, 92). Most patients were Caucasian (68.4%), followed by Black (12.1%), with smaller proportions of Unknown (10.7%), Other (4.9%), Asian (3.7%), and Mixed (0.3%) ethnicities. Survival analysis revealed a 5-year survival rate of 76% and a 10-year survival rate of 57%. Social deprivation analysis showed that 69% of patients were in the fifth decile or below for the Index of Multiple Deprivation (IMD), highlighting significant socioeconomic challenges within the cohort. IMD data were available for 838 patients (38% of the total cohort). Among those in the fifth decile or below with liver stiffness measurements (LSM) data, the mean LSM was 10.77 (IQR: 5.23), and

41.1% had high LSM, suggesting significant fibrosis. Treatment data and its impact will be presented.
Conclusion: The use of NLP tools show significant potential in improving the identification of HCV-positive patients and evaluating the impact of screening and elimination strategies. The findings emphasize the need for targeted interventions, especially in socioeconomically deprived populations, to achieve the WHO's 2030 elimination metrics. This study underscores the value of connected advanced data extraction techniques in supporting public health initiatives to eliminate HCV, as well as identify those with risk factors for screening.

SAT-013

Knowledge and perception of chronic hepatitis B infection and attitude towards point-of-care testing among the general population in primary care settings in Hong Kong

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Background and aims: Chronic hepatitis B (CHB) infection caused by hepatitis B virus (HBV) remains a leading cause of liver disease worldwide. Early detection and linkage to care are essential to mitigate complications. However, universal screening program for CHB is still lacking even in areas with high prevalence. This study aimed to evaluate the feasibility and patient attitude of implementing point-of-care (POC) testing for CHB in a community primary care setting.
Method: A cross-sectional study was conducted to evaluate POC hepatitis B surface antigen (HBsAg) testing in primary care settings. Participants were recruited from the Central and Western District Health Centre Express in Hong Kong from October to November 2024 during member registration and health events, targeting adults aged ≥18 who could provide consent, read and write Chinese, excluding those with known CHB diagnosis, pregnancy, or serious medical conditions. Participants underwent POC testing for HBsAg by Abbott Diagnostics Determine™ HBsAg 2 rapid test kit, which has a lower limit of detection of 0.1 IU/ml, followed by a structured validated questionnaire in Chinese that collected data on demographics, hepatitis B history, knowledge, perceptions, and attitude.
Results: A total of 28 participants were included (mean age of 60.9 years; 71.4% female). Vaccination history against HBV was reported by 39.3%. Knowledge about HBV transmission was variable; 89.3% correctly identified both mother-to-child and blood-borne transmission, but only 53.6% agreed that CHB can be transmitted by sexual contact. 35.7% disagreed with the misconception of HBV transmission through sharing of food utensils. Most participants understood HBV-related complications, with 92.9% aware of its asymptomatic nature. 96.4% and all of participants recognizing its link to cirrhosis and liver cancer respectively. While 100% would test if recommended by their doctor, only 14.3% reported prior discussions about HBV POC testing with their doctor. All participants expressed high satisfaction with the POC testing, rating convenience (mean score 9.4/10) and immediate results to allow timely interaction with healthcare professionals (mean score 9.6/10) as key advantages.
Conclusion: POC testing for HBV in primary care settings is well-received and can improve accessibility and early detection. However, educational interventions are needed to address persistent misconceptions about transmission. Expanding POC testing could enhance hepatitis B screening rates and facilitate timely intervention.

SAT-014

Setting the record straight: utility and outcomes in patients with HCV related HCC

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Background and aims: The effectiveness of direct acting antiviral (DAA) therapy in patients with hepatocellular carcinoma (HCC) is poorly defined. Although there is agreement regarding HCV treatment in patients who have received curative HCC treatments, the optimal timing for DAA therapy in those with active HCC or those with advanced stage remains undefined. AASLD and IDSA guidance recommends against HCV treatment in those with advanced HCC and limited life expectancy (less than 12 months). In 2015, DAA therapy was approved in the UK for all viraemic patients (including those with HCC independent of the cancer stage). Preliminary data from the England HCV elimination programme suggests that almost 4% of viraemic patients treated during 2016 and 2023 had documented HCC at the time of DAA therapy. The aim of this retrospective study is to provide a real-life data of HCV treatment in those with HCC since the introduction of DAAs.
Method: Patients with HCV related HCC from the National Hepatitis C registry in South-East England between 2016 and 2023 were retrospectively included. The primary outcome was to assess HCV care cascade (treatment pathway) in patients with HCV related HCC (HCC cohort) in comparison with those without cancer (non-HCC cohort) as well as to assess treatment outcome and overall survival (OS) in patients with varying stages of HCC.
Results: 228/6850 (3.3%) HCV related HCC patients were identified. 71.8% (4755/6622) from the non-HCC cohort and 63.2% (144/228) from the HCC cohort initiated DAA therapy ($p < 0.05$). By ITT, SVR rate in HCC cohort was 85.8% (97/113) vs 89.3% (3643/4081) in the non-HCC cohort ($p = 0.992$). 11% (17) in the HCC cohort and 3.5% (168) in the non-HCC cohort were re-treated ($p < 0.05$). Patients in the HCC cohort were older (67 vs 55 years; $p < 0.05$), had a significant greater degree of fibrosis (moderate fibrosis, 22.6 vs 7.1%, cirrhosis 55.6 vs 18.7%; $p < 0.05$), were infected with genotype 3 (41 vs 27.3%, $p < 0.05$), had higher alcohol intake (31 vs 15%, $p < 0.05$) and required sequential treatment with more than one DAA regimen (11.8 vs 3.5%, $p < 0.05$) in comparison with those without HCC. At the time of DAA therapy 88% had an active HCC and the majority (64%) had early stage cancer (BCLC stage 0 = 4; BCLC stage A = 80). SVR rate was 95%, 56.3% and 78% in BCLC 0/A, B, and C respectively. The death rate during HCV treatment or before SVR was 77% in BCLC stage D, 20% in BCLC stage C, 4.3% in BCLC stage B and 2.4% BCLC 0/A. The median OS after DAA therapy was 105, 32, 18 and 4 months for BCLC 0-A/B/C/D respectively. 80% had a median OS more than 12 months.
Conclusion: More than two thirds of patients with HCV-related HCC initiated and completed DAA therapies in South-East England. This high level of treatment uptake has led to an acceptable cure rate. The majority of patients had an overall survival of more than 12 months and so we believe that HCV treatment needs to be recommended in those with BCLC stages A, B and C.

SAT-019

Knowledge of hepatitis D epidemiology and access to hepatitis D diagnostic testing among healthcare providers in Africa: a multi-country survey

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Background and aims: Chronic hepatitis D infection, a disease associated with accelerated progression to liver cirrhosis and hepatocellular carcinoma, is considered the most severe form of viral hepatitis. An estimated 1.6 million people in the WHO Africa region are living with hepatitis D. However, the HDV prevalence data in this region are likely suboptimal due to low awareness and limited access to HDV screening and diagnostic tests. This multi-country survey aimed to assess health care providers' knowledge of HDV prevalence and the availability of hepatitis D screening and confirmatory diagnostic testing across all African countries. Additionally, a literature review was conducted on HDV prevalence and available diagnostic testing in Africa.
Method: A web-based questionnaire created by members of the Society on Liver Disease in Africa (SOLDA) and the European Association for the Study of the Liver (EASL) was distributed to all SOLDA and Project ECHO Viral Hepatitis members through African network channels.
Results: In total, 608 surveys were completed, representing 43 of the total of 54 (80%) countries in Africa. The distribution of respondents was as follows: eastern Africa (266 respondents, 44%), western Africa (217, 36%), southern Africa (50, 8%), northern Africa (37, 6%), and central Africa (38, 6%). Participants from 24 of 43 countries (56%) were aware of their HDV epidemiological data, and 33 (61%) of 54 countries reviewed in the literature had published data. There were no statistical differences between these percentages ($p = 0.598$), Survey participants reported that data on hepatitis D seroprevalence had been assessed in the following populations: HBsAg carriers (77%), blood donors (23%), chronic liver disease (25%), hepatocellular carcinoma (18%), children and adolescents (12%), dialysis patients (16%), and people who inject drugs (13%). Anti-HDV antibody determination was available in 17 of 43 countries (39%), while published data indicated availability in 14 of 54 countries (26%) ($p = 0.153$). Anti-HDV and HDV RNA testing in the context of clinical studies is reimbursed in only 12 countries.
Conclusion: Healthcare providers' knowledge of HDV prevalence varies across African countries. Access to anti-HDV and HDV RNA testing in Africa is limited and seldom reimbursed, and diagnostic tests are not incorporated into routine clinical practice.

SAT-020

Patient perspectives on barriers and enablers to a treatment for all approach for hepatitis B

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Background and aims: Major gaps exist in diagnosis, linkage to and maintenance in hepatitis B care in Australia and globally. To meet the World Health Organization's (WHO) 2030 viral hepatitis elimination targets, access to and engagement in clinical care needs to be increased. Under current Australian treatment guidelines, not all people with hepatitis B are eligible for antiviral treatment. The recent WHO updated hepatitis B treatment guidelines vastly expanded hepatitis B treatment eligibility, with all people with hepatitis B provided with the opportunity to access treatment, including from the point of diagnosis. This qualitative study explored patient perceptions of hepatitis B treatment and opinions on a "treatment for all approach.".
Method: Twenty-three semi-structured interviews were conducted with patients from a metropolitan gastroenterology clinic in Melbourne, Australia. Of the interviewed participants, 13 were female and 10 were male, and 21 patients were born in countries other than Australia (the most common country of birth being Vietnam) and 2 were born in Australia. Participants were aged between 33 and 69 years. Data from semi-structured interviews were thematically analysed.
Results: Thirteen participants were open to a "treatment for all approach," eight were not, and two were unsure. Five enablers and four barriers were identified from the thematic analysis. Enablers included: 1) perceived seriousness of hepatitis B and its complications, 2) belief in medications, 3) belief in benefits of early intervention, 4) receiving support through the treatment experience, and 5) trust in medical professionals. Barriers included: 1) psychological impact related to long-term medication, 2) perceived culture of overmedicalisation, 3) belief that the medication is unnecessary, and 4) cost and logistics associated with prescription medication.
Conclusion: Perspectives both for and against a "treatment for all" approach were discussed by people with hepatitis B in this study. A key enabler identified was of psychological support for patients throughout treatment decision making. Given that cure for hepatitis B is a future possibility, exploring the acceptability of a treatment for all approach and patient considerations for treatment is crucial preparatory work to determine acceptability of treatment.

SAT-021

Initiation of direct acting viral therapy in prison is associated with a significant loss to follow-up: relevance to WHO elimination metrics?

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Background and aims: Prisons represent an area of high HCV prevalence. There has been a focus on improving the testing and treatment of incarcerated individuals. The sustained virological response (SVR) rates at 12 weeks, however in patients initiating treatment in detention centres is unclear.
Method: All patients treated with DAA therapy within 18 centres in London from September 2013 -March 2024 were collated on a central registry. Within London, a metropolis of 9.7M with significant diversity, there are 7 prisons where DAA therapy can be initiated, including remand facilities. This data was interrogated for all patients initiated on DAA therapy whilst in prison. The demographics and outcomes were compared with all patients initiating therapy in other treatment settings over the same period. All comparisons are with patients treated outside of prisons.

Results: 687 patients were initiated on therapy whilst in detention and 15,784 treatment initiations in other settings in the same period. Patients treated in prison were almost exclusively male (99.6%) with a significant component who currently inject drugs (PWID) (33.8% vs 11.3%), genotype 1 (48.9% vs 53.3%) or genotype unknown (15.3% vs 4.9%) and of white ethnicity (51.4% vs 60.1%); [ethnicity was not recorded in 28.8% of prisoners (vs 11.2% of non-prisoners)]. The planned treatment duration was 8 weeks in 317; 12 weeks in 360; 16 weeks in 9 and 24 weeks in 1 patient. In those receiving 8 weeks of therapy, 23 (7.3%) received < 8 weeks; in those receiving 12 weeks, 45 (12.5%) received <12 weeks of therapy. Of the patients starting treatment in prison, 274 (39.9%) were lost to follow up or had no outcome recorded. In those, starting treatment in non-prison settings, the lost to follow-up/outcome not recorded rate was 13.7% (2157 patients) ($p < 0.01$).
Conclusion: Patients who initiate DAA therapy whilst incarcerated have excellent outcomes based on per-protocol analysis. However, a significant proportion are LTFU, impacting ITT outcomes. Given that a third are PWID at treatment initiation, this poses a significant public health risk for reinfection and may impact on HCV elimination initiatives.

SAT-022

Screening for risk factors for hepatitis C infection with a large metropolitan primary care population - The size of the problem

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Background and aims: The Hepatitis C (HCV) elimination programme within England has identified primary care as a priority where a large number of people with unidentified HCV infection may be identified. Outside of universal screening, targeting patients with risk factors for HCV infection, identified through primary care records, may represent the best way to identify these patients. Northwest London (NWL) whole systems integrated care (WSIC) is an integrated care record that stores data on individuals from primary, secondary and community care records. NHS England has developed a case-finding tool for HCV infection that identifies patients with risk factors utilising >1800 SNOMED codes. Our aim was to quantify the number of patients at risk of HCV infection in NWL with the case-finding tool searching Discover-NOW, an integrated database comprising de-identified, linked electronic health records for >2.8 million residents registered with a GP in North West London (NWL).
Method: All patient records between 31/12/1989 and 01/12/2023 were interrogated. Patients were excluded if they were deceased or in palliative care. Six searches were run (1: Hepatitis C positive; 2: Hepatitis C resolved; 3: All patients with exactly 2 risk factors; 4: All patients with 3 or more risk factors; 5: All patients with at least 3 low risk factors or 1 high risk factor; and 6: all patients born within countries with a high prevalence of HCV infection). The searches were stratified by primary care practice and primary care network.
Results: The records of 2,842,509 patients across 337 primary care practices within 44 primary care networks was interrogated. The background prevalence of HCV infection was 0.3%. The range of HCV antibody positivity prevalence varied between 0.1% and 15.3% between practices. The number of patients with 2 risk factors was 479,471 (median 17%, IQR 15–20%). The prevalence of 3 or more risk factors was present in 240,948 patients (median 9% and IQR 7–10%). Search 5, using a combination of 3 or more low risk factors or 1 high risk factor, identified 431,444 patients (median 15%, IQR 12–19%. This study identified 472,112 patients (median 16% and IQR 7–27%) within NWL born within countries with a high prevalence of HCV infection.
Conclusion: The prevalence of risk factors for HCV infection is common in the NWL population with 1 in 6 patients having 2 or more risk factors and 1 in 11 patients having 3 or more risk factors. There was a wide variation between primary care practices. These data can inform strategies to screen for HCV infection based on the prevalence of risk factors within each practice or primary care network.

SAT-023

Treatment of Hepatitis C in the over-80 s in the direct anti-viral therapy era: age is no barrier!

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Background and aims: The use of direct anti-viral (DAA) therapy to treat chronic hepatitis C virus (HCV) infection has expanded access of therapy to populations that would otherwise not have been offered treatment. Previous studies have shown that DAA treatment is well tolerated with comparable outcomes in those aged 75 years, however data in patients aged >80, and of mixed ethnicity remains limited.
Method: All patients treated with DAA therapy within 18 centres in London from September 2013–March 2024 were entered into a central registry. Data was interrogated for all patients initiated on DAA therapy aged 80 and above. The demographics and outcomes were compared with all patients undergoing a single treatment episode.
Results: In total,16,471 patients received treatment of whom 592 were aged ≥80, with a median age of 84 years (range 80–101). More patients were female (56.8% vs 28.9% in under 80 s). The ethnicity of the ≥80 s cohort was documented as Asian in 98 (16.5%); black in 170 (28.7% vs 6.7% in under 80 s, $p < 0.01$); mixed race in 7; white in 193, other in 53, and not recorded in 71 (12.0%). The fibrosis stage was none or mild in 244 (41.2%); moderate in 72 (12.2%) and 244 (41.2%) had cirrhosis. The predominant genotype was 1 (307/592); [Genotype 2 (70/592); Genotype 3 (108/592); genotype 4 (83/592); other genotypes n = 9 and unknown in 15]. Renal failure (eGFR <30 ml/min) was present in 40/592, 9 had co-infection with HIV and 25 had HCC at the time of treatment. The mode of acquisition was unknown in 334 (56%). Only 24 (4%) patients died prior to SVR12 delineation. The mortality rate between treatment initiation and SVR12 was 5.2% in the cirrhotic patients and 3.2% in the non-cirrhotic patients (p = NS). The SVR rate overall was 76.4% as intention to treat with the SVR12 being 72.9% in patients with cirrhosis and 78.8% in those without cirrhosis. The SVR12 rate in the under 80 s was 78.1% (77.9% in those without cirrhosis and 79% in those with cirrhosis).

There was no significant difference in SVR12 rate in between the over vs. under 80 s, regardless of fibrosis stage.
Conclusion: Treatment of chronic HCV infection with DAA therapy in those aged >80 is associated with comparable outcomes to those <80. The significantly higher number of women in this cohort is likely secondary via healthcare acquisition. The higher proportion of individuals of black ethnicity identifies a population that may be under-screened for HCV infection. DAA, treatment, however should be available to all.

SAT-024

Semi-qualitative feedback from individuals living with HBV newly diagnosed in the emergency department ED opt-out testing program – high acceptability but better platforms of advocacy and support required

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Background and aims: Widespread opportunistic screening is critical to achieving WHO global elimination goals for HBV and HCV. From April 2022, in areas of high (>5/1000) HIV prevalence, NHS England launched 'opt out' testing for HIV, HBV and HCV in London Emergency Departments (EDs) with integrated linkage to clinical care. In the first 18 months of testing a cohort of new HBV diagnoses were found at King's College Hospital, which serves a diverse multi-ethnic population. We collected semi-formalised qualitative patient feedback from those with newly diagnosed HBV who had been linked to care, with the aim to assess their experience with the opt-out screening process, their knowledge of HBV and what holistic support individuals with HBV require.
Method: Between November 2022 and April 2024, a total of 173 patients were found to have a new diagnosis of HBV out of 434477 tests performed. Telephone interviews were conducted with 78/153 (51%) of those patients that had been linked to care. Demographic data and feedback regarding their knowledge of HBV and their experience was collected via F2F or phone discussion.
Results: 78/153 (51%) consented to be interviewed. 7/78 (9%) were in ages ranging from 21–30, 12/78 (15%) 31–40, 19/78 (24%) 41–50, 18/78 (23%) 51–60, 12/78 (15%) 61–70 and 10/78 (13%) over the age of 71. 59/78 (75%) were of Black- African/Caribbean/British ethnicity, 11/78 (14%) White, 6/78 (8%) Asian and 2/78 (3%) of mixed ethnicity. 1/78 (1%) had no formal education, 4/78 (5%) primary education, 29/78 (37%) secondary education, 10/78 (13%) vocational education and 34/78 (44%) had a university degree.19 different languages were reported as first language. 49/78 (63%) live within the bottom 30% most deprived areas in England, calculated by the index of multiple deprivation. 62/78 (79%) reported they had no prior knowledge of hepatitis B and 55/78 (71%) were initially alarmed when they received their diagnosis. However, 66/78 (85%) believed testing of blood borne viruses and receiving a diagnosis through opt-out testing was beneficial. 46/78 (59%) had asked their family members and close contacts to be tested and vaccinated. We found that only 18/78 (23%) were aware of the peer led support group, HepB companion. Rating their knowledge of hepatitis B now on a scale of 1–5, 5/78 (7%) rated their knowledge to be 1 (very poor), 13/78 (17%) 2 (poor), 26/78 (34%) 3 (good), 17/78 (22%) 4 (very good) and 17/78 (22%) 5 (excellent). Only 15/71 (19%) knew about new treatments for HBV.
Conclusion: Feedback from a diverse group of newly diagnosed individuals living with HBV, shows acceptability of the ED opt-out scheme. Linkage to clinical care has improved their knowledge and newly diagnosed individuals feel comfortable discussing HBV with families and close contacts. However, more easily accessible information that reaches out to diverse communities with holistic support and education, allied to opportunities for novel therapy, and provision of a patient advocacy platform is required.

SAT-025

Epidemiological, economic and budgetary implications of expanding screening strategies for hepatitis C virus in Brazil: a modelling study

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Background and aims: Brazil's current hepatitis C virus (HCV) screening strategy targets people at high risk of infection through a complex algorithm. Despite the availability of antiviral treatment, the country is struggling to identify infected individuals. However, improved early detection and treatment are essential for achieving the World Health Organization (WHO) targets for HCV by 2030. We aim to evaluate the cost-effectiveness and budget impact of expanding HCV screening strategies in Brazil.
Method: A Markov model was used to simulate the prevalence of chronic hepatitis C (CHC), life years (LY), disability-adjusted life years (DALY), and costs in the Brazilian general population in 2024, aged 18 to 80, undiagnosed for CHC. We compared different one-time screening strategies: S1 = risk-based screening (status quo); S2 = S1 and all individuals aged 40 and over; S3 = all individuals between 18 and 80 years old (universal). Antiviral treatment was proposed once diagnosed for CHC and linked to care. Data were derived from published literature. Future costs and clinical benefits were discounted at 5% per year using a lifetime horizon. We assessed the budget impact of universal screening by projecting undiscounted costs over five years. The public health system perspective was adopted.
Results: The universal screening strategy led to the lowest CHC prevalence in 2030 (0.25% compared to 0.26% with S2 and 0.28% with S1), and the lowest incidence of clinical complications from 2024 to 2030 (32,471 cases of hepatocellular carcinoma and 34,130 cases of decompensated cirrhosis, compared to 32,928 and 34,538 cases with S2, and 35,304 and 36,508 with S1). Universal screening was the most effective and least expensive strategy, i.e. cost-saving. This strategy saved $548 million, achieved a gain of 75,870 LYs, and prevented 73,782 DALYs over lifetime compared to S1. Deterministic sensitivity analyses were performed including, but not limited to, seroprevalence and people at high-risk of HCV infection to account for regional differences: the universal screening remained cost-saving. The probabilistic sensitivity analysis indicated that universal screening was the most cost-effective strategy over 76% of iterations, regardless of the willingness-to-pay threshold. To achieve the WHO target of treating 80% of people diagnosed with CHC by 2030, coverage rates of universal screening and linkage to care must exceed 84%. The budget impact analysis showed that universal screening could save around U$ 26.6 million over five years for an additional 25.6 million people tested compared to S1.
Conclusion: Our findings demonstrate that universal HCV screening in the general population is a promising strategy for hepatitis C elimination in Brazil. Such recommendation could also simplify the

current complex algorithm used to screen specific sub-populations at high-risk of infection.

SAT-026

Delta in Denmark: prevalence of hepatitis delta virus infection

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Background and aims: Recent reviews of the global prevalence of hepatitis delta virus (HDV) infection have revealed the scarcity of data from general population studies and absence of information from many countries, including Denmark. We aimed to estimate the current prevalence of HDV in Denmark.
Method: Data on diagnoses, blood tests for hepatitis B and D infection, and demographic data were obtained from the Danish national health records for the period from 1992 to January 2024. The susceptible population was defined by a positive test for HBsAg or a diagnostic code for hepatitis B (HBV). History of HDV was defined by diagnostic code or positive test for anti-HDV Ab or HDV-RNA. Current HDV infection was defined by a positive test for HDV-RNA with no subsequent negative test.
Results: 8.1% of individuals with HBV had a history of HDV and were resident in Denmark on 1st January 2024. Of those tested for HDV-RNA, 39% had at least one positive test, and 37% were positive for HDV-RNA on their last recorded test. Thus, 8.1% * 37% = 3.0% of HBV-positive individuals in Denmark were estimated have current coinfection with HDV. This figure did not vary significantly by age, sex and native-born or foreign-born patients. Only amongst Greenland-born HBV-positive individuals was there some evidence for a higher rate of current HDV infection. The overall prevalence for Denmark translates into an estimated 236 cases of current HDV infection, or 4 cases per 100,000 in the general population.
Conclusion: Three percent, a small, but not negligible, proportion of the HBV-infected population in Denmark have a current coinfection with HDV, justifying routine testing amongst the chronic HBV population.

SAT-027

Therapy of HCV infections among patients of ukrainian origin during the influx of war refugees to Poland

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Background and aims: The wave of war migration from Ukraine has raised a number of concerns about infectious diseases, the incidence of which is higher in Ukraine than in the host countries and these include hepatitis C virus (HCV) infection.
Method: Our analysis aimed to assess the share of HCV-infected Ukrainians in Polish centers providing diagnostics and antiviral therapy, the assessment of their characteristics, and the effectiveness of direct-acting antiviral (DAA) treatment compared to Polish patients. The study included patients from the EpiTer-2 database treated due to HCV infection, which is an ongoing, retrospective, multicenter, national study initiated by investigators.
Results: Of the 3,911 individuals included in the study, 429 (11%) were patients of Ukrainian origin (UKR). The highest percentage of UKR patients among all treated patients (>20%) was recorded in centers located in northern and southern Poland, while the lowest (<3%) was in the eastern part of the country. UKR population was significantly younger and had a higher proportion of females. No significant differences were observed in BMI, and proportion of nonresponders to previous therapy. UKR population was characterized by less advanced liver disease, as expressed by a significantly (p = 0.017) lower percentage of patients with F3 or F4 (32.2% vs. 38.1%), significantly lower liver stiffness assessed by elastography (10.3 ± 9.7 vs. 12.0 ± 11.4 kPa) and MELD score (7.6 ± 2.5 vs 7.8 ± 2.5). UKR patients had significantly less frequently comorbidities and comedications, less frequently had a history of hepatocellular carcinoma and decompensation, as well as the presence of esophageal varices or ascites at the start of therapy. HIV co-infection was reported significantly more often in UKR population, while the incidence of HBV co-infection was comparable. In UKR population infections with genotypes 2 and 3 occurred significantly more frequently than in POL population (34.2% vs. 21.1%), and genotype 1 was less frequent (48.2% vs. 69.4%). Patients regardless of nationality received similar types of therapy, with glecaprevir/pibrentasvir being the most common. The proportions of patients who completed therapy according to plan were similar, but significantly more often UKR patients did not report for a visit assessing the effectiveness and were considered lost to follow-up. As a result, the sustained virologic response (SVR) rate among Ukrainians was significantly lower in the intent-to-treat analysis, but the SVR calculated per protocol exceeded 97% and were similar in both study populations.
Conclusion: Differences in patient characteristics did not affect the effectiveness of the antiviral therapy, which exceeded 97% in both populations, but among Ukrainian patients, there was a higher percentage of people lost to follow-up.

SAT-028

The impact of peers on sustaining hepatitis C elimination in people who inject drugs - a network based model

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Background and aims: The United Kingdom (UK) is on target to meet the World Health Organisation (WHO) objective to eliminate Hepatitis C (HCV) by 2030. The elimination programme in the UK has involved a multifaceted and multi-agency approach. Peers have been utilised to support people who inject drugs (PWID) engage with HCV testing and treatment services. There is however uncertainty concerning the role for peers after HCV elimination is achieved.
Method: We used a validated dynamic network-based model connecting PWID. 100 simulations were conducted in 100 network structural iterations matching properties of UK-net (a validated network structure). At baseline HCV prevalence matched the WHO defined elimination threshold for Southampton (UK) - a large city in the South of England with an estimated 689 people actively injecting drugs. HCV transmission, testing rates and treatment engagement parameters matched real-world (Southampton, UK) and published empirical data. At monthly intervals HCV was transmitted within the

network and a fixed proportion of the nodes in the network underwent testing. A proportion of tested nodes were then treated with directly acting antiviral therapy. As per published empirical data the likelihood of a positive node achieving sustained virological response was higher with peer support. The primary outcome was prevalence of HCV 5 years after the HCV elimination was achieved with and without peers to support treatment engagement.
Results: 5 years post the elimination target being met, without peer support the prevalence increased from 11.68% to 15.75% (95% CI is 15.7–15.8). With peer support the prevalence of HCV in the network continued to decline from 11.68% to 9.11% (95% CI is 15.32 to 5.10%). In the network simulation without peer support, 94 (95% CI 93.3–94.0) tests were needed to maintain the prevalence of HCV at the elimination threshold. In the network simulation with peer support, 47 (95% CI 31.8 to 88.8)) tests per month were needed.
Conclusion: Without continued peer support the elimination of HCV in networks connecting PWID will be more difficult to sustain. Further research is needed to assess cost-effectiveness and the additional impact of peer support on engagement with HCV testing and harm reduction services.

SAT-029
Hepatitis C incidence in Pakistan – large scale test and recall analysis shows that infection rates can be reduced by pro-active 'find and treat' programs
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Background and aims: Elimination of HCV requires treatment of sufficient intensity to reduce the incidence to very low levels. The prevalence of HCV in Pakistan is the highest in the world (estimated at 6.8%) and treatment programs with sofosbuvir/daclatasvir are being rolled out nationwide in an effort to eliminate the infection. The efficacy of these, predominantly local, programs on preventing new infections is unclear and it is not known whether 'treatment as prevention' strategies are effective in high prevalence settings.
Method: HepFreePak is an observational 25,000 person study of the impact of sofosbuvir/daclatasvir treatment in Pakistan that examines, prevalence, incidence over 12 months in uninfected and successfully treated patients and response to current standard of care (sofosbuvir/daclatasvir for 12 weeks in people with an APRI score of <1.5 or 24 weeks in those with features of cirrhosis). We examined incidence of new infections by re-testing people 12 months after a negative test and we studied re-infection by testing people 12 months after achieving SVR12. We examined three different treatment programs: a 'door-to-door' case finding approach (Malir, Karachi); an urban clinic and community testing events (Karachi) and a community camp based 'test and treat' strategy (Gujranwala).
Results: In a 'door-to-door' test and treat strategy in Malir, Karachi 12,021 people (from 14,523 due to be assessed - 83%) were tested for new infections and 22 (incidence rate = 0.18%) were infected, 530 people post SVR (from 930 treated (57%)) were re-tested and 1 was reinfected (0.18%). In an urban clinic and community testing program in Karachi 2064 people (from 3960–52%) were retested and none had developed a new infection but 3 of 189 (1.6%) people with an SVR (from 540 treated –35%) were reinfected. In Gujranwala in a rural outreach community screening program 21 people of 1986 retested (from a cohort of 3247–64%), were newly infected (incidence of 1.06%) and 8 of 94 people (8.5%) with an SVR (from 305 treated –31%) were reinfected.
Conclusion: Assessment of HCV incidence in high prevalence settings by direct assessment is possible, although recall rates are sub-optimal. High intensity treatment programs with domicile based testing and treatment led to low incidence and re-infection rates but rural opportunistic clinics may be associated with higher rates of infections. Effective elimination programs in high prevalence settings will need strategies that have high rates of testing and treatment in defined geographical areas in order to maintain low levels of infection.

SAT-030-YI
Eliminating hepatitis C in Nouvelle Aquitaine, the largest region of France: the SCANVIR® project
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Background and aims: Achievement of Hepatitis C virus (HCV) elimination means getting closer to at-risk individuals outside conventional care structures. The SCANVIR® project aims to "create the event on dedicated days" to optimize screening efficiency and initiate HCV treatment and patient's return to the care pathway. With three teams based in Limoges, Poitiers and Bordeaux, we visited 43 facilities throughout the Nouvelle Aquitaine region to offer screening and treating days.
Method: Since May 2017 for Limoges team and 2019 for the 2 others, dedicated screening days were organized to bring together in each structure the multidisciplinary staff involving hepatologists/infectiologists, addictologists, nurses and social workers, and the screening tools (HCV, HBV, HIV RDTs, FibroScan®, GeneXpert® Point-of-Care molecular testing for HCV RNA detection). A risk prevention, addiction and psychosocial management were proposed at the same time.
Results: Since May 2017, 222 dedicated days have been scheduled and 1706 patients (sex ratio between 2.5 to 3.7 and median age between 39.8 and 46) in 43 different structures taking care of IVDU, migrants or prisoners. Globally, 19.3% were active injectors, 38.2% had substitution treatment, 59.5% excessive alcohol consumption, and 77.3% smoked. 98.9% of patients accepted FibroScan®.17% were suspected to have advanced fibrosis (FS > 8 kPa) and severe fibrosis (FS > 12 kPa) was very likely in 7.2% of the participants. Among the 234 patients in whom CAP was available with FS, 18% had severe steatosis (CAP > 300 dB/m). Depending on structures, RDTs were accepted by 77% to 99% of the participants with 1.6% AgHBs+ and 0.3% HIV Ab+. On average, over the region, 23.6% (390 patients) were HCV Ab+; the percentage of replicating patients varied from 22.6% to 54% (162 patients). Between 82 and 85% of patients have started treatment, of which 80% have been cured or still undergoing treatment. Mean of 10% were not treated.
Conclusion: The Scanvir project is an innovative pathway promoting the "Test, Treat and Prevent" strategy to eliminate HCV. Created in 2017 in Limoges, the SCANVIR® concept has been extended to the whole Nouvelle Aquitaine region with two other teams based in Poitiers and Bordeaux. This concept makes diagnostic testing cost-effective for high-risk patients far from healthcare facilities, with an HCV cure rate of up to 85%. In addition to the educational role played by FibroScan® in "catching" patients who refused RDTs, we highlighted the interest of screening for liver fibrosis and steatosis, a consequence of increasingly frequent alcoholic and metabolic disorders in this population. SCANVIR® is an European trademark registered by Limoges University Hospital.

SAT-031-YI

The cost of HCV elimination in Kazakhstan based on the current disease burden

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Background and aims: Kazakhstan faces challenges in meeting WHO elimination targets for hepatitis C virus (HCV) by 2030 without scaling up its effort in screening, diagnosis and treatment. This study evaluates the current and future burdens of HCV, estimates the economic impact and provides a roadmap for achieving overall elimination goals.
Method: A comprehensive analysis was conducted using a literature review, consultation with local experts and mathematical modelling to assess the HCV burden and associated costs in Kazakhstan. Two scenarios were modelled: the 2024 base case (status quo in the country) and a WHO elimination scenario (outlining interventions required to achieve designated targets). Cost-effectiveness comparisons were made between a national elimination program and the existing healthcare framework, highlighting the elimination scenario's feasibility.
Results: At of the end of 2024, Kazakhstan is estimated to have 340,140 RNA-positive HCV infections, with 89% of cases concentrated in the 20–69 age group, representing only 58% of the country's total population. To meet WHO elimination targets, the country must annually diagnose 13,000 individuals starting in 2025 incrementally increasing to 73,000 by 2028. They also need to annually treat 3,900 patients beginning in 2025 incrementally increasing to 52,200 by 2028. A national elimination program could reduce HCV prevalence by 51% relative to 2024, preventing 1,700 cases of decompensated cirrhosis, 2,180 hepatocellular carcinoma cases and 1,890 liver-related deaths. Simplified diagnostics, including rapid testing, cost-effective PCR assays, along with decentralized care, having general practitioners treat non-cirrhotic patients, would significantly reduce healthcare costs. Although expanding screening and treatment will increase short-term costs, an elimination program will result in long-term savings by reducing direct costs associated with hospitalization, transplantation and cancer treatment, currently accounting for 55 million USD annually.
Conclusion: Implementing a national elimination program is the only path forward for Kazakhstan to meet WHO targets by 2030. Investment in expanded targeted screening within the young to middle-aged adult cohort could identify over 80% of HCV cases. This along with simplified diagnostics and decentralized care will reduce the HCV burden, prevent liver-related deaths and result in long-term cost savings, ensuring better health outcomes for the country.

SAT-033

Using community partnerships to achieve micro-elimination of HCV and HIV in inner-city Vancouver

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Background and aims: Vancouver's inner city has some of the highest rates of HCV and HIV in Canda. It is therefore crucial to examine the efficacy of approaches being used to eliminate these diseases among this community. We aimed to determine whether the current approach VIDC is using to identifying and treating PWIDs in Vancouver's inner city has led to a reduction in the number individuals viremic for both HCV and HIV.
Method: Since 2022, the Vancouver infectious diseases centre (VIDC) has been hosting weekly or twice-weekly community pop-up clinics, or CPCs, at various locations in Vancouver's inner city. At each event, point-of-care HCV and HIV antibody testing is offered to up to 30 individuals. Individuals testing antibody positive for HCV often have their blood drawn on site and those confirmed to be viremic are followed up with by outreach. Individuals confirmed to be viremic for HCV and/or HIV are engaged in treatment under a multi-disciplinary model of care which includes immediate access to OAT and/or safe supply and treatment within a multidisciplinary program of care to address all medical, social, psychological and addiction-related needs in a comprehensive manner. As part of a partnership with Atira housing society, since 2022 CPCs have regularly been held in the common spaces of Atira buildings with the goal of achieving micro-elimination of HCV, and virologic suppression of HIV, among the individuals living in these spaces.
Results: As a preliminary analysis, we chose to evaluate the prevalence of HCV and unsuppressed HIV in 4 Atira buildings, each of which was visited 6 times in 2022 through 2024. We evaluated both the proportion of individuals viremic for HCV and HIV. We saw a clear reduction in the proportion of individuals who are viremic for HCV (14% in 2022 vs. 4% in 2024; $p = 0.1$). We saw a similar trend in the number of individuals unsuppressed for HIV (3.7% in 2022 vs. 1.5% in 2024); however, due to the small number of people in this sample statistical significance can not be evaluated.
Conclusion: This study has demonstrated while PWID may be a particularly difficult demographic to target for HIV and HCV treatment, with the help of community partnerships and a multidisciplinary approach to care we can achieve HCV and HIV micro-elimination. Our findings show that through the use of community partnerships, continued testing and follow-up, and a multidisciplinary model of care, we are on our way to achieving elimination of HCV, and HIV viremia, among the residents of Vancouver's inner city.

SAT-034

Early diagnosis of HCV in people who inject drugs in the Czech Republic: preliminary results of a pilot project

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Background and aims: The Czech Republic is a country with a low HCV prevalence (0.5%); nevertheless, people who inject drugs (PWID) represent an important HCV reservoir. Despite regular screening in addiction services and low-threshold centres, only a small number of patients start antiviral treatment and achieve sustained virological response (SVR). The Programme of Early Diagnosis of HCV in PWID, organised by the National Screening Centre of the Institute of Health Information and Statistics of the Czech Republic, aims to describe the HCV cascade of care among PWID, identify gaps, and explore barriers to HCV care.
Method: A single-arm prospective pilot multicentre study of adult former, recent and current PWID has been conducted in 25 low-threshold centres and street work facilities lasting from 12/2023 to 12/2025, performing anti-HCV screening by capillary blood or saliva tests in a targeted number of 3,000 PWID, terminating according to which occurs first. Patients screened positive for HCV are linked to antiviral (DAA) treatment at 13 dedicated healthcare facilities (HCF) providing direct-acting antiviral therapy. The study's primary endpoints are to assess anti-HCV prevalence in PWID and linkage to HCV treatment centres; secondary endpoints include DAA initiation and completion of therapy.

Results: During the first 11 months of the project (12/2023–10/2024), 1,581 individuals were recruited, 1,019 (64.5%) males and 561 (35.5%) females, 42.9% of the individuals belonging to the 30–39 year-old age group. The prevalence of anti-HCV positivity at screening was 31.4% (496 individuals); 149 (30.0%) individuals reported anti-HCV treatment in the past. Forty anti-HCV individuals had negative HCV RNA point-of-care test, 419 individuals were subsequently referred to HCF, and 33 people refused further evaluation. Only 164/419 (39.1%) individuals underwent an HCV assessment in an HCF. 112 (68.3%) patients had positive HCV RNA results, and 96 (85.7%) initiated anti-HCV treatment. The prevalence of cirrhosis (liver stiffness measurement ≥12.5 kPa) was 10.6%, and the most prevalent genotype was genotype 3 (39 individuals, 34.8%). So far, 40 patients have completed antiviral therapy, and 15 of them have achieved an SVR.
Conclusion: The study shows that the unsatisfactory referral from addiction services to anti-HCV treatment centres represents the main gap in the cascade of care in PWID living with HCV. The establishment of PWID-friendly treatment centres and assistance to HCF visits by social and peer workers could enhance linkage to care. The pilot project is funded by Operational Program Employment Plus (Ministry of Labour and Social Affairs of the Czech Republic) and co-funded by the EU.

SAT-035

Results of the national program for the elimination of viral hepatitis in Uzbekistan

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Background and aims: In 2022, Uzbekistan implemented the National Program for the Elimination of Viral Hepatitis B and C. The program's primary objectives are to annually screen the population for hepatitis B and C viruses and provide antiviral treatment for individuals infected with hepatitis C virus (HCV).
Method: Testing was conducted using rapid tests in primary healthcare facilities, with subsequent confirmation of positive results by enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) in regional hepatology centers. HBV-positive patients were provided with a complimentary quantitative HBsAg analysis, while patients were charged for the quantitative PCR test. Residents with a positive anti-HCV antibody were offered a complimentary qualitative PCR test. Individuals with a positive PCR test were provided with antiviral therapy (Sofosbuvir + Daclatasvir) for 12 weeks without cirrhosis and 24 weeks with cirrhosis, manufactured in the Arab Republic of Egypt. All data pertaining to the examined residents were entered into the Redcap electronic database.
Results: From January 1, 2024 to November 20, 2024, 1,100,278 individuals underwent testing for HBV and 1,100,118 for HCV. Of these, 34,186 (3.1%) were HBsAg positive and 41,869 (3.8%) were anti-HCV positive. A quantitative confirmatory test for HBsAg was performed on 5,572 (16.3%) of those who tested positive for HBsAg which were provided with anti-viral treatment if met the national treatment guidelines. HBeAg positivity rate was less than 5%. PCR testing was conducted for 25,747 people (61.5%) of those who were anti-HCV positive. On average, 1,488 patients with HCV are identified every month, according to Redcap database. A positive result for HCV RNA was detected in 17,934 people (69.7%) of those who underwent PCR testing. A total of 19,300 HCV patients were treated during this period.
Conclusion: According to the study, the prevalence of HBV in Uzbekistan was 3.1%, while the prevalence of HCV was 3.8%. The lower prevalence of HBV compared to HCV could be attributed to the introduction of HBV vaccination in Uzbekistan in 2000. The low rates of confirmatory quantitative HBsAg were primarily due to the fact that these tests were financially supported by the state. In the case of HCV, the rate of PCR diagnostics and antiviral therapy (61.5% and 69.7%, respectively) underscored the necessity for enhanced awareness regarding the complications of viral hepatitis among both the general population and primary care professionals.

SAT-036

Physician perspectives on hepatitis C treatment for women of childbearing age and during pregnancy: results from a global multispecialty survey

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Background and aims: There is limited guidance regarding hepatitis C virus (HCV) treatment in pregnancy but emerging data suggests direct acting antiviral (DAA) therapy for these patients is safe and effective. We performed a global survey among gastro-hepatologists (GI-hep), infectious disease (ID) specialists, obstetricians (ob-gyn), and primary care physicians (PCPs) to explore current perspectives on HCV treatment in pregnancy.
Method: A 39-item survey was designed by members of The Global Liver Council (GLC) through an iterative process including revisions by experts at GLC, American College of Obstetricians and Gynecologists (ACOG), and the Coalition for Global Hepatitis Elimination (CGHE). The survey was distributed electronically starting in 9/2024 through GLC, CGHE, ACOG and institutional

provider networks. Multivariable regression was performed to evaluate predictors of willingness to treat HCV in pregnancy.
Results: To date, 442 surveys have been completed from 49 countries (53% GI-hep, 29% PCPs, 18% Ob-Gyns, 10% ID). 30% of respondents reported that ≥50% of their patients were women of childbearing age. Regarding HCV knowledge, 66% of providers self-assessed as adequate or superior (89% GI-hep, 49% PCPs, 26% Ob-Gyn, $p < 0.01$), and 63% reported being comfortable treating HCV (88% GI-hep, 42% PCP, 21% Ob-Gyn, $p < 0.01$). Majority (80%) reported discussing pregnancy plans with HCV-positive women; 77% screen for pregnancy prior to initiation of DAAs. Only 12% reported treating a pregnant woman with DAAs (8% GI-hep, 13% PCP, 22% Ob-gyn, $p < 0.01$), and 21% would consider treating these patients (14% GI-hep, 24% PCP, 37% Ob-Gyn, $p < 0.01$). The main reasons for not considering DAAs in pregnancy were lack of safety data for DAAs in pregnancy (60% of responders) and adequate guidelines (56%). Majority of Ob-Gyns (57%) would refer to specialty care for HCV treatment during pregnancy. If an individual became pregnant while on DAAs, 29% would continue, 31% would stop, 23% would refer to another specialist, and 13% did not know. Across regions of the world, the highest acceptance of DAA use in pregnancy was in North America (45% vs. <20% in other regions ($p < 0.01$). In multivariate analysis, the only predictor of a greater willingness to treat HCV in pregnancy was having ≥10% of practice that are injection drug use population (adjusted OR (95% CI) = 2.5 (1.5–4.2)) while GI-hep specialty was associated with a lower willingness (OR = 0.4 (0.2–0.7)).
Conclusion: Despite adequate levels of HCV knowledge, few providers have experience with HCV treatment in pregnancy or would consider it. Ob-gyns are more in support of HCV treatment in pregnancy, but less comfortable treating themselves, which can lead to referral to specialists who are reluctant to treat. Further availability of safety evidence and inclusion of specific recommendations in guidelines could increase uptake of DAAs for pregnant individuals.

SAT-037
The clinical characteristics and antiviral treatment status among chronic HBV mono and HDV co-infected patients

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Background and aims: The prevalences of Hepatitis B virus (HBV) and Hepatitis D virus (HDV) infection were respectively estimated with 11.1% of the general population, and with more than 60% of HBsAg carriers in Mongolia. Among those co-infected with HBV and HDV, 70–80% of those have a threefold increased risk of developing cirrhosis and liver cancer. In this study, we assessed the rates of chronic infection and liver cirrhosis in individuals with chronic HBV mono-infection and those co-infected with HBV and HDV, as well as their use of antiviral treatment.
Method: This study involved 63 participants with chronic HBV mono-infection and 233 participants with HBV and HDV coinfection, who voluntarily participated in the study named Detect HCC at the Liver Center, Mongolia. The information on blood tests, antiviral drug usage, and Fibroscan, CE-MRI, AFP, and PIVKA II tests were collected from study participants. qHBsAg and qAnti-HCV tests were detected by the chemiluminescence analyzer (HISCL-5000 analyzer, Sysmex, Japan), and HDV infection was assessed using the ELISA test. HBV-DNA level was measured using Genexpert (Cepheid, USA), and RT-PCR quantified HDV RNA.
Results: A total of 296 participants were included in the study, of which 21.2% (n = 63) had mono HBV infection and 78.7% (n = 233) had HBV+HDV co-infection. The mean age was 47 ± 11.2 years and 47.5 ± 9.3 years, respectively. Among those with mono HBV infection, 93.6% (n = 59) had chronic hepatitis (CH) and 6.4% (n = 4) had liver cirrhosis (LC). In the HBV+HDV co-infection group, 55.3% (n = 129) had CH and 44.6% (n = 104) had LC, with 79.8% (n = 83) in Child-Pugh A, 12.5% (n = 13) in Child-Pugh B, and 7.6% (n = 8) in Child-Pugh C. Regarding the NUC status, 66.7% (n = 42) of those with mono HBV infection had indications for antiviral therapy, and 33.3% (n = 21) were on NUC treatment. In contrast, 38.2% (n = 89) of the HBV+HDV co-infection group had indications for NUC therapy, and 61.8% (n = 144) were receiving NUC treatment. Only 0.6% (n = 3) of the co-infected group were on antiviral treatment for HDV, including Peg-Interferon and Bulevirtide. Liver inflammation was significantly higher in the HBV +HDV co-infection group compared to the mono HBV group.
Conclusion: Our study revealed that individuals with HBV+HDV co-infection have a higher rate of LC compared to those with mono HBV infection. Regarding the treatments for HBV and HDV, among those with mono HBV infection, only 33.3% are currently on NUC treatment while only 0.6% of HBV+HDV co-infected participants on antiviral treatments including peg-IFN and BLV. The elevated liver function indicators and the higher incidence of cirrhosis in HBV and HDV-infected individuals emphasize the urgent need for treatment against HDV.

SAT-038
Atherosclerotic cardiovascular disease risk in chronic hepatitis C patients with metabolic dysfunction-associated steatotic liver disease after viral eradication: a multi-center cohort study

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Background and aims: Steatotic liver disease (SLD) and cardiometabolic risk factors (CMRF) are not uncommon in chronic hepatitis C (CHC) patients. The risk of atherosclerotic cardiovascular disease (ASCVD) in CHC patients achieving sustained virological response (SVR) is unclear. This study aimed to assess the impact of CMRF grade and items on ASCVD risks among CHC SLD patients after HCV eradication.
Method: We constructed a nationwide multi-center registry cohort in Taiwan. SLD was identified via ultrasonography and hepatic steatosis index (HSI) >36. Metabolic dysfunction-associated steatotic liver disease (MASLD) was defined when SLD with at least one of five CMRFs. Competing risks of death and liver transplant were considered using Gray's cumulative incidence method and Cox sub-distribution hazards.
Results: Among 8,755 CHC patients achieving SVR with SLD, 624 (7.1%) developed ASCVD over a median follow-up of 3.9 years. MASLD patients had a higher ASCVD incidence than those in simple SLD patients (190.2 vs. 84.0 per 10,000 person-years, $P < 0.001$). Adjusted

hazard ratios showed a dose-dependent ASCVD risk increase with higher CMRF grades in MASLD (aHR: 1.72 for grade 1, P = 0.013, 1.78 for grade 2, P = 0.010, 2.21 for grade 3, P < 0.010, 2.33 for grade ≥4, P < 0.001, respectively). Hypertension (aHR: 1.43, P < 0.001) was the major CMRF increasing ASCVD risk. Subgroup analysis indicated increased ASCVD risk with MASLD, CMRF grades, and CMRF items in non-cirrhotic or normal renal function patients, but not in those with liver cirrhosis or abnormal renal function.
Conclusion: ASCVD risk management is crucial for CHC MASLD patients post SVR, especially in those non-cirrhotic and normal renal function.

SAT-039
Revisiting hepatitis B and delta viral infections in the brazilian Amazon: current epidemiological, clinical and molecular characteristics
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Background and aims: Updated estimates of the prevalence, clinical and molecular characteristics of hepatitis B (HBV) and delta (HDV) virus infections are crucial to formulate public health strategies aimed at eliminating viral hepatitis as a public health threat by 2030, as proposed by the World Health Organization. The aim of the present study was to analyze current epidemiological, clinical and molecular characteristics of HBV- and HDV- infected individuals in the Brazilian Amazon.
Method: This was a descriptive and prospective study, performed with HBV- infected individuals (HBsAg +) followed at two Viral Hepatitis Referral Units in the state of Amazonas, Brazil, from October 2022 until February 2024. All patients consecutively seen at these two reference units were invited to participate and to respond to a specific questionnaire regarding clinical and epidemiological issues and aspects related to access to medical care. Additional clinical and laboratory information was taken from medical records. Blood samples collected after the interview were evaluated for HBV and HDV serological markers. Commercial kits (Architect i1000TM, Abbott Diagnostics, Brazil and DiaSorin®, Italy) were used to detect HBsAg, anti-HBc, anti-HBs, HBeAg, and anti-HDV. HBV DNA and HDV RNA were also tested by commercial kits (Abbott RealTime HBV Viral Load Assay and Altona Diagnostic RealStar® HDV RT-PCR kit) and subjected to genome sequencing by the Sanger method.
Results: A total of 356 were included in the study, the mean age was 45 years, and most, 51.4% (183), were female. Most, 75.6% (n = 269) tested positive for HBsAg+ without markers for HDV (anti-HDV-). Overall, 275 (77.6%), were HBV DNA positive, and11 (3.2%) were HBeAg positive. Among 275 HBV DNA positives, the HBV genotypes identified were: A1 (12.7%), A 2 (0.9%), D1 (0.9%), D2 (5.5%), D4 (2.7%), F1 (20%), F2 (57.3%). Of the 356 total participants, 87 (24.4%) tested anti-HDV positive, of which 43 (49.4%) were HDV RNA positive. All HDV positive samples tested were genotype 3. When asked about previous care for hepatitis, 162 (45.8%) reported that this was the first time they sought or had access to a health unit dedicated to viral hepatitis care; 65 (29.3%) presented with signs and symptoms of advanced liver disease; 36 (10.7%) reported previous or current HBV treatment; 28 (9.4%) reported they were previously receiving care but have since discontinued. Among 87 anti-HDV positive individuals: 22 (33.5%) presented with signs and symptoms of advanced liver disease.
Conclusion: We confirmed the presence of HDV-3 and the prevalence of HBV genotypes A, D and F in the Brazilian Amazon. Our data also revealed that access to medical care and medication for HBV and HDV infections were limited to a restricted proportion of affected individuals in this area. HBV and HDV elimination by 2030 are probably not a realistic goal given the current medical and logistic approach to detection and treatment.

SAT-040
Identifying people who are HBV positive but undiagnosed: a model-based approach informed by health administrative data
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Background and aims: Hepatitis B virus (HBV) infection continues to pose a major public health threat worldwide. The development of effective and tailored strategies to ensure access to HBV care requires an understanding of trends in the geographic and demographic distribution of the disease burden in terms of the number of infections and, more importantly, the number of patients who remain undiagnosed, as the majority of infections remains asymptomatic until the onset of late-stage disease. Such evidence can guide strategic planning and resource allocation of programs to reduce disease transmission, improve screening, and improve treatment uptake. Our objective is to estimate the chronic hepatitis B (CHB) prevalence and undiagnosed proportion in two Canadian provinces, British Columbia (BC), and Ontario, using a back-calculation modeling approach informed by population-level health administrative data.
Method: We first conducted population-based retrospective analyses of health administrative data for the two provinces from 2003 to 2018 to generate the annual incidence of patients with newly diagnosed hepatocellular carcinoma (HCC), decompensated cirrhosis (DC) and CHB as well as patients treated for HBV. We then developed a back-calculation framework to estimate the historical prevalence of CHB. We used a Bayesian Markov Chain Monte Carlo (MCMC) algorithm to back-calculate the historical CHB prevalence and the undiagnosed proportion through a calibration process. The algorithm constructs the probability distribution of the historical CHB prevalence and the undiagnosed proportion by comparing the model-generated predictions of the annual number of CHB health events against observed health administrative data such as the diagnosed HCC and diagnosed DC incidences generated in the retrospective analysis.
Results: Our results indicated a decreasing trend in the undiagnosed CHB proportion and CHB prevalence over time in the two provinces. The mean prevalence estimates for BC, and Ontario in 2018 were 0.834% (95% CI: 0.719%–0.975%), and 0.424% (95% CI: 0.399%–0.460%), respectively. The undiagnosed proportion estimates for BC, and Ontario were 21.8% (95% CI: 17.3% – 26.8%), and 17.3% (95% CI: 15.2%–20.1%) in 2018, respectively.
Conclusion: This is the first study to estimate CHB prevalence and undiagnosed proportion in Canada using provincial health administrative data. Our findings provide evidence to guide decision-making on HBV screening strategies and linkage to care to reach undiagnosed individuals and help meeting the elimination target.

WEDNESDAY 07 MAY

Rare liver diseases (including paediatric and genetic) – Basic

WED-323

Fazirsiran for alpha-1 antitrypsin deficiency-associated liver disease: long-term efficacy and safety results from a phase 2 extension study

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease. The protease inhibitor (Pi)*ZZ genotype causes accumulation of Z-alpha-1 antitrypsin (Z-AAT) in the liver, which may lead to AATD-associated liver disease (AATD-LD). We report data from the long-term extension phase of the phase 2 AROAAT-2002 trial (NCT03946449; primary study: Strnad *et al. NEJM* 2022) that evaluated the efficacy and safety of fazirsiran (an investigational small interfering RNA therapy for AATD-LD) in patients (pts) with AATD-LD.
Method: In the primary study, 16 adults with the Pi*ZZ genotype and liver fibrosis received fazirsiran 200 mg (cohorts 1 [n = 4] and 2 [n = 8]) or 100 mg (cohort 1b [n = 4]) on Day 1 and Week (W) 4 and then every 12 weeks (Q12W) for 24 weeks (cohorts 1/1b) or 48 weeks (cohort 2). Pts who entered the extension phase received fazirsiran 200 mg Q12W for up to 36 months. Efficacy and safety endpoints were assessed.
Results: In total, 15/16 pts who completed the primary study entered the extension phase; mean (standard deviation [SD]) follow-up across both phases was 172 (36) weeks. Mean (SD) total intrahepatic Z-AAT declined from baseline (N = 16; 60 [36] nmol/g) to W24 (n = 8) by 81% (8%), to W48 (n = 7) by 90% (9%), to W72 (n = 3) by 93% (2%) and to W96 (n = 2) by 93% (7%). Mean (SD) serum Z-AAT declined from baseline (255 [55] μg/mL) to W40 (N = 16) by 83% (10%) and to W148 (n = 15) by 88% (5%). Periodic Acid-Schiff staining with diastase globule burden score improved in all pts in the primary and extension phases. METAVIR fibrosis stage improved in 7/15 (47%) pts during the primary study and 3/5 (60%) in the extension phase. Two pts in the primary study and no pts in the extension experienced worsening of fibrosis. Mean (SD) liver stiffness, measured via vibration-controlled transient elastography, declined from baseline (N = 16; 10 [4] kPa) to W24 (n = 8) by 10% (15%), to W48 (n = 7) by 15% (35%), to W72 (n = 7) by 14% (16%) and to W96 (n = 6) by 24% (30%). Mean (SD) Pro-C3 declined from baseline (N = 16; 20 [6] μg/L) to W40 (N = 16) by 14% (25%) and to W148 (n = 15) by 26% (18%). Liver enzymes that normalized during the primary study remained in the normal range through the extension phase. Treatment emergent adverse events (TEAEs) were reported in all pts, most were mild/moderate, and none led to treatment discontinuation; 8 (50%) pts experienced ≥ 1 serious TEAE and none were considered treatment-related. The most common TEAEs were nasopharyngitis (n = 13, 81%) and COVID-19 (n = 10, 63%). Variability in pulmonary function tests was observed, but there was no overall decline throughout the study.
Conclusion: Fazirsiran showed sustained activity and long-term (≤3 years) safety in pts with AATD-LD during the extension phase. Fazirsiran was associated with reductions in liver/serum Z-AAT, improvements in measures of AATD-LD and a long-term safety profile that supports further clinical development in pts with AATD-LD.
Study/writing funding: Takeda Development Center Americas, Inc.

WED-324

Single-cell sequencing reveals heterogeneity differences in cholangiocyte organoids derived from biliary atresia patients compared to non-biliary atresia controls

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Background and aims: Biliary atresia (BA) is a poorly understood cholangiopathy characterized by progressive extrahepatic bile duct obstruction in newborns, making it the leading cause of pediatric liver transplantation worldwide. Despite extensive research, its etiology and pathogenesis remain elusive. The primary treatment, Kasai portoenterostomy, aims to restore bile flow but yields unsatisfactory outcomes, highlighting the need for deeper insights into disease mechanisms to drive therapeutic development. Human organoids have emerged as powerful in vitro models for studying toxicology, drug discovery, and disease modeling. Here, we utilized BA and non-BA extrahepatic human cholangiocyte organoids (EHCOs) to investigate transcriptional heterogeneity at the single-cell level and uncover novel insights into BA pathophysiology.
Method: EHCOs were generated from extrahepatic bile ducts of BA patients undergoing Kasai portoenterostomy and non-BA controls undergoing liver transplantation for metabolic syndromes. EHCOs from six BA patients and six non-BA controls were dissociated into single cells with >90% viability and processed using the 10x Genomics Chromium platform. Libraries were prepared per manufacturer protocol and sequenced on the Illumina NextSeq 500 platform. Single-cell data were analyzed using 10x Cell Ranger software (v3.01) and mapped to the GRCh38 human genome.
Results: Single-cell analysis revealed eleven distinct cell clusters across BA and non-BA EHCOs. Differentially expressed gene analysis revealed significant transcriptional differences between BA and non-BA EHCOs, consistent with previous findings. BA-derived EHCOs exhibited remarkable heterogeneity, for example, MMP7, previously implicated in BA, was consistently overexpressed in BA EHCOs but showed substantial variability in expression levels across cell clusters, suggesting heterogeneous disease effects. Interestingly, cell clusters enriched for markers of other cell types were identified, despite all EHCOs originating from extrahepatic bile ducts. In non-BA controls, a specific cluster expressed hepatocyte markers, indicating potential cholangiocyte-to-hepatocyte differentiation, a capacity that appeared restricted in BA-derived EHCOs.
Conclusion: BA-derived EHCOs exhibit distinct and heterogeneous transcriptional patterns compared to non-BA controls. This heterogeneity may reflect variability in cellular responses within the diseased bile ducts. Additional analysis and functional studies are carried out in order to understand the relevance of this data to BA etiology. Further studies are needed to define these transcriptional

patterns and uncover their implications for BA pathophysiology, potentially paving the way for targeted therapeutic approaches. Understanding the transcriptional heterogeneity and impaired differentiation capacity of BA-derived EHCOs may inform personalized therapeutic approaches or regenerative strategies targeting bile duct repair.

WED-325

The omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, improve the response to fibrates in human liver cell models

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Background and aims: The accumulation of toxic bile acids (BA) in the liver is a key factor in the development of primary biliary and sclerosing cholangitis (PBC and PSC), two autoimmune liver diseases deprived of any curative options. *Reducing hepatic BA concentration is thus an important pharmacological target for the treatment of PBC and PSC.* Currently, ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are two of the few drugs approved for the treatment of PBC, while no drugs are available for PSC. However, even if these drugs have many beneficial effects, including the lowering of hepatic BAs, a significant proportion of PBC patients either do not respond to or are intolerant to UDCA and/or OCA. *Therefore, there is still a need for new therapeutic options.* Fibrates, such as fenofibrate and bezafibrate, are currently tested in off-labeled trials. Since we already reported that omega-3 polyunsaturated fatty acids, such as the eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), improve the response to UDCA and OCA, we sought to test the possibility that similar improvement also occurs with fenofibrate and bezafibrate.
Method: Human HepG2 cells were treated for 24H with vehicle (DMSO-ethanol 0.01%/0.01% v/v), 100μM fenofibrate and 100μM bezafibrate, in the presence or absence of EPA/DHA (50:50μM). Afterward, the expression of essential genes related to BA transport, synthesis and detoxification was quantified by qRT-PCR.
Results: In the presence of EPA/DHA, liver cells exhibited a stronger response to fenofibrate and bezafibrate when compared to the drugs alone. Indeed, when used alone, fenofibrate and bezafibrate caused an inhibition of respectively 37% and 34% in the CYP7A1 transcript levels. However, the addition of EPA/DHA led to a stronger reduction of this rate-limiting enzyme in BA synthesis by 58% and 52% with the same dosage of fenofibrate and bezafibrate. Accordingly, the addition of EPA/DHA to fenofibrate ($p < 0.001$) and bezafibrate ($p < 0.01$) caused a 58% and 47% reduction of the CYP27A1 synthesis gene, encoding another essential BA-synthesizing enzyme, while when used alone, the 2 drugs failed to modulate this gene expression. Moreover, the combination EPA/DHA + fenofibrate also reinforced the overexpression of the MRP2 export gene from 1.5 to 29-fold over control. A similar inhibition was also observed for the NTCP transcripts but only with the EPA/DHA + bezafibrate combination.
Conclusion: The addition of EPA/DHA to fibrates seems to be a promising way to reduce hepatic BA concentration. Further analysis is, however, required to validate this hypothesis.

WED-326

A potent tool to study progressive familiar intrahepatic cholestasis: urine – derived human induced – hepatocytes

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Background and aims: Human induced hepatocytes (hiHeps) derived from human induced pluripotent stem cell (hiPSC) represent a potent tool to study Progressive Familial Intrahepatic Cholestasis (PFIC). Urine is an advantageous source of cells since it can be obtained in a non-invasive way. Proximal tubular epithelial cells (PTEC) have a remarkable ability to be reprogrammed into hiPSC. This study aimed to improve the yield of the process for generating hiHeps from iPSC obtained from PTEC.
Method: 108 urine samples were collected from 6 healthy donors (3 females, 3 males, 6 samples/day for 3 days) added with antibiotics and stored at 4°C for 24 h before being processed after urine strips analysis. In step 1, PTEC were isolated from urine samples, in step 2 reprogrammed into hiPSC, and in step 3 differentiated into hiHeps. Improved step 1 protocol involves the addition of phosphate buffer (final concentration 0,5 M) and the use of 20 uM cells strainers. For step 3, protocol 1 (doi: 10.1016/j.jhep.2019.03.031), protocol 2 (doi: 10.1007/978-1-0716-2557-6_4), protocol 3 (doi: 10.1002/9780470151808.sc01g04s26) and protocol 4 (STEMdiff™Hepatocyte Kit) were compared to study the expression of hepatic genes and the release of albumin.
Results: Yield is critical in step 1 and 3. A higher percentage of urinary cells adhesion was found in male samples (37% ± 30%) compared to female samples (6% ± 10%); moreover, two out of the three female samples failed to give cells. The adhesion percentage for samples with a pH ≥ 7 was significantly higher than samples with a pH <7. Using 20 uM cell strainers to filter squamous cells during preparation and adding phosphate buffer to increase pH, cell yield increased in female samples from 6% ± 10% to 26% ± 20%. PTEC were obtained even from the two female samples from which we had previously been unable to obtain cells, reducing also the standard deviations and obtaining a final yield comparable between the two sexes. Three out of four protocols of step 3 showed albumin release into the medium (35,5 ng/mL; 58 ng/mL; 18 ng/mL) with a similar mRNA behavior. Protocol 3 and 4 showed the higher number of hepatic markers expressed with the higher expression.
Conclusion: Buffering the pH and using cell strainers increased the yield of PTEC. Selecting the most effective hepatocytes differentiation protocol enabled optimization of this long process to maximize its efficiency. Improvements allow this tool to be more applicable for studying PFIC.

WED-327-YI

Rare but not forgotten - comprehensive molecular and histological analysis of the primary yolk sac tumor of the liver and corresponding patient-derived cell line

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Background and aims: Primary yolk sac tumor (YST) of the liver is uncommon disease with less than 15 cases reported worldwide and is often misdiagnosed as HCC. It is a type of germ cell tumor that arises from embryonic tissue left over from fetal development and may be initiated by the occurrence of genetic alterations or oncogenic mutations. Survival can vary widely depending on the stage of the tumor and the effectiveness of therapy. Therefore, in-depth molecular and histological characterization of YST and the development of representative models are essential to better understand and diagnose this disease and to develop patient-specific therapeutic options.
Method: Samples of adjacent liver and core tumor tissue were collected and processed from a 66-year-old female patient. Long-term culture of primary cell line (PCL) was established. Morphological and histological characteristics of the obtained

tissues, xenograft tumors and cell line were analyzed by immunohistochemistry (IHC) and immunofluorescence (IF). Immune cell composition was inferred from RNA-seq data and validated by IHC. Transcriptomic profiling was performed by RNA sequencing followed by time-course, GSEA and IPA analyses. Key oncogenic alterations and potentially actionable mutations were identified by targeted NGS. Dose-response and synergistic effects between classical and targeted therapies were determined.
Results: Tumor tissue showed a solid trabecular growth pattern with the presence of necrosis. The newly derived cell line fully resembled the morphological features of the primary cancer in vitro and in vivo. IF and IHC showed expression of typical YST markers AFP, CK19, which were effectively maintained in xenografts, PCL and spheroids. Transcriptomic profiling revealed activation of embryonic markers, enrichment of T cells and reduction of macrophages and allowed identification of potentially effective therapeutics. In addition, the study revealed previously unknown genomic alterations and the presence of a novel driver mutation. Amplifications on chromosomes 22q12.2, 9q34.11, 8q24.3, previously associated with poorer survival in pancreatic neuroendocrine tumors, were detected, suggesting a potentially more aggressive disease. NGS approaches confirmed that key oncogenic mutation TP53 as well as potentially actionable mutation KDR were present in tumor and were highly conserved in PCL. Specific targeting of detected actionable mutation confirmed superior response and sustained sensitivity to specific inhibition compared to non-mutated control cells.
Conclusion: Here, for the first time, we were able to dissect the liver YST at an unprecedented molecular level and at the same time establish a primary cell line. We identified molecular alterations that could be used to effectively predict patient response to targeted therapy and serve as an effective model for this extremely rare disease.

WED-328
Integrated multiomic analysis of hepatoblastoma and patient-derived organoids
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Background and aims: Hepatoblastoma (HB) is the most common liver malignancy in children and often involve an N-terminal mutation in β-catenin, inducing unregulated WNT signaling. Currently, there are no targeted therapies. General chemotherapy is often used as a first line approach, followed by surgical resection. This disease is commonly stratified via histology and the two most common subtypes are known as “fetal” (more differentiated) and “embryonal” (stem-cell like). We recently demonstrated through single cell analysis that these two subtypes can be distinguished through the expression of two transcription factors: HNF4A for fetal HB and LEF1 for embryonal HB. The transcriptional profiles of the two subtypes indicate a divergence in WNT signaling. In this study, we investigate the downstream consequences from this divergence in terms of alterations to the (spatial) gene expression that contributes to metabolic programming and modulation of the immune environment.
Method: Biopsy, resection, and patient-derived xenograft tissues and organoid models were analyzed by single cell RNA-seq, ATAC-seq or Visium spatial RNA-seq. The output data were analyzed using Seurat, ScanPy and SquidPy.
Results: In total, we analyzed tissues and organoid models resulting in transcriptional data from over 30 unique cases of HB. This revealed a clear segregation of the two tumor subtypes via the expression of HNF4A and LEF1. These subtypes are often present in the same tumor and exhibit mutually exclusive expression of their respective markers. Building on our previous observations, we will further elucidate the metabolic programming of the fetal subtype, which has higher expression of genes involved in the urea cycle and glycolysis than the embryonal subtype, which favors beta-oxidation and lactic acid metabolism. The difference in metabolism can be advantageous for targeted pharmacological interventions to disrupt the associated enzymes that are preferentially enriched in the embryonal subtype. Beyond metabolic differences, there is a consistent immune suppression in the tumor microenvironment (TME) amongst both subtypes where lymphocytes are staged at the periphery of the TME with minimal propensity for invasion.
Conclusion: In summary, we present an integrated analysis for investigating tumor heterogeneity and TME for a substantial cohort of HB cases. We have identified that divergence in WNT signaling between fetal and embryonal tumor cells correlates with differences in metabolic programming. Finally, both HB subtypes have low numbers of infiltrating lymphocytes in the tumor microenvironment. Our findings in this study will provide insights into future targeted therapies to treat different cases of HB.

WED-333-YI
Recreating Wolman disease in human liver organoids: a new model for pathophisiology and therapeutic exploration
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Background and aims: Wolman disease (WD) is a rare genetic disorder inherited in an autosomal recessive pattern, resulting from mutations in the lysosomal acid lipase (LAL) gene. It is characterized by the accumulation of cholesteryl esters and triglycerides within lysosomes, which leads to severe dysfunction of the liver and other organs. At present, there is no cure for this debilitating disease, and available treatments are limited to supportive care. The goal of this project is to create an in vitro model of WD using human liver organoids (HLO) derived from human induced pluripotent stem cells (iPSCs) and test potential treatments for the disease.
Method: To this aim, we implemented a reproducible method to derive multi-cellular human liver 3D.
organoids are composed of hepatocyte-, stellate-, biliary- and Kupffer-like cells. LAL KO iPSCs were obtained by CRISPR-Cas9 technology, differentiated toward a hepatocyte-like state and treated with fatty acids to induce metabolic stress. Single cell RNA sequencing (scRNA-seq) was then used to characterize this model.
Results: scRNA-seq revealed the presence of all the expected cell populations within the HLOs, confirming that the organoid model accurately mirrors the cellular composition of human liver tissue. Furthermore, scRNA-seq analysis identified differential gene expression patterns related to pathways which might be key contributors to disease progression in WD. LAL KO organoids displayed hallmark features of Wolman disease, including the accumulation of lipid droplets, which led to steatosis, as well as activation of inflammatory pathways and fibrotic changes. These phenotypic characteristics were observed in a multi-step, time-dependent manner, closely resembling the progression of the disease in vivo.
Conclusion: This study successfully establishes a robust and reproducible human liver organoid model derived from both WT and LAL KO iPSCs, offering a powerful platform for studying the molecular and cellular underpinnings of Wolman disease. The model recapitulates key disease features, including lipid accumulation, inflammation, and fibrosis, providing valuable insights into the pathophysiology of the disorder.

WED-334

Prognostic factors and regulatory pathways in porto-sinusoidal vascular disorder: a longitudinal cohort and transcriptomic study

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Background and aims: Porto-sinusoidal vascular disorder (PSVD) is a rare liver disease marked by portal hypertension in the absence of cirrhosis. This study explored prognostic factors and regulatory pathways implicated in PSVD progression by integrating clinical data with transcriptomic analyses.
Method: A total of 114 PSVD patients were included, with 78 followed longitudinally for liver-related events. RNA sequencing was conducted on 21 liver samples and compared to six histologically normal controls. Associations between clinical features, such as the liver-to-spleen volume ratio (LSVR) and fibrosis stage, with liver outcomes were evaluated. Transcriptomic profiling, including co-expression networks and cell deconvolution, was performed based on these parameters.
Results: Of the 114 patients, 32 (28.1%) underwent liver transplantation at diagnosis. Fibrosis stage was strongly associated with liver transplantation risk (per 1-stage increase: adjusted OR, 14.88; 95% CI, 3.72–59.58) and correlated with LSVR. Over a median follow-up of 4.9 years, 8 (10.8%) of the longitudinal cohort experienced liver-related events. LSVR was identified as a reliable prognostic indicator, with a threshold of 1.33 predicting liver-related events. Transcriptomic analysis based on LSVR and fibrosis stage revealed distinct gene expression patterns and cellular changes in PSVD, including shifts in liver sinusoidal endothelial cell (LSEC) distribution, an increased hepatic stellate cell population, and upregulation of IL-6 signaling, while immune cell composition remained unchanged across disease progression.
Conclusion: This study highlights LSVR as a novel prognostic marker in PSVD and suggests that IL-6 trans-signaling-induced endotheliopathy in LSECs may drive pro-inflammatory and fibrotic processes during disease progression.

WED-335

Ex vivo application of chemically derived hepatic progenitors for the treatment of maple syrup urine disease (MSUD)

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Background and aims: Maple syrup urine disease (MSUD) is a rare metabolic disorder inherited in an autosomal recessive manner. This condition can result in neonatal mortality as a consequence of the buildup of branched chain amino acids (BCAAs) in the blood. MSUD patients are unable to decompose BCAAs due to dysfunction of branched chain alpha keto acid dehydrogenase complex (BCKDC) caused by mutation in one of BCKDHA, BCKDHB, or DBT gene.
This study aims to approach the development of cell therapy for the fundamental treatment of MSUD.
Method: Due to the low survival rate, we isolated mouse primary hepatocytes (mPHs) from the BCKDHA-/- mouse at postnatal day 7, using the magnetic associated cell separation (MACS) with an E-cadherin antibody. A full length human BCKDHA gene sequence was efficiently inserted in the established BCKDHA-/- mCdHs using advanced gene editing technologies, including twin prime editing (twin PE) and integrase.
Results: We observed significantly increased BCAA concentrations in plasma and decreased BCKDHA expression levels in BCKDHA-/- mice which had a survival rate of less than 11 days after birth. Additionally, we successfully established BCKDHA-/- mCdHs with the capability to differentiate into hepatocytes by treating HGF, A83-01 and CHIR99021. The edited mCdHs developed in this study are anticipated to be suitable for ex-vivo cell therapy applications.
Conclusion: In conclusion, our study indicated the feasibility of ex vivo cell therapy for the treatment of MSUD by utilizing mCdHs, which possess proliferative capabilities distinct from hepatocytes. The gene editing technology utilized in this study allows a stable editing while minimizing off-target efficiency and does not interfere with the types of mutations associated with the disease, suggesting its potential as a clinically applicable gene editing method.
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WED-336

Studying the enterohepatic circulation in progressive familial intrahepatic cholestasis type I

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Background and aims: Progressive familial intrahepatic cholestasis type I (PFIC1) is a rare congenital hepatopathy caused by mutations in the *ATP8B1* gene that may lead to liver transplantation (LT). Patients, after LT, can develop diarrhea and graft steatosis and fibrosis. The underlying pathophysiology may be due to the disturbance of enterohepatic circulation of bile acids (BA) and interplay with the gut microbiome. Here we aim to study the gut microbiome and enterohepatic circulation of BA in PFIC1 patients pre and post-LT.
Method: The study is a multicenter basic research project integrating clinical course and patient characteristics with multi-omics to study the enterohepatic circulation in pediatric PFIC1 patients pre and post-LT. Shotgun-metagenomic-sequencing is used to profile the gut microbiome. Claudin-3, lipopolysaccharide (LPS) binding-protein (LBP), fibroblast-growth-factor-19 (FGF19) and C4 levels are measured in fasting serum samples. Healthy individuals and biliary atresia patients post-LT are used as controls.
Results: At this stage of interim analysis, 67 sampling time points (27 pre, 40 post-LT) of 46 PFIC1 patients are included. Gut microbiota is altered in PFIC1 patients, even after LT, compared to controls ($p < 0.001$). Abundance of commensial *Faecalibacterium prausnitzii* is reduced and abundance of *Escherichia coli* is increased in PFIC1 patients compared to controls (all $p < 0.001$). This is corroborated by differential abundance analysis. Here, abundance of *Escherichia coli* and *Veillonella parvula* differentiate controls from PFIC1 and PFIC1 subtypes. Microbial metabolic LPS abundance analysis showed increased levels in PFIC1 post-LT. Serum LBP, claudin-3 and FGF19 levels are increased in PFIC1 patients before and after LT compared to healthy controls ($p < 0.001$). C4 serum levels did not differ between groups.
Conclusion: Gut microbial community structure, altered gut barrier homeostasis, bacterial translocation and enterohepatic signaling is disturbed in patients with PFIC1. This is even pronounced after restoration of bile flow after LT. Increased gut leakiness and bacterial translocation might drive hepatic inflammation and fibrotic changes.

WED-337
Matrix metalloproteinase-7 and osteopontin secretion are specifically upregulated in a novel human precision-cut liver slices model of biliary atresia-associated liver fibrosis

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Background and aims: Biliary atresia (BA) is a rare cholangiopathy affecting the neonatal bile ducts, leading to significant liver injury early in life. BA is surgically treated with Kasai portoenterostomy (KPE), though liver fibrosis often progresses afterwards. The mechanisms underlying the ongoing fibrosis is incompletely understood, as is the role of matrix metalloproteinase-7 (MMP-7) and osteopontin (OPN) as potential biomarkers. Precision-cut-liver slices (PCLS) provide an *ex vivo* model to study organ function *in vitro* while preserving natural cell-cell and cell-matrix interactions. This study aims to establish a novel model using PCLS to investigate BA-associated liver fibrosis post-KPE and to compare their viability with PCLS from healthy and disease controls.
Method: Precision-Cut Biliary Atresia Liver Slices (PCBALS) were prepared from liver explants obtained during transplantation of BA patients who had undergone prior KPE. PCBALS were cultured and sampled up to 48 h. Viability was evaluated by measuring ATP/protein content and histology (H&E staining). MMP-7 and OPN secretion into the culture medium was quantified via ELISA to examine its association with BA pathology. Additionally, liver explants from healthy and disease control livers were used to prepare Precision-Cut Healthy Liver Slices (PCHLS), Primary Biliary Cholangitis Liver Slices (PCPBCLS), and Primary Sclerosing Cholangitis Liver Slices (PCPSCLS). The ATP/protein content and ELISA results are shown as mean with standard error (SE).
Results: PCBALS were generated from four BA patients, with a mean time of 123 (SE: ± 46.8) days between KPE and transplantation. The mean ATP/protein content of PCBALS was 5.1 ± 1.2 pmol/µg at 24 h and remained constant at 4.9 ± 1.9 pmol/µg at 48 h. The percentage of viable hepatocytes on H&E staining showed variability (mean 29 ± 9%), correlating strongly with ATP/protein content (Pearson r 0.96; $p = .0001$). After 48 h, the mean ATP/protein content of PCBALS was comparable to PCPSCLS (6.0 ± 0.9 pmol/µg; n = 8), PCPBCLS (6.1 ± 0.6 pmol/µg; n = 3) and PCHLS (7.4 ± 1.1 pmol/µg; n = 9). The mean MMP-7 secretion after 48 h was profoundly higher in PCBALS (35.1 ± 5.0 ng/mL; n = 4) compared to PCPSCLS (6.0 ± 2.5 ng/mL; n = 3), PCPBCLS (5.5 ± 1.0 ng/mL; n = 3) and PCHLS (0.5 ± 0.4 ng/mL; n = 2). Similarly, the mean OPN secretion was upregulated in PCBALS (73.7 ± 28.9 ng/mL; n = 4) compared to PCPSCLS (5.9 ± 2.4 ng/mL; n = 3), PCPBCLS (19.5 ± 7.0; n = 3) and PCHLS (2.3 ± 0.4 ng/mL; n = 2).
Conclusion: PCBALS can be cultured for 48 h and secreted markedly higher levels of MMP-7 and OPN compared to healthy and disease controls, aligning with known features of BA-associated liver fibrosis. We conclude that PCBALS provide a promising *ex vivo* platform for investigating the mechanism and possible treatments of BA-associated liver fibrosis.

WED-338-YI
A promising new treatment for Wilson disease: 64Cu-Methanobactin (ARBM-101) pharmacokinetics examined in animal models by whole-body PET

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Background and aims: Wilson disease (WD) is caused by a malfunction in the copper-transporting protein ATP7B, essential for hepatic copper clearance. Methanobactins (MB), copper-chelating peptides, demonstrate potential in removing hepatic copper in WD animal models. The MB biodistribution is largely unknown and therefore, this study investigates the biodistribution and excretion of ^{64}Cu-MB in ATP7B$^{-/-}$ rats and healthy pigs.
Method: The MB, ARBM-101, was pre-bound with ^{64}Cu (^{64}Cu-ARBM-101). ATP7B$^{-/-}$ rats were PET-scanned after i.v. injection of either ^{64}Cu or ^{64}Cu-ARBM-101. Five healthy pigs received i.v. 50 MBq ^{64}Cu and

eight healthy pigs received i.v. 50 MBq ^{64}Cu-ARBM-101, followed by a 90-minute dynamic PET/CT scan. Arterial blood samples were continuously collected. In three of the ^{64}Cu-ARBM-101-injected pigs, flow probes were surgically implanted on the hepatic artery and portal vein and catheters were placed in the portal and liver vein. The hepatic extraction fraction of ^{64}Cu-ARBM-101 was quantified based on blood and flow measurements.
Results: In ATP7B$^{-/-}$ rats, ^{64}Cu accumulated in the liver, while most ^{64}Cu-ARBM-101 was localized in the gut 90 minutes after injection. In the pigs, ^{64}Cu accumulated in the liver reaching 26.6% (± 5.55 SD) of the injected dose (%ID) after 90 minutes. The ^{64}Cu-ARBM-101 PET-scans demonstrated rapid hepatic uptake, peaking at 31.5%ID (± 4.46 SD) within 10 minutes, followed by a 73% reduction (%ID liver, $p < 0.001$). Minimal ^{64}Cu excretion to the gut was observed, while ^{64}Cu-ARBM-101 showed significant excretion, reaching 47.6%ID (± 9.10 SD) at 90 minutes ($p < 0.001$). Furthermore, ^{64}Cu accumulated in the renal parenchyma, while ^{64}Cu-ARBM-101 was excreted to the urinary bladder (%ID renal at 90 minutes, $p < 0.001$). There was no notable accumulation of ^{64}Cu-ARBM-101 in other organs. The hepatic ^{64}Cu-ARBM-101 extraction fraction was ~34% in the three pigs equipped with flow probes.
Conclusion: ^{64}Cu-ARBM-101 is rapidly excreted through the liver and kidneys. Hepatic elimination was observed in ATP7B$^{-/-}$ rats, and ^{64}Cu-ARBM-101 exhibits a faster elimination rate than ^{64}Cu in healthy pigs, demonstrating an ATP7B-independent hepatic elimination. The absence of ^{64}Cu-ARBM-101 accumulation in other organs supports that MB's primary pharmacological action is in the liver, the principal organ affected in WD.

WED-339
Modeling rare genetic cholestasis using human hepatocyte organoids

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Background and aims: The liver hepatocytes produce and secrete bile into the bile canaliculi (BC). Disruptions of bile production and secretion lead to accumulation of bile in the hepatocytes, inducing liver damage. Progressive familial intrahepatic cholestasis (PFIC) is a rare disorder caused by mutations in genes essential for maintenance of BC and for hepatocyte function (*ATP8B1, ABCB11, ABCB4, TJP2, NR1H4, MYO5B,* and *PLEC)*. Currently, there are at least seven recognized PFIC subtypes, with the latest subtype identified as recently as 2019. Here, we use state of the art CRISPR base editing techniques in hepatocyte organoid models to emulate mutations found in PFIC patients and establish a biobank. Furthermore, we aim to develop a method to evaluate the severity of cholestasis as well as perform drug screening to develop new PFIC therapies.
Method: We combine human fetal hepatocyte organoids and CRISPR-based genome editing to generate disease models carrying clinically relevant patient-specific amino acid changes. We developed an organoid assay that allows us to assess the structural changes of the BC in the mutants using fluorescent bile analogs. We also assess hepatotoxicity levels and lipid accumulation in the mutants.
Results: We generated a biobank representing seven different mutations representing the different subtypes of PFIC. The mutants show difference in speed of growth and morphology. We are currently investigating phenotypic differences between these mutants, as well as their ability to transport bile acids. We are also able to monitor structural alterations of the canaliculi in organoid models bound between extracellular matrices.
Conclusion: The combination of state of the art CRISPR-based editing techniques and human fetal hepatocyte organoids allows us to rapidly generate human cholestatic models.

WED-340
10 year short-term outcomes of a therapeutic stepwise approach involving low-dose systemic thrombolysis for managing acute portomesenteric thrombosis

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Background and aims: Acute non-malignant portomesenteric thrombosis (PMVT) is associated with high morbidity and mortality in a young patient population. There are no prospective interventional studies assessing therapeutic options outside of standard anticoagulation and supportive care. We report the largest series of patients presenting with this condition who received a stepwise therapeutic protocol, published originally in 2019, it adopts an initial infusion of systemic low-dose tissue plasminogen activator (L-tPa) for 72 hours. Depending on the clinical and radiological response, the treatment is escalated to Transjugular Intrahepatic Portosystemic Shunt (TIPSS) followed by thrombectomy and Catheter-Directed Thrombolysis (CDT) when indicated.
Method: We conducted a retrospective analysis of clinical records of patients with acute PMVT transferred to a tertiary centre (Royal Free Hospital) for stepwise management between 2014–2024.
Results: 106 patients were included; 65 (61%) were males. The mean age was 47years (SD = 15). There was a known thrombophilia diagnosed in 37 patients. 2 had a recent COVID-19 infection and 3 received the ChAdOx1 vaccine. 8 patients had underlying chronic liver disease. All patients had thrombosis of the superior mesenteric vein (SMV) on imaging. Main portal vein thrombosis (PVT) was found in 93 (88%) patients. All patients had persistent abdominal pain despite standard anticoagulation prior to the initiation of L-tPa. The median time to initiation of L-tPa (n = 99) was 12 (IQR = 13) days of symptoms and the median duration of L-tPa infusion was 80 (IQR = 57) hours. TIPSS was inserted in 48 patients (45%) and remained patent at discharge in 41/48 (85%). CDT was undertaken in all TIPSS patients, of whom, 30/48 had the local therapy delivered through EKOS™ endovascular system. Overall, a degree of recanalization was observed in 73 (69%). At discharge 93% were pain free and 85% had intact gut with oral nutrition. 16 patients required small bowel resection (mean length 71 cm [SD = 51 cm]). 1 patient was discharged with a stoma and needed parenteral nutrition. Minor bleeding occurred in 57 patients. One death was recorded (due to bowel ischemia). A major complication was intracranial haemorrhage (n = 4). 65/107 patients were followed up at 3 months, 40/65 (61.5%) had complete symptom resolution – this further improved as length of follow up increased. 4/65 had required further IR intervention and 5 patients had occluded their TIPSS stent (2 asymptomatic).
Conclusion: Our protocol achieved good recanalization and patency rates, and sustained symptom control in the majority of patients. While some patients inevitably required surgical intervention, bowel continuity was eventually achieved in almost all cases. Serious adverse events are a concern. Prospective, randomised studies are required to expand the justification for using this approach in the future.

WED-341-YI
Kinetics of copper uptake in liver cells using the novel ligand tracer method

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Background and aims: Copper (Cu) is toxic when in excess yet is essential for various cellular processes. Patients with Wilson disease are unable to excrete copper into the bile, while those with Menkes disease cannot absorb it. Both conditions can be life-threatening if left untreated. Still, the kinetics of copper transport by living cells remains little studied in dynamic terms, which limits the understanding of copper-related diseases and the development of new treatments. For the first time, we obtained data on cellular copper uptake by using the ligand tracer method.
Method: The Ligand Tracer White (Ridgeview, Uppsala, Sweden) system consists of a beta-emission detector and a tilted rotating platform holding a Petri dish. HepG2 cells were plated 48 h before experiments. The 135-min experiments included nine 15-min additions of increasing amounts of 1 µM copper chloride (Cu(II)Cl) and radioactive 64Cu, maintaining a constant tracer-to-tracee ratio. In 30-sec cycles, the Petri dish alternately immersed cells in the Cu-enriched medium and positioned them under the detector. The intracellular activity of 64Cu was recorded as counts per sec, which, given the constant tracer-to-tracee ratio, reflects the total uptake of Cu. In some experiments, silver nitrate, a specific competitor for the copper transporter, was added to the medium.
Results: As recorded in real-time, we found a linear copper concentration dependent increase in the cells' copper uptake until saturation. The average copper concentration required to achieve half-saturation of uptake (Km) was estimated to be 2.0 µM. This is consistent with the Km for the high-affinity primary copper transporter. The addition of silver markedly reduced the copper uptake.
Conclusion: The ligand tracer assay allowed for the characterization of real-time copper uptake kinetics in living liver cells. The Km value and the inhibition by silver support that our results reflect the activity of the primary copper transporter. This novel method provides new insights into cellular copper dynamics and holds potential for individualized drug-effect screening and treatment assessment.

WED-342
Artificial intelligence-driven qFibrosis® in alpha-1-antitrypsin deficiency-associated liver disease: correlation with METAVIR stage and other disease specific features

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disease that may lead to the development of AATD-associated liver disease (AATD-LD). Liver biopsy is the reference standard for assessing AATD-LD. There is a need for advanced artificial intelligence (AI)-driven methods of liver fibrosis quantification that incorporate collagen morphology and zonal distribution of fibrosis. This study aimed to compare second harmonic generation/two-photon excitation (SHG/TPE) and AI-driven qFibrosis analyses to pathologist-reported METAVIR fibrosis stage, non-invasive tests (NITs) of fibrosis and intrahepatic Z-alpha-1 antitrypsin (Z-AAT) burden using data from phase 2 clinical trials of fazirsiran.
Method: Samples from patients with AATD-LD who received fazirsiran/placebo in AROAAT-2001 (NCT03945292)/-2002 (NCT03946449) were included. Unstained liver biopsy samples were utilized for HistoIndex's proprietary SHG/TPE imaging and AI analysis platform (qFibrosis). Correlation of qFibrosis analyses (METAVIR stage, continuous value, zonal distribution) with pathologist-reported METAVIR fibrosis stage, intrahepatic Z-AAT burden assessed by Periodic Acid–Schiff staining with diastase (PAS-D), and other NITs were evaluated by Spearman correlation analysis. Further methodology is described in Strnad *et al*, *NEJM*, 2022 and Clark *et al, Gastroenterology*, 2024.
Results: Overall, 41 patients from the AROAAT-2001 (n = 25)/-2002 (n = 16) trials were analysed. qFibrosis (METAVIR) stage and continuous value showed a positive correlation with pathologist-reported METAVIR fibrosis stage (n = 78 [pre-/post-treatment visits combined]; $\rho = 0.56$ and $\rho = 0.60$, respectively; $p < 0.0001$) and with liver stiffness measurement (LSM) via FibroScan® (n = 70; $\rho = 0.58$ and $\rho = 0.59$, respectively; $p < 0.0001$) or magnetic resonance elastography (MRE; n = 39; $\rho = 0.39$ and $\rho = 0.40$, respectively; $p < 0.05$). Aspartate aminotransferase to platelet ratio index (APRI) significantly correlated with qFibrosis stage and continuous value (n = 73; $\rho = 0.42$ each; $p < 0.001$). Intrahepatic Z-AAT burden, assessed by PAS-D, positively correlated with qFibrosis stage and continuous value (n = 78; $\rho = 0.39$ and $\rho = 0.38$, respectively; $p < 0.001$). Zonal distribution of fibrosis demonstrated that periportal fibrosis specifically correlated with Z-AAT burden.
Conclusion: qFibrosis stage (METAVIR) and continuous value correlated with pathologist-reported METAVIR fibrosis stage, LSM via FibroScan/MRE and APRI, and identified a spatial correlation with distribution of Z-AAT burden. This suggests value in qFibrosis, an AI-driven, fully quantitative measure of fibrosis and its zonal distribution in AATD-LD. Novel digital pathology approaches may support therapeutic development in AATD-LD but require validation in larger cohorts. Study/writing funding: Takeda Development Center Americas, Inc.

WED-343
The metabolism of TH104; a new drug for the treatment of pruritus in primary biliary cholangitis

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Background and Aims: TH104 is a buccal nalmefene film developed for the treatment of pruritus in primary biliary cholangitis (PBC). Buccal administration avoids the liver first drug metabolism and therefore may be more suitable for use in patients with liver disease. We herein report, a comparison of nalmefene metabolism, between buccal and intravenous formulations.
Method: This was a single-dose, single-center, open-label, randomized, 2-way crossover study of TH104 with the comparator (nalmefene injection), involving 20 normal healthy volunteers (12 male and 8 female volunteers). After an overnight fast of at least 10 hours in each study period, subjects received a single dose of either TH104 (16 mg) or intravenous dose of nalmefene injection (1 mg) in a crossover design according to the 2-sequence randomization schedule. Adverse events (AEs) and vital signs were monitored throughout the study and for 7 days following the last study dose. Plasma samples were assayed for nalmefene and its metabolites nornalmefene, nalmefene glucuronide, and nalmefene sulfate.
Results: Twenty healthy adult subjects were enrolled in the study and are included in the safety population. A total of 20 subjects were dosed with the Test treatment (1 × TH104 16 mg nalmefene buccal film), and a total of 19 subjects were dosed with the Reference

treatment (1 mg nalmefene intravenous bolus injection). Adverse events profile was similar between the two formulations. Absorption was slower for the buccal formulation compared to IV administration. The median value of Tmax for nalmefene was 2 hours for Th104 compared to 10 minutes for the IV product. Tmax results for the metabolites followed similar trends. The ratio AUCinf of nalmefene glucuronide to nalmefene was about twice as high for the TH104 as for IV administration (average intrasubject ratio 1.97 ± 0.075) indicating that this metabolite was formed at a higher rate. Nalmefene sulfate and nornalmefene pK were significantly ($p < 0.05$) delayed with TH104 compared to the IV; levels were first detected 10 minutes after application (compared to 0 minutes in the IV) and steady state reached at 36 minutes (compared to 10 minutes in the IV).
Conclusion: Both drugs showed early phase 2 metabolism (glucuronidation), but TH104 showed a delayed phase 1 metabolism. As phase 1 metabolism are primarily catalyzed by cytochrome P450 enzymes, whereas phase 2 metabolism is through enzymatic conjugation reactions, this difference in metabolism may represent an advantage for TH104 formulation in patients with liver disease.

WED-344
The alpha-1 Pi*MZ genotype is an independent risk factor for hepatocellular carcinoma development in patients with advanced chronic liver disease

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Background and aims: Homozygosity for the SERPINA1 Pi*Z deficiency allele (i.e., the rare Pi*ZZ genotype) is the culprit of alpha-1 antitrypsin deficiency-related liver disease (AATLD), while harbouring a single Z allele (e.g., the common Pi*MZ genotype) is the strongest genetic risk factor for ACLD in steatotic liver disease as well as liver transplantation/death in established ACLD. While Pi*ZZ genotype predisposes to HCC in the general population, the impact of the Pi*MZ genotype on HCC development in patients who have already progressed to ACLD (i.e., those at high risk) has yet to be established. Thus, we investigated the impact of the Pi*MZ genotype on the development of HCC among thoroughly characterized and longitudinally followed ACLD patients.
Method: Patients undergoing hepatic venous pressure gradient (HVPG) measurement and genotyping at the Vienna Hepatic Hemodynamic Lab were included. Patients with HCC at baseline were excluded. Competing risk analyses with HCC as outcome of interest and death/liver transplantation as competing event were performed.
Results: We included 815 patients (mean age 54 ± 11 years; viral hepatitis: 53%, alcohol-related liver disease: 37%, and metabolic-dysfunction associated steatotic liver disease: 10%). Overall, 30 patients (4%) harboured the Pi*MZ genotype. During a median follow-up of 47.3 months, 68 patients developed an HCC (8/30 harbouring the Pi*MZ genotype). The SERPINA1 Pi*MZ genotype was associated with increased risks of HCC development in univariable as well as in multivariable analysis, the latter accounting for other important factors (i.e., age, sex, removal of the primary aetiological factor, AST, serum albumin level, and HVPG) identified by our analysis (adjusted subdistribution hazard ratio [aSHR]: 3.31 [95%CI: 1.26–8.65]; $p = 0.015$). Other common small nucleotide polymorphisms were not associated with HCC development during follow-up. The impact of the Pi*MZ genotype was further confirmed in a multivariable analysis adjusted for the aMAP score (aSHR: 2.94 [95%CI: 1.45–5.97]; $p = 0.003$).
Conclusion: The SERPINA1 Pi*MZ genotype is associated with a more than 3-fold increased risk of HCC development in patients who already progressed to ACLD, independently of other HCC risk factors.

WED-349-YI
Disruption of primary cilia in hepatobiliary development: insights into biliary atresia pathogenesis

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Background and aims: Biliary atresia (BA) is a devastating paediatric liver disease characterized by extrahepatic and subsequently intrahepatic bile duct obstruction, liver fibrosis and eventual liver failure. Despite the severity of BA, its pathogenesis remains elusive. Emerging evidence suggests that defects in primary cilia – specialized cellular organelles crucial for signal transduction in vertebrate cells – may play a pivotal role in BA pathology. Notably, aberrations in cilia-associated signalling pathways, including Hedgehog, Wnt, and Notch, have been observed in biliary epithelial cells (BECs) of BA patients, indicating a ciliary basis for bile duct dysmorphogenesis. Moreover, pathogenic gene variants encoding ciliary proteins have been detected in over 30% of BA patients. A liver-specific knockout of one of the ciliary genes, polycystin-1-Like 1 *(PKD1L1*), recapitulates features of BA in a mouse model. How *PKD1L1* deficiency affects ciliary function and hepatobiliary development is unknown. In this work we investigated the role of primary cilia in hepatobiliary development in a zebrafish model. Zebrafish (*Danio rerio*) share highly conserved mechanisms of liver development with mammals, and their transparent embryos allow dynamic, live time-lapse visualization of hepatobiliary development during critical developmental windows.
Method: Zebrafish embryos were injected with morpholino constructs at the one-cell stage. Live *in vivo* imaging was performed on embryos at 5 days post-fertilization (dpf) using spinning disk confocal microscopy. qRT-PCR assays were performed on 5 dpf dissected livers.
Results: Morpholino-mediated knockdown of *pkd1l1* in zebrafish embryos resulted in profound hepatobiliary abnormalities, including reduced BEC density, malformed biliary networks, and expanded hepatocyte populations, closely mirroring the cholangiopathy observed in human BA. High resolution imaging with a cilia-specific reporter demonstrated disrupted ciliary structure and misorientation in BECs of *pkd1l1*-deficient embryos, directly linking ciliary dysfunction to defective biliary architecture. Further pathway analysis demonstrated aberrant upregulation of Hedgehog (Hh) signaling in *pk1l1*-deficient livers.
Conclusion: Together these findings suggest that loss of ciliary integrity through *pkd1l1* impairment amplifies Hh signaling and disrupts normal biliary tree development. Our study underscores the essential role of primary cilia in hepatobiliary development and offers mechanistic insights into how *PKD1L1* deficiency may drive BA pathogenesis. Ongoing work includes single-cell and spatially resolved transcriptomic analyses of *pkd1l1*-deficient livers to pinpoint gene expression alterations specific to intrahepatic vs extrahepatic biliary structures, advancing our comprehension of ciliary gene regulation in BA.

WED-350

Missense mutation predominates in moldavian patients with Wilson's disease

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Background and aims: Wilson's disease (WD), being widespread across the globe and observed in all races and ethnic groups, is highlighted by the presence of variants specific to certain populations or geographical areas. In the Republic of Moldova, no data on genotypic peculiarities are known. Therefore, we aimed to analyze the genotypic expression of WD within the Moldovan population.
Method: A retrospective and prospective observational cohort study was conducted between 2020 and 2024, involving 53 Moldavian patients with a modified Leipzig score (2019) of ≥4 points. Genetic testing was performed using DNA sequencing by the Sanger method, with the Taq DyeDeoxy Terminator Cycle Sequencing Kit (Applied Biosystems) and an ABI-Prism 3100 genetic analyzer (Applied Biosystems).
Results: Mutations were identified in 46 of the 49 genetically tested patients, while testing was not feasible for 3 individuals at that moment. The mean age at diagnosis was 22.62 ± 9.63 years (range: 5–46 years), with 32.1% of patients diagnosed under the age of 18. Most participants were of Moldovan ethnicity, although other ethnic backgrounds were also represented. None of the patients reported consanguineous relationships or associations with isolated communities. In 60.97% of cases (25 patients), compound heterozygosity was observed. The group exhibited high mutational heterogeneity, with 19 different variants identified: 8 pathogenic, 4 probably pathogenic, and 7 benign. Most mutations were located in exons 3 and 8. Missense mutations were predominant (87.06%), followed by frameshift (7.05%), silent/synonymous mutations (3.53%), and nonsense (2.35%). The most common allele, p.H1069Q, located in exon 14, was found in 53% of alleles. Other notable variants included p.G1341D (14%), p.Met769Hisfs*26 (5%), and several mutations present in < 4% of alleles. A rare mutation, p.Phe764 = , considered probably pathogenic, was detected; in homozygosity or combined with another pathogenic variant, it is associated with WD. Regional analysis revealed distinct genotypic distributions: Northern region - p.A1227 T, p.Asn728Ile, and p.Ala1135GlnfsX13; Central region - p. E541K; Southern region - p.T991 T; Left Bank of the Dniester - p. Val845SerfsTer28 and p.Q544X; Nationwide - p.H1069Q, p.G1341D, and p.Met769Hisfs*26. A family with the paradoxical transmission of pseudodominant inheritance was also identified.
Conclusion: Our research group is characterized by a high genotypic variety with the detection of 19 mutations with different pathogenicity degrees. In 87.06% of patients, the missense mutation predominates. The most frequent pathogenic variant was p.H1069Q, with rare variants p.Phe764 = also being recorded. Regional analysis revealed distinct genotypic distributions.

WED-351

Correction of the Wilson disease H1069Q point mutation by CRISPR/Cas9-mediated gene editing in induced pluripotent stem cells

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Background and aims: Wilson disease (WD) is characterized by toxic copper (Cu) accumulations, mainly in the liver and central nervous system. With up to 40%, the point mutation H1069Q is the most common mutation of the Cu transporter ATPase7B in western populations. The aim of this study was to assess if a CRISPR/Cas9-mediated gene correction of H1069Q in WD induced pluripotent stem cells (iPSCs) may interfere with their ability to differentiate into hepatocyte-like cells (HLCs) and confer Cu resistance.
Method: In this study, urinary epithelial cells of WD patients, carrying the compound heterozygous mutation H1069Q/N1270S, were reprogrammed into iPSCs using transient transfection methods. For initiation of homology-directed repair, iPSCs were transfected with the plasmid PX459.H1069Q, which carries the H1069Q-specific sgRNA sequence and the sequence for the Cas9 enzyme, plus a set of single-stranded-oligodeoxynucleotides (ssODNs), which serve as repair templates. Single iPSC clones were analysed by Sanger sequencing. Corrected iPSC clones were differentiated into HLCs and analysed for hepatocyte-specific marker genes via real-time RT PCR. The cell viability of ATP7B-corrected and uncorrected HLCs were determined via MTT assays after incubation in toxic Cu concentrations.
Results: 46% of all analysed iPSC clones were successfully corrected after CRISPR/Cas9-mediated repair. The second mutation was not affected. Corrected iPSC clones were differentiated into HLCs. The corrected HLCs showed an upregulation of hepatocyte-specific marker genes (e.g. Albumin, AFP, HNF4α), confirming their hepatic character, as well as an improved resistance to high Cu concentrations.
Conclusion: This study demonstrates that CRISPR/Cas9 engineering is highly efficient in iPSCs and does not affect their ability to differentiate into HLCs. This technology has a remarkable therapeutic potential to correct the ATP7B gene, leading to an improved Cu resistance, thus further contributing to new therapeutic approaches for WD.

WED-352

Human biliary atresia extra-hepatic cholangiocyte organoids: elevated ER and oxidative stress, altered drug metabolism, and modified cell-to-cell junction

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Background and aims: Biliary atresia (BA) is a form of biliary fibrosis typically diagnosed in previously healthy newborns before the age of 3 months, with extrahepatic bile duct obstruction and progressive liver fibrosis. The etiology of the disease is unknown. We previously showed that BA-derived human cholangiocyte organoids (HCOs) display abnormal shape in culture compared to normal controls and thus performed RNA-seq analysis to determine the pathway of injury of extra-hepatic cholangiocytes in BA. Based on RNA sequencing (RNAseq) analysis we aimed to functionally assess the role of Endoplasmic reticulum (ER) stress and unfolded protein response (UPR) response in BA HCOs. In addition, the analysis revealed differences in drug metabolism between BA patients and controls and cell-to-cell adhesion alterations.
Method: we isolated and propagated extrahepatic human cholangiocyte organoids from both biliary atresia (BA) patients and non-BA controls to explore the molecular mechanisms of BA. We performed RNAseq on these organoids to identify critical pathways and gene expression linked to the disease. We performed RT-PCR to verify the results along with immunofluorescence (IF) staining for various

proteins and electron microscopy (EM) to look at the ER. Additionally, we investigated the role of cytochrome P450 enzymes in ER stress by inhibiting cytochrome P450 using HET0016.

Results: RNAseq analysis revealed differences between BA and controls in ER stress, UPR, cell-to-cell adhesion, and drug metabolism. We studied epithelial integrity by IF staining the cholangiocyte organoids to E-cadherin which regulates cell-to-cell adhesion and mobility, Sox17 which has a role in cell polarity, and RhoU which has a role in cell adhesion. Patients with BA had decreased E-cadherin and Sox17 staining of the cholangiocyte organoids and increased RhoU compared to controls. We determined gene expression related to ER stress and unfolded protein response using RT-PCR. BiP which alleviates the cellular stress in the ER had increased in BA patients and PERK which is activated in response to UPR had increased in BA patients compared to controls. We looked at ER morphology using EM and found that BA-derived EHCOs display irregular and dilated ER structures. To look for differences in drug metabolism, we performed RT-PCR for CYP4A isoforms which have been implicated in the modulation of endoplasmic reticulum stress and were highly expressed in BA patients compared to control. To determine if cytochrome activity may influence ER stress, we inhibited CYP4A activity using HET0016, which resulted in a reduced ER stress marker compared to BA patients with non-treated.

Conclusion: Our findings suggest that human organoids from BA patients demonstrate increased ER stress and abnormal polarity and inhibiting cytochrome P450 attenuates ER stress. These results pave the way for further investigation into targeted therapeutic strategies that may facilitate ER stress in BA, potentially altering the disease course.

Rare liver diseases (including paediatric and genetic) – Clinical

TOP-330

Prevalence and prognostic impact of sarcopenia in porto-sinusoidal vascular disorder

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Background and aims: Sarcopenia is a recognized prognostic factor in cirrhosis, but its role in porto-sinusoidal vascular disorder (PSVD) remains unclear. This study investigates sarcopenia prevalence in patients with PSVD and its impact on prognosis.

Method: We conducted a retrospective, multicenter observational study in three phases. First, using data from two European tertiary care centers, we evaluated the prevalence of sarcopenia in PSVD patients (n = 197; mean age 49 ± 16 years; 57% male) and compared it to that in advanced chronic liver disease (ACLD) patients (n = 720; mean age 55 ± 12 years; 61% male) matched for sex, ascites and Child-Turcotte-Pugh score (CTP) using propensity score matching. Sarcopenia was defined as a transversal psoas muscle thickness (TPMT) of <8 mm/m in females and <12 mm/m in males, measured at the L3 level using cross-sectional imaging. Secondly, we conducted a competing risk regression analysis in a cohort of 606 PSVD patients from 20 VALDIG centers to identify factors associated with the composite endpoint of first/further hepatic decompensation and liver-related death. Finally, in a subset of 126 patients, TPMT was independently measured in a blinded manner by two expert radiologists to assess interobserver variability using the intraclass correlation coefficient (ICC).

Results: The prevalence of sarcopenia in PSVD patients was similar to that in propensity score-matched ACLD patients (18% vs 16%; p = 0.592). The overall VALDIG cohort of patients with PSVD (age 49 ± 16 years, 59% male; CTP score 6 ± 1 pts; 33% decompensated) was followed-up during a median time of 53 (IQR: 21–105) months. Multivariable competing risk regression analysis identified age, history of decompensation, CTP score, creatinine, and sarcopenia as independent predictors of liver-related survival free of first/further hepatic decompensation (adjusted subdistribution hazard ratio [aSHR] for sarcopenia: 1.48 [95%CI, 1.01–2.17], p = 0.045). These results remained consistent after adjustment for the recently proposed PSVD prognostic score (aSHR: 1.53 [95%CI, 1.04–2.24], p = 0.029). Sarcopenia had a more pronounced impact on prognosis

among patients with a history of hepatic decompensation. The reproducibility of TPMT measurements was excellent (ICC: 0.919; p < 0.001) in a subset of 126 patients.
Conclusion: The prevalence of sarcopenia in PSVD mirrors that observed in ACLD when matched for liver dysfunction severity. Sarcopenia independently predicts poor outcomes, highlighting the potential of exercise- and nutrition-based interventions to improve prognosis in PSVD.

TOP-331-YI
Standalone medical therapy versus early endovascular intervention as the first step in the management of patients with primary Budd-Chiari syndrome: a randomized controlled trial
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Background and aims: There is no randomized clinical trial comparing early endovascular intervention to medical therapy alone as the initial management of Budd-Chiari syndrome (BCS).
Method: Symptomatic patients with primary BCS having either hepatic vein (HV) obstruction [Type II disease] or combined obstruction of HV and inferior vena cava (IVC) [Type III disease] were enrolled. Patients were randomized to receive SMT for 12 weeks or medical therapy with early endovascular intervention guided by vascular anatomy and length of obstruction. The primary outcome measure was complete clinical response at 12 weeks defined as resolution of ascites, normalization of serum bilirubin, prevention of first episode of variceal bleeding or its recurrence and absence of spontaneous bacterial peritonitis.
Results: Of 44 patients randomized, 23 received SMT and 21 received early endovascular intervention. The baseline characteristics of both groups were comparable. In the early intervention group, 12 (52.2%) patients had Type II BCS (6 patients underwent TIPS and 6 underwent HV angioplasty and stenting), while 9 (47.8%) patients had Type III BCS (1 underwent IVC angioplasty alone while 8 underwent TIPS with IVC angioplasty). A significantly higher proportion of patients undergoing early intervention (19 [90.5%, 95%CI: 69.6%–98.8%]) achieved complete clinical response at 12 weeks, compared to those receiving SMT (4 [17.4%, 95%CI:4.9%–38.7%]; p < 0.01). Early endovascular intervention was associated with significant improvement in hepatic congestion (mean reduction in LSM of −16.9 [−24.9 to −8.8]) kPa as compared to the SMT group (−2.0 [−11.8 to 7.8]; p = 0.02) over 12 weeks. Patients in the SMT group had a higher (3, 13%) but statistically insignificant mortality rate than those in the early intervention group (0, p = 0.23).
Conclusion: Early endovascular intervention combined with medical management is associated with higher rates of clinical response and resolution of hepatic congestion compared to standalone medical therapy in symptomatic primary BCS patients. (CTRI/2022/10/046661).

TOP-332-YI
Automated reflex testing for AAT deficiency in liver dysfunction: is it worth it?
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Background and aims: Guidelines recommend an aetiological liver screen for all patients with abnormal liver function tests (LFTs). Patients with low serum alpha-1 antitrypsin (AAT) concentration and specific phenotypes may have a modified risk of developing liver disease (PiMZ) and/or an increased risk of developing fibrosis and liver cancer (PiSZ and PiZZ). The population prevalence of these phenotypes is ~1:30 (MZ), 1:500 (SZ) and 1:2000 (ZZ), however, penetrance is variable. Intelligent LFT [iLFT] is an automated aetiological screen that is performed on patients in primary care with abnormal LFTs (ALT > 30 U/L, ALP > 200 U/L and/or GGT > 73 U/L) in NHS Tayside (NHST). We aimed to: 1) determine the frequency of abnormal phenotypes identified using reflex AAT measurements within the iLFT pathway and compare this to routine clinical care; 2) investigate the impact of reflexing AAT based on suspicion of fibrosis rather than elevated liver enzymes.
Method: All AAT concentration and phenotype results in adult patients (18 or older) between August 2018 and July 2023 were extracted from the NHST laboratory database and grouped by requesting indication (iLFT vs routine clinical care). Phenotyping is automatically added where AAT is <1.0 g/L. Fibrosis-4 indices (FIB-4) from iLFT patients were evaluated using age specific cut-offs: ≥1.3 (18–64) or ≥2.0 (65 and above).
Results: 18,215 AAT tests were performed of which 1,754 were phenotyped: MM, n = 682 AAT median level 1.08 g/L (interquartile range [IQR] 0.97–1.15); MZ, n = 568, 0.83 g/L (0.74–0.91); MS, n = 372, 0.97 g/L (0.91–1.06); SZ, n = 49, 0.55 g/L (0.47–0.68); SS, n = 31, 0.55 g/L (0.78–0.95); ZZ, n = 11, 0.15 g/L (0.10–0.24). 41 rarer deficiency alleles were identified and 30 were not phenotyped due to pre-analytical error. Overall prevalence for phenotypes implicated in liver disease were 3.12% MZ, 0.27% SZ, and 0.06% ZZ. Median ALT (IQR) for each phenotype were 55 U/L (38–79), 57 U/L (40–85), and 66 U/L (41–79), respectively. In the iLFT subgroup (n = 15,141), prevalences were 3.06% MZ, 0.22% SZ, 0.04% ZZ. Prevalences in the routine clinical care group (n = 3,074) were significantly higher at 3.42%, 0.49%, and 0.16%, respectively (Chi-square, p = 0.013). Using elevated FIB-4 as an additional gatekeeper for AAT testing in iLFT would have identified only 17.3% of MZ, 23.5% of SZ and 50.0% of ZZ cases, although with a saving of 11,715 tests (77.4%).
Conclusion: iLFT identifies pathological AAT phenotypes at proportions in keeping with prevalence studies. Whilst still low, the yield of pathology was higher in the routine clinical care group where we would anticipate more targeted assessment. Using elevated FIB-4 as an additional gatekeeper for AAT would reduce overall testing by >75% but miss over 80% of abnormal phenotypes. Healthcare providers need to balance the cost of testing with the clinical utility of diagnosing AAT deficiency when deciding who and how to test.

TOP-345-YI
A 10-year review of obstetric admissions to a quaternary liver intensive care unit: learning from morbidity and mortality
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Background and aims: Maternal mortality in the UK is at its highest in two decades, with increasing proportions of high-risk obstetric patients. A challenging patient cohort are those with liver pathology, which includes pre-existing liver disease, gestational specific liver disorders and non-pregnancy related new liver pathology. This study aims to review the outcomes of obstetric patients with liver pathology requiring admission to a quaternary care liver centre's intensive care unit (ICU).
Method: A retrospective single centre study of pregnant/post-natal patients identified from the hepatology ICU handover archives (Jan 2014–Dec 2023). Electronic records were reviewed collating demographics, labs and admission outcomes including maternal and foetal mortality.
Results: 42 patients were identified, comprising of 9 (21.4%) patients with pre-existing liver disease, including 2 acute on chronic liver failure (ACLF), 28 (66.7%) pregnancy specific liver pathologies and 5 (11.9%) non-pregnancy related new liver pathologies. 29 patients

were post-partum. The other 13 had a median gestation of 24 weeks (range 8–38 weeks). Pre-existing liver disease included autoimmune hepatitis (AIH) cirrhosis, alcohol related liver disease, Budd Chiari Syndrome (BCS) and various causes of non-cirrhotic portal hypertension. Pregnancy specific liver pathology included hyperemesis gravidarum with ischemic hepatitis, Acute Fatty Liver of Pregnancy (AFLP) and Haemolysis, Elevated Liver enzymes, and Low Platelet count (HELLP syndrome). New onset non-pregnancy specific aetiologies included acute liver failure (ALF) secondary to paracetamol overdose, acute hepatitis B infection, herpes simplex hepatitis and Hemophagocytic lymphohistiocytosis (HLH). Mean duration of critical care admission was 5 days (range 1–60 days). 2 patients received liver transplantation- 1 patient on the ACLF tier for decompensated AIH cirrhosis and 1 on the super urgent list for ALF secondary to hepatitis B with transplantation taking place during pregnancy at 25+5 gestation. 6 (66.7%) patients with pre-existing liver disease presented with a variceal bleed. There were 4 cases of maternal mortality, which were due to HLH, ischaemic hepatitis and 2 patients with ACLF. There were 12 foetal or neonatal deaths, including 2 medical terminations of pregnancy and 1 miscarriage. There were 8 intrauterine deaths, 4 associated with HELLP, 1 due to AFLP and 3 in patients presenting with a variceal bleed. 1 baby died at 8 days old due to HSV infection.

Conclusion: In this cohort of patients, pre-existing liver disease was associated with half of the maternal deaths and a third of foetal deaths, confirming the high-risk nature of these pregnancies. This emphasises the importance of multi-disciplinary care between obstetricians and hepatologists to ensure these patients receive pre-pregnancy counselling and antenatal monitoring.

SATURDAY 10 MAY

SAT-323

Prognostic value of factor VIII, D-Dimer, and high mutation risk variants in re-thrombosis risk stratification for non-cirrhotic splanchnic vein thrombosis

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Background and aims: Long-term anticoagulation in patients with non-cirrhotic splanchnic vein thrombosis (SVT) is only indicated for those with underlying thrombophilia. However, approximately 25% of patients without such indications experience recurrent thrombosis (RT). Elevated factor VIII (≥150%), D-dimer (≥500 ng/mL), and high mutation risk (HMR) variants detected via next-generation sequencing (NGS) have been proposed as predictors of RT risk. This study aimed to compare the prognostic value of these markers in a cohort of patients with idiopathic or local factor-associated SVT, excluding those with thrombophilia or criteria for long-term anticoagulation.

Method: A multicenter, retrospective, observational study including 123 patients with idiopathic or local factor-associated SVT who underwent factor VIII and NGS testing. D-dimer was measured in 60 patients. The primary endpoint was the occurrence of RT, defined as either splanchnic or extra-splanchnic thrombosis.

Results: During a mean follow-up of 89.3 months (IQR 36–129), 33 patients (27%) experienced 36 venous RT events (24 splanchnic, 12 extra-splanchnic), with a cumulative incidence of 6%, 8%, and 11% at 5, 10, and 20 years, respectively. Factor VIII ≥150% was independently associated with RT risk (HR 4.43, 95% CI 1.12–17.62, p = 0.03). HMR (Log-rank 2.95, p = 0.08) and D-dimer ≥500 (Log-rank 3.76, p = 0.052) showed trends toward significance. Multivariate analysis confirmed factor VIII ≥150% (HR 4.43, 95% CI 1.12–17.62, p = 0.03) and HMR (HR 4.97, 95% CI 1.00–24.75, p = 0.05) as independent predictors of RT. HMR provided additional prognostic value only in patients with factor VIII <150% (RT 8% in NGS-negative patients vs. 17% in NGS-positive patients, p = 0.45). In patients with factor VIII ≥150%, NGS did not enhance risk stratification. These results were reproducible when splicing the cohort according to idiopathic or local factor-associated SVT.

Conclusion: Patients with idiopathic or local factor-associated SVT remain at risk for RT. Factor VIII ≥150% is a reliable marker for identifying high-risk patients. NGS adds prognostic value in cases with factor VIII <150%, while the role of D-dimer is promising but requires further validation in larger cohorts.

SAT-324

Understanding treatment efficacies of progressive familial intrahepatic cholestasis via a prospective world-wide registry, TreatFIC

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Background and aims: Progressive familial intrahepatic cholestasis (PFIC) is a group of rare pediatric cholestatic liver diseases. Our retrospective "NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion" registry allowed us to identify genotype-phenotype relationships for FIC1- and BSEP-deficiency. Recently, however, more PFIC subtypes have been characterized and in addition, ileal bile acid transporter inhibitors (IBATi) are increasingly used for treatment. Therefore, we initiated a prospective analysis of the treatment of PFIC, TreatFIC, in 2023. The objective of TreatFIC is to determine the natural history of all PFIC subtypes and collect real world data on the efficacy and safety of current treatments, including IBATi. Here, we provide the first update on TreatFIC.
Method: This multicenter prospective registry includes genetic and clinical data from individuals with genetically confirmed PFIC subtypes. For each individual demographic and clinical characteristics were collected retrospectively and, after entering TreatFIC, prospectively every 6 months using REDcap.
Results: Upon starting in January 2023, legal procedures with 43 centers worldwide have started, of which 25 centers have full IRB approval and data transfer agreements as of November 2024. The average patient inclusion rate has increased from 2 per quarter to ~10 per quarter since May 2024. As of November 2024, 84 individuals from 13 centers across Europe and Asia have been included. The included individuals encompass different PFIC subtypes, including FIC1- (n = 17), BSEP- (n = 41), MDR3- (n = 15), MYO5B- (n = 2), TJP2- (n = 1), and USP53-deficiency (n = 3) and others (n = 5). Twenty nine individuals are using odevixibat, 4 individuals used odevixibat in the past, 9 individuals are using maralixibat and 42 individuals are not treated with an IBATi. The first analyses will be presented.
Conclusion: TreatFIC is rapidly expanding and provides prospective data on the treatments of individuals with PFIC and its efficacy. The number of included individuals has grown rapidly since its initiation in 2023. TreatFIC will allow to assess real-world data on the current treatments for PFIC diseases. To further increase the impact of the registry, centers that treat children or adults with PFIC are invited to participate (pfic@bkk.umcg.nl).

SAT-325
Quantitative biliary metrics may add to predictive ability of liver stiffness in patients with primary sclerosing cholangitis

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Background and aims: Primary Sclerosing Cholangitis (PSC) is a rare chronic cholestatic liver disease that can progress to liver failure requiring liver transplant (LT). Quantitative magnetic resonance cholangiopancreatography (qMRCP) uses artificial intelligence (AI) to generate quantitative measurements of the biliary tree from standard MRCP data. We aimed to investigate the individual and combined ability of qMRCP and liver stiffness (LSM) using transient elastography in predicting outcomes in patients with PSC.
Method: Patients with PSC followed at the Toronto Centre for Liver Disease undergoing non-contrast 3D MRCP as part of standard of care were retrospectively included. All patients had a baseline MRCP and at least 2 follow up scans over the follow-up period. LSM was obtained using transient elastography (Fibroscan) and was available for 106 patients. Stepwise time-dependent Cox proportional hazards models were used to estimate the ability of qMRCP and LSM to predict a) death or LT, b) hepatic decompensation or cancer, and c) a composite of a and b. A qMRCP model, LSM model, and combined model were created for each outcome. A qMRCP model for different stages of disease (advanced > LSM 11.1 kPa) was also generated for each outcome. The C-index was used to assess discriminative ability of the individual models.
Results: 140 patients meeting eligibility were included. The mean age at PSC diagnosis was 39 years, 55% (n = 77) were male, 91% (n = 127) had large duct disease, and 74% (n = 103) had IBD. The median follow up time was 14 years (IQR 11–18). Quantitative biliary metrics, such as biliary dilation and/or stricture scores, were significantly associated with death/LT (HR 2.87 [95% CI 1.05–7.87], p = 0.04), hepatic decompensation (HR 26.49 [95% CI 5.39–130.08], p < 0.01), and the composite of death/LT/decompensation (HR 1.71 [95% CI 1.11–2.65], p = 0.01). LSM independently predicted death/LT (HR 1.04 per 1 kPa increase [95% CI 1.03–1.06], p < 0.01), hepatic decompensation (HR 1.06 [95% CI 1.04–1.07], p < 0.01), and the composite death/LT/decompensation (HR 1.05 [95% CI 1.04, 1.07], p < 0.01). LSM showed superior discriminatory ability than qMRCP metrics for death/LT (c-index 0.79 vs. 0.67), hepatic decompensation (c-index 0.81 vs. 0.79), and the composite of death/LT/decompensation (c-index 0.77 vs. 0.76). In the combined model, qMRCP did appear to improve discriminative performance when added to LSM in predicting death/LT (c-index 0.80), hepatic decompensation (c-index 0.89), and the composite of death/LT/decompensation (c-index 0.84). qMRCP performed better in predicting outcome in patients with more advanced disease when predicting death/LT (c-index 0.80 vs. 0.67), decompensation (c-index 0.85 vs. 0.79), and the composite of death/LT/decompensation (c-index 0.80 vs. 0.76).
Conclusion: LSM is a robust predictor of outcome in patients with PSC. Quantitative and objective biliary metrics over time may add additional predictive value in assessing risk of outcome in these patients.

SAT-326
HLA associations with specific anti-nuclear antibody reactivity in people living with primary biliary cholangitis

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Background and aims: Primary biliary cholangitis (PBC) is the archetypal autoimmune liver disease. Although anti-mitochondrial antibodies represent the characteristic serologic profile, highly specific anti-nuclear antibody reactivity (e.g. against gp210 and sp100) are pathognomic. Prior genetic studies have confirmed human leukocyte antigen (HLA) associations with disease, and have

identified *DRB1*03:01*, *DRB1*15:01*, *DRB1*01*, and *DPB1*03:01* as being associated with sp100 positive serology. No genetic associations have been reported for gp210 positivity. We sought to replicate associations identified in existing literature between HLA genotype and sp100 and gp210 status in unselected sequential patients with PBC attending the Autoimmune and Rare Liver Disease Programme in Toronto.

Method: 94 subjects (94.7% female, median age 61, 75.5% Caucasian) were sequentially recruited. Blood was drawn and the full HLA panel sequenced via next-generation sequencing (NGS). Serologic profiles were abstracted from chart review (EUROLINE Autoimmune Liver Diseases 9 antigen Immunoblot assay). Patients were identified as sp100 positive (+ve) or negative (–ve), and gp210 +ve or –ve. The hospital deceased donor (DD) transplant cohort (n = 1492) was used as a control. Association analysis using chi square tests was performed. Tests were done to evaluate distribution of *DRB1*03:01*, *DRB1*15:01*, *DRB1*01* and *DPB1*03:01* between sp100 +ve vs. sp100 –ve patients, sp100 +ve vs. the DD control, sp100 –ve vs. the DD control, gp210 +ve vs. gp210 –ve patients, gp210 +ve vs. DD control, and gp210 –ve vs. the DD control. P values were reported as significant if $p < 0.05$.

Results: The chi-square test was significant for *DRB1*03:01* distribution among sp100 +ve vs. sp100 –ve patients ($p = 0.0045$) and sp100 +ve vs. the DD control ($p = 0.0035$). Hence, in our cohort, the *DRB1*03:01* allele was found to be over-represented in sp100 +ve PBC patients (44%, as compared to 15.9% in sp100 –ve and 20.2% among the DD control). For gp210, chi square tests were significant for *DRB1*01* distribution among gp210 +ve vs. –ve patients ($p = 0.0078$) and gp210 –ve vs. the DD control ($p = 0.027$). Therefore, within our cohort, the *DRB1*01* allele was found to be over-represented in gp210 –ve patients as compared to the DD control (29.4% vs 18.6% respectively), and under-represented in gp210 +ve patients (3.5%) as compared to gp210 -ve patients (29.4%).

Conclusion: We replicate the association between *HLA DRB1*03:01* and sp100 positivity, and identify a potential new HLA association for gp210 seropositivity.

SAT-327-YI

Advanced phenotyping of hepatic involvement in AL Amyloidosis: the D-Amy-LIPHE study

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Background and aims: Light-chain (AL) amyloidosis is a systemic disease caused by monoclonal light chain deposition in various organs, including the liver. Hepatic involvement, though common, is poorly defined, relying on criteria like hepatomegaly (>15 cm) or elevated ALP (>1.5 times the upper limit of normal). While 123I SAP scintigraphy is highly sensitive for detecting amyloid, its limited availability restricts use. Conversely, 99mTc-labeled bisphosphonates are widely available but inconsistently applied. This study aimed to evaluate the prevalence of hepatic dysfunction or amyloidosis, classified patients using clustering, and assessed the prognostic impact of hepatic involvement.

Method: This retrospective study included 200 AL amyloidosis patients with cardiac involvement treated at a French center (2008–2020). Hepatic involvement was defined by MRI/CT-confirmed hepatomegaly or elevated ALP. Liver uptake was evaluated using early-phase (10-minute) 99mTc-HMDP bone scintigraphy, assessed both visually by an experienced nuclear medicine physician and via liver-to-mediastinum (H/M) ratio (>0.7 considered positive). The diagnostic performance of early-phase liver uptake for hepatic amyloid deposits was evaluated using the ROC curve (AUC). Logistic regression identified predictors of hepatic involvement and liver uptake. Unsupervised clustering (Self-Organizing Maps) classified patients in subgroups, and survival analysis assessed mortality differences across clusters.

Results: Hepatic involvement was identified in 71 patients (35%), with liver uptake observed in 38 patients (24%). Among those with hepatic involvement, scintigraphy showed positive liver uptake in 20 patients (35%). Multivariate logistic regression identified platelet count (OR 4.46, $p = 0.04$), gastrointestinal amyloidosis involvement (OR 4.91, $p = 0.002$), and right atrial volume (OR 4.98, $p = 0.009$) as significant predictors of hepatic involvement. For liver uptake, troponin (OR 1.73, $p = 0.04$) and hepatic involvement (OR 2.53, $p = 0.02$) were significant predictors. Clustering analysis identified three subgroups: Group 1 predominated by cardiac involvement and Group 3 characterized by hepatic and renal dysfunction, which had the highest 6-month mortality. Early-phase liver uptake (H/M ratio ≥0.7) demonstrated high diagnostic performance for hepatic amyloid deposition, with 84% sensitivity, 83% specificity, and an AUC of 0.891.

Conclusion: Hepatic abnormalities are prevalent in AL amyloidosis and are associated with both amyloid deposition and cardiac dysfunction. Hepatic involvement correlates strongly with hepatic uptake on scintigraphy. Early-phase scintigraphy emerges as a reliable diagnostic tool for detecting hepatic involvement, offering high sensitivity and specificity. Clustering analysis revealed phenotypic variability with distinct prognoses, providing valuable insights for stratifying patients by risk.

SAT-328

Comparison of disease presentation features, morbidity and mortality rates of screening or index cases in patients with Wilson's disease

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Background and aims: Wilson disease (WD) is a genetic disease transmitted by autosomal recessive inheritance. Due to the wide variety of clinical manifestations, diagnosis is difficult if not suspected. Early diagnosis is important for preventing morbidity and irreversible complications of the disease. Family screening is one of the most important steps in early diagnosis of WD. We aimed to reveal the diagnostic features of screening and index cases in the Wilson disease group.

Method: Diagnostic criteria of patients followed up with a diagnosis of Wilson's disease in a tertiary university hospital were retrospectively evaluated from the outpatient clinic files of the patients.

Results: Of the 336 patients followed up with the diagnosis of WD, 194 (57.7%) were male. The mean age at diagnosis of the entire patient group was 21.7 ± 11.9 years. The type of involvement was hepatic in 53% of the patients, neurological in 16% of the patients, and mixed in 31% of the patients. Of the WD, 69 (21.8%) were screening cases. The consanguineous marriage rate was 42.2% in the entire group, while 42% of screening cases were consanguineous. The age at diagnosis in the screening group was younger than the index cases and was 21.82 ± 11.51 years and 21.66 ± 13.45 years, respectively ($p = 0.048$). In terms of the type of WD involvement, hepatic involvement was more common in screening cases than in index cases, 69.5% vs. 49% ($p = 0.02$). In screening cases, 15.25% had neurological and 15.25% had mixed type involvement. The rate of mixed type involvement in index cases was 35% and was higher than in screening cases ($p < 0.05$). The rate of cirrhosis at the time of diagnosis was 49% vs. 23% in index and screening cases, respectively ($p < 0.05$). The mean Leipzig score was 5.49 ± 1.5 vs. 5.2 ± 1.4 in index and screening cases, respectively ($p < 0.05$). Kayser Fleischer ring was detected in 30.2% of patients in the

screening group, while it was present in 54.8% of index cases (p = 0.05). 24-hour urine copper was 448.34 ± 900.29 µg vs 518.20 ± 635.03 ± µg in the screening and index case groups, respectively (p = 0.81). In the mutation analysis of the ATP7B gene, positivity was detected in 40% of the index cases, while the screening cases had a positivity rate of 45% (p < 0.05). When index cases and screening cases were compared in terms of mortality and need for liver transplantation, mortality and liver transplantation rates were higher in index case patients (p < 0.05).

Conclusion: Mortality and liver transplantation need were found to be lower in Wilson's disease patients detected by family screening compared to index cases.

SAT-333

Quality of life of patients living with vascular LIVEr diseaseS: Results of the LIVES european project

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Background and aims: Vascular liver diseases (VLD) are rare chronic diseases with scarce data on quality of life (QoL). This study aimed to assess QoL in patients with VLD and to identify associated socioeconomic and clinical factors.

Method: A questionnaire was sent to all eligible patients with non-cirrhotic portal vein thrombosis (PVT) or Budd-Chiari syndrome (BCS) from 4 centres in France, Spain and Switzerland in 2024. QoL outcomes included health-related quality of life (HRQoL; EQ-5D-5, from 0 to 1), fatigue (modified fatigue impact 5-items, from 0 to 20) and depression (PHQ-9 > = 10). Linear and logistic regression analyses were used to identify factors associated with QoL measures.

Results: Of the 1168 eligible patients with clinical data, 52% completed the questionnaire and 31% all QoL scales. Of the 363 respondents, 55% were men, 26% had BCS and 74% had PVT. Associated diseases were present in 58% and 26% had myeloproliferative neoplasm. The median age [interquartile range (IQR)] was 53 [43–64] years and the median time since diagnosis was 8.9 [4.9–14.2] years. A severe prognosis was identified in 11% of BCS patients (Rotterdam score class III) and 1% of PVT patients (intestinal resection for mesenteric infarction). Treatments for VLD included anticoagulation (78%), angioplasty or transjugular intrahepatic portosystemic shunt (9%) and liver transplantation (1.4%). Educational level was high in 53%, 15% were unemployed or unable to work, 13% were born outside the European Union (EU), and 12% had severe financial difficulties. Median [IQR] HRQoL and fatigue scores were 0.93 [0.86–0.98] and 8 [5–12] respectively, while 25% of patients experienced depression (32% among those <45 years). QoL outcomes were similar in patients with BCS and those with PVT. In multivariable analysis, being born outside the EU and having severe financial difficulties were associated with poorer HRQoL (adjusted coefficient (aCoeff) [95% confidence interval (CI)]: −0.74 [−1.36; −0.12] and −0.94 [−1.58; −0.31]), increased fatigue (aCoeff [95% CI]: 2.94 [1.10;4.78] and 5.17 [3.38;6.95]) and depression (adjusted odds ratio (aOR) [95% CI]: 2.18 [1.12;4.27] and 5.60 [2.38;13.16]). Associated diseases were linked to worse HRQoL (aCoeff [95% CI]: −0.46 [−0.74; −0.17]) and greater fatigue (aCoeff [95% CI]: 1.64 [0.50; 2.77]). Female gender was associated with more depression (aOR [95% CI]:2.35 [1.37; 4.04]).

Conclusion: HRQoL scores were comparable to those observed in the general population, but a significant proportion of patients reported fatigue and depression, likely due to the high physical and psychological burden of their condition. Socioeconomic factors were more associated with QoL than clinical variables. Implementing tailored therapeutic education programs for the most vulnerable patients is needed to provide psychological support or help them manage fatigue.

SAT-334

Fatigue is common in adults with PBC and PSC: prospective analysis of two cohorts encompassing 1267 patients

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Background and aims: Fatigue, a common symptom of chronic cholestasis, is often observed in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). While its etiology remains unclear, it significantly affects quality of life (QoL) and is frequently associated with pruritus, cognitive symptoms, and emotional burden (Younossi, J Hep 2024). In this study, we compared the severity of fatigue and its correlates in PBC and PSC using data from two large cohorts of Polish patients.

Method: A total number of 1267 adult Polish Caucasian patients with PBC and PSC (514 PBC: age range 23–87, 470 females, 38% cirrhosis; 753 PSC: age range 18–74, 257 females, 20% cirrhosis), were enrolled in the study. All patients were prospectively recruited between 2006 and 2023. Health-related quality of life (HRQoL), including pruritus, was assessed in all patients using the PBC-40 questionnaire. Clinically significant fatigue was defined as a score exceeding 33 points in the fatigue domain.

Results: Fatigue was more prevalent and severe in PBC patients as compared to the ones with PSC. The median fatigue in patients with PBC was 30 (range: 11–54), compared to 23 (range: 11–55) in PSC (p < 0.001). In total, 37% of patients with PBC reported clinically significant fatigue, which was present in 22% of patients with PSC. Females in the PSC cohort reported significantly higher fatigue than males (p < 0.001). We also detected a trend (p = 0.058) for higher fatigue in females in the PBC cohort. Fatigue correlated with ALP and GGTP levels in PSC (p < 0.001 and p = 0.027, respectively) and with cirrhosis in PBC (p = 0.018). Patients with the lowest pruritus also had the lowest fatigue in the PBC and PSC cohorts, indicating a correlation between the two symptoms (p < 0.001 in both cohorts).

Conclusion: Fatigue is common in patients with PBC and PSC. While the etiology of this symptom remains unclear, it significantly affects patient's quality of life and might be associated with pruritus. These

results underscore the need of developing new therapeutic strategies to alleviate fatigue in patients with PBC and PSC.

SAT-335

Genetic variant analysis in low phospholipid-associated cholelithiasis patients of the HiChol registry

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Background and aims: Low phospholipid-associated cholelithiasis (LPAC) syndrome is a specific gallstone disease affecting around 1% of adult hospitalized symptomatic gallstone patients. Half of the LPAC patients carry a potentially relevant variant in the ABCB4 gene, encoding the multidrug resistance protein 3 (MDR3), responsible for biliary phospholipid secretion. Reduced phospholipid secretion promotes cholesterol crystallization and recurrent gallstone formation, often persisting after cholecystectomy (CCE). Genetic variants in other genes can contribute to gallstone formation, including ABCB11 encoding the bile salt export pump (BSEP) which maintains a balanced bile composition. Method: Patients fulfilling the clinical LPAC criteria are included in the prospective multicenter HiChol registry, funded by the Federal Ministry of Education and Research (01GM2204A). Approval by the respective local ethics committee and the patients' written informed consent for genetic analysis and clinical data collection was obtained. Genetic variants were determined via panel and whole exome sequencing (WES) and subsequent bioinformatics analysis. Specific questionnaires were used to determine quality of life data and clinical aspects regarding disease onset, symptoms, interventions, medication, lab values, and personal and family medical history.
Results: The HiChol registry data from Magdeburg comprises 20 LPAC patients, 19 (95%) of whom underwent CCE at a median age of 32 years. The gender distribution showed a slight predominance of females (11 patients, 55%) over males (9 patients, 45%). WES results revealed heterozygous potentially pathogenic variants in ABCB4/MDR3 in 6 patients (30%), reinforcing the established genetic basis of the disorder. In around two-thirds of this cohort, no relevant ABCB4/MDR3 variant was detectable. In these cases, variants affecting ATP8B1, ABCB11, NR1H4, MYO5B, ABCC12, and ABCC4, representing genes involved in bile metabolism and transport, were detected. In Leipzig and Düsseldorf, another 15 patients (53% female) with a LPAC phenotype were included in the HiChol registry. At least one potentially relevant ABCB4/MDR3 variant was detected in 40% of these patients. Analyzing WES data sets is currently ongoing for further LPAC patients included in the HiChol registry. Moreover, clinical and quality of life data is assessed for a genotype-phenotype correlation.
Conclusion: LPAC was clinically diagnosed in 35 patients included at three sites of the HiChol registry. Next generation sequencing analysis revealed ABCB4/MDR3 variants underlying about one third of the cases. Suspected pathogenic variants in other cholestasis-related genes may contribute to a LPAC-similar phenotype of recurrent gallstone disease requiring further detailed analysis regarding potential pathomechanisms.

SAT-336

Prevalence and characterization of hepatobiliary involvement in cystic fibrosis patients at a referral hospital

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Background and aims: Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects the CFTR gene and has multi-organ involvement, including hepatobiliary complications. Various definitions have been proposed to assess liver involvement. Koh's classification defined Cystic Fibrosis Liver Disease (CFLD). In 2024, new definitions were published that classify patients into Cystic Fibrosis Hepatobiliary Involvement (CFHBI) if hepatomegaly, hepatic steatosis, elastrography >5.95 kPa, persistenly abnormal blood markers, cholelitiasis or hepatolithiasis; and Advanced CFLD (aCFLD) if nodular liver, elastography >8.7 kPa, cirrohosis with or without portal hypertension or noncirrothic portal hypertension). The aim of this study is to evaluate and characterize the prevalence of hepatobiliary involvement and compare the different definitions.
Method: This is a single-center, retrospective, observational study of a cohort of adult CF patients at our center. Demographic, radiological, analytical data, risk scales (FIB-4, APRI, Forns, Liver Risk Score), and elastography were analyzed to evaluate the prevalence of hepatobiliary involvement.
Results: Thirty-six patients were included, with a mean age of 33 years (53% male). Ninety-two percent had a typical CF mutation (DF508/DF508 or DF508/other). Twenty-three patients (69%) had started treatment with modulators, of whom five (15%) discontinued due to gastrointestinal side effects or hypertransaminasemia. Regarding liver involvement, 22.2% showed persistent analytical abnormalities, predominantly elevated AST and ALP levels. On ultrasound, 11.1% had cholelithiasis, 13.8% showed a homogeneously hyperechoic pattern, and 2.7% had a nodular pattern. The mean elastography value was 4.4 kPa (IQR 1.7 kPa), and the values for FIB-4, APRI, Forns, and Liver Risk Score were 0.52 (IQR 0.71), 0.22 (IQR 0.155), 1.73 (IQR 2.38), and 4.75 (IQR 1.27), respectively. According to the definitions, 8.3% met Koh's criteria, 36.1% met CFHBI criteria, and 5.5% met aCFLD criteria. No statistically significant differences were found in analytical data or elastography between patients with and without CFHBI. However, in patients meeting Koh and aCFLD criteria, significant differences ($p < 0.05$) were observed in elastography (aCFLD 15 kPa [IQR 6.3] vs 4.4 kPa [IQR 1.7]; Koh 8.7 kPa [IQR 7.05] vs 4.4 kPa [IQR 1.62]), APRI (aCFLD 1.94 [IQR 1.54] vs 0.21 [IQR 0.12]; Koh 0.41 [IQR 1.54] vs 0.21 [IQR 0.09]), and LRS (aCFLD 11.5 [IQR 2.02] vs 4.7 [IQR 1.1]; Koh 9.48 [IQR 3.86] vs 4.63 [IQR 1.04]).
Conclusion: The prevalence of CFHBI in our cohort is 36%, similar to that reported in the literature. Koh's and aCFLD classifications identify patients with advanced liver involvement. CFHBI may detect patients with early involvement who could benefit from close monitoring. APRI, LRS, and elastography indices identify advanced liver involvement in CF patients.

SAT-337

Liver disease is highly prevalent in patients with hereditary transthyretin-related amyloidosis

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Background and aims: Hereditary transthyretin-related amyloidosis [ATTRv amyloidosis (AA)] is a rare and progressive disease characterized by the deposition of transthyretin amyloid in various organs, mostly in the heart (cardiac phenotype) and peripheral nerves (neurological phenotype). However, data on the possible co-presence of liver damage in patients with AA are scant. Aims of the study were to assess prevalence and characteristics of possible liver disease in a cohort of patients with AA.
Method: Consecutive patients with AA, regularly followed up at the Cardiology and Neurology referral centres of the University Hospital of Messina, were enrolled. Demographic, clinical, laboratory, transthoracic echocardiography and electromyography data were collected. All patients were evaluated at the Unit of Medicine and Hepatology by means of liver biochemistry, elastography and ultrasonography. Liver stiffness measurement (LSM) was considered abnormal when stiffness values were above 8 kPa, and ultrasonography was considered altered when signs of chronic liver disease or cirrhosis were present.
Results: Fourty-six patients (37 males, mean age 70.3 ± 11 years) were enrolled. Twenty-five (54.3%) had a cardiac phenotype, 13 (28.3%) neurological manifestations, and 8 (17.4%) a mixed phenotype. Overall, 19/46 (41.3%) patients had alteration of liver biochemistry and/or stiffness and/or ultrasonography. No patient had viral or autoimmune hepatitis, nor alcohol use disorder. Fourteen/46 patients (30.4%) had LSM > 8 kPa, and they were older (median age 76.8 vs 67.7 years, $p = 0.007$), with larger spleen diameter (11 vs 10 cm, $p = 0.02$) and lower platelet count (150×10^9/L vs 212.5×10^9/L, $p < 0.0001$) than patients with lower LSM; no differences in prevalence of diabetes, obesity and dyslipidemia was found among patients with different LSMs. Ten/14 patients with LSM > 8 kPa had cardiac and 4/14 a neurological phenotype, while patients with LSM <8 kPa had cardiac phenotype in 15/32 cases, neurological in 9/32, and mixed in 8/32 (p = n.s.). Overall, liver stiffness was directly correlated with NT-proBNP and troponin I values ($p = 0.003$ and $p = 0.005$, respectively), and inversely related to platelet count and portal vein flow ($p < 0.0001$ and $p = 0.02$, respectively).
Conclusion: Patients with AA have a high prevalence of liver disease and should therefore promptly be referred to liver centres for a careful assessment of possible liver damage. Liver involvement seems independent of the AA phenotype and associated with markers of advanced stages of cardiomyopathy in patients with cardiac phenotype.

SAT-338-YI

The role of metabolic factors in alpha-1 antitrypsin deficiency

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a prevalent rare genetic condition that increases the risk of developing lung emphysema and liver fibrosis. We assessed the relevance of key metabolic factors, i.e. body mass index (BMI) and diabetes, including their impact on the development of liver and lung endpoints.
Method: We collected an international, multi-centric Pi*ZZ cohort of 1,862 individuals from 17 different countries with severe AATD (Pi*ZZ), of whom 929 had a follow-up examination after a minimum of 6 months. At baseline, participants received a thorough liver assessment including clinical evaluations, laboratory tests, and liver stiffness measurement (LSM) via transient elastography (Fibroscan®). Subjects with liver comorbidities and hepatic decompensation before baseline were excluded. Liver endpoints were defined as liver transplantation, liver-related mortality, and first hepatic decompensation. We compared the results with data from 16,715 Pi*MZ and 415,208 non-AATD (Pi*MM) individuals from the population-based UK Biobank.
Results: At baseline, 64 Pi*ZZ participants had diabetes, 614 were overweight (BMI 25.0–29.9 kg/m²), and 295 obese (BMI ≥30 kg/m²). Participants with diabetes had significantly higher liver transaminases compared to those without (21/44% vs. 11/18%). A surrogate of

advanced fibrosis (APRI ≥1.0 units/LSM ≥15.0 kPa) was four to five times more frequent in subjects with diabetes (18/21%, aOR = 3.7/5.0, p < 0.01). Among normal-weight Pi*ZZ individuals, elevated transaminases were rare (9/12%), but more common in overweight (14/23%; aOR 1.7/2.1) and obese individuals (17/29%; aOR 2.2/3.1). APRI ≥1.0 units was more than five times more frequent in obese individuals (8.2%; aOR 5.4, p < 0.001) and almost three times more frequent in overweight individuals (5.3%; aOR 2.5, p = 0.006). During a median follow-up of 4.5 years, 56 Pi*ZZ participants experienced a liver and 55 a lung endpoint. Diabetic and obese Pi*ZZ participants had an increased risk of hepatic endpoints (aHR = 4.1/5.7, p < 0.001), whereas overweight status was associated with a decreased risk for lung endpoints (aHR = 0.3, p = 0.004). In the diabetic Pi*MZ and Pi*MM subcohorts from the UK Biobank, the ORs for elevated liver markers, advanced fibrosis, and hepatic endpoints were smaller than in the diabetic Pi*ZZ subcohort, whereas overweight and obese status conferred similar aHRs in all genotypes. Overweight was associated with a decreased (aHR = 0.6/0.8, p = 0.001) and diabetes with an increased risk (aHR = 2.1/2.3, p < 0.001) for lung endpoints in Pi*MZ and Pi*MM subjects.

Conclusion: Diabetes and obesity are associated with elevated liver surrogate markers and an increased risk of decompensation, independent of genotype. However, the individual impact is most pronounced in Pi*ZZ individuals. These findings will inform daily patient counseling and risk stratification.

SAT-339

Comparison of pyogenic liver abscess of biliary and non-biliary origin

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Background and aims: Biliary pathologies, including common bile duct stone (CBDS), cholecystitis, and recurrent pyogenic cholangitis, are the major identifiable causes of pyogenic liver abscess (PLA) and may be associated with poor prognosis. We conducted this retrospective study to identify the association factors for biliary PLA by comparing their characteristics with non-biliary PLA. We will also review the results of magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) performed for certain PLA patients to further investigate biliary pathologies.

Method: The demographics, comorbidities, clinical features, investigation results, management strategies, and outcomes of PLA patients were studied. Univariate and multivariate analyses were conducted to identify the association factors for biliary PLA. Additional biliary findings in follow-up MRCP or EUS would be investigated.

Results: Two hundred seven PLA patients were included. Biliary pathologies were the most commonly identifiable cause (22.7%). CBDS, stricture, or cholangitis were the most frequent biliary etiologies. Transabdominal ultrasound and computed tomography identified more than 90% of biliary pathologies. EUS identified two more cases of CBDS. Two patients without follow-up imaging developed cholangitis later. In univariate analysis, patients with biliary PLA had higher mean age and alkaline phosphatase levels and more incidences of cerebrovascular accident history, Escherichia coli, Enterococcus, or polymicrobial infection, surgical drainage, and recurrence. In multivariate analysis, advanced age (p = 0.004; odds ratio (OR), 1.047; confidence interval (CI), 1.015–1.080), polymicrobial PLA (p = 0.036; OR, 3.681; 95% CI, 1.087–12.469), and recurrent PLA (p = 0.015; OR, 4.534, 95% CI 1.337–15.371) were associated with biliary PLA.

Conclusion: Biliary pathologies are common and significant causes of PLA. They should be considered in patients with advanced age, polymicrobial PLA, and recurrent PLA.

SAT-340

Liver disease and prevalence of liver transplantation in ZZ alpha-1 antitrypsin deficiency – a systematic review and meta-analysis

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Background and aims: Alpha-1 antitrypsin deficiency (A1ATD) is a monogenic inherited metabolic disorder caused by a mutation (ZZ) in the SERPINA1 gene. This mutation leads to the misfolding, polymerisation and accumulation of alpha-1 antitrypsin (A1AT) within hepatocytes, causing cellular dysfunction, inflammation, cirrhosis, and increased cancer risk. Patients are also prone to lung pathology due to unopposed neutrophil elastase activity in the lungs. The severity of A1ATD-associated liver disease is highly variable, necessitating further quantification and characterization. This study aims to investigate the extent of liver disease, and liver transplantation rates in ZZ A1ATD (PiZ) patients.

Method: We conducted a comprehensive systematic review and meta-analysis of studies investigating liver disease and liver transplantation in PiZ patients. Several established databases including Ovid, EBSCO, PubMed and Cochrane Library, were searched from inception to May 12, 2024. Data on liver disease, blood markers, and liver transplantation were pooled using random effects model and study weight was calculated using the inverse variance method. Crude odds ratios (cOR) were calculated using homozygous wild type participants as the comparator. The study was registered in PROSPERO (CRD42022335666).

Results: Of the 4,420 studies identified, 45 studies and 8,638 PiZ patients (38.8% female) were included. Of PiZ patients, 19.26% experienced transaminitis, characterised by elevated liver enzymes, with cOR 2.01 [95% CI 1.43, 3.08] for ALT, 6.18 [95% CI 2.01, 18.97] for AST, 2.34 [95% CI 0.89, 6.15] for GGT, and 1.85 [95% CI: 0.60, 5.74] for ALP. Additionally, these patients demonstrate an increased risk of liver diseases compared to controls, including steatosis (cOR): 1.52 [95% CI: 1.21, 1.91]), fibrosis (cOR: 9.85 [95% CI: 5.70, 17.03]), cirrhosis (cOR: 10.43 [95% CI: 5.51, 19.73]), and liver cancers (cOR: 14.12 [95% CI: 6.50, 30.66]). The prevalence for liver transplantation is considerable, with rates reaching 4.97% [95% CI: 0.00, 12.34].

Conclusion: Our findings confirm the substantial burden of liver disease in PiZ patients, including subclinical manifestations such as transaminitis, steatosis and fibrosis that may remain undetected and thus screening patients with known AATD for liver pathology may be beneficial. Given the lack of approved treatments for A1ATD-associated liver disease, prioritising the development of novel therapies to stop or reverse liver disease is essential.

SAT-341

Propranolol for primary prophylaxis for variceal bleed in infants and children with biliary atresia – results of a single blind placebo controlled randomized controlled trial (BABB-Trial)

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Background and aims: Non-selective beta-blockers (BB) decrease portal pressure and thus bleeding and non-bleed decompensation in cirrhotic adults. Portal hypertension (PHT) is progressive in biliary atresia (BA) and is a reason for listing children for Liver transplantation (LT). Usage of BB in infants and children with BA has not been studied in a controlled manner. In this single blind randomized controlled trial we aimed to study the effect of propranolol in comparison to placebo for primary prophylaxis on bleed free survival and survival with native liver (SNL) at 18 months.

Method: Infants and children under-5 years of age with BA were screened for presence of esophageal varices starting at the age of 6 months. Those with varices (small or large) were randomized in a 1:1 ratio to receive either propranolol at 1–4 mg/kg/day (dose titrated to

achieve heart rate reduction to 25%) or placebo in a single blind manner. Primary and secondary outcomes were bleed-free survival and SNL at 18 months. Predictors of bleed were analysed using multivariate Cox regression analysis. Fine and Gray competing risk analysis was done considering death and LT as competing events, sub-distribution hazard ratios (SHR) were calculated. Trial was registered as NCT04494763 following ethical clearance.
Results: Total 50 BA children (19 females) were enrolled at a median age of 8.2 (6.4, 12) months. Three children had large varices, while rest had small varices, one-third of whom were high risk with presence of red colour signs. 26 received propranolol while 24 received placebo. At 18 months from the time of enrolment, 2 lost to follow-up – 8 patients developed variceal bleed (5 in propranolol, 3 in placebo, $p > 0.05$) at a median interval of 4 (1.5, 12) months from first endoscopy. There were 20 LT and 9 deaths (6 following variceal bleed). Bleed-free survival (115 vs 115 days, $p = 0.786$) and SNL (40% vs 39%, $p = 0.951$) at 18 months was not different between the 2 arms. On multivariate cox-regression analysis, albumin [Exp(B) 0.060, $p = 0.002$], unsuccessful Kasai [Exp (B) 31.2, $p = 0.016$] and INR [Exp (B) 60.3, $p = 0.019$] were found to be predictors of bleed. On competitive risk analysis, weight (SHR 0.63, $p = 0.033$), height (SHR 0.89, $p = 0.010$), albumin (SHR 0.33, $p = 0.006$) and gastric varices (SHR 6.44, $p = 0.010$) predicted death or LT, however none of the variables was significant on multivariate analysis.
Conclusion: PHT in infants and children with BA show poor response to BB. Heterogeneity due to bilirubin and drop-outs due to competing events (death and LT) affected the results. Larger studies on BB with uniform cohorts of BA based on bilirubin levels are required.

SAT-342
Modified leipzig versus leipzig score: an agreement for diagnosis in wilson disease
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Background and aims: Leipzig score was developed at 8th international meeting in Leipzig, Germany, in 2001 and is a scoring system validated in adults and children (sensitivity 94.3%, specificity 94.4%, positive predictive value 90.9%, and negative predictive value 96.6%). In 2019, "modified leipzig score" was derived, where additional points were allotted to positive family history, ceruloplasmin <5 mg/dl, and magnetic resonance imaging (MRI) changes whereas D-penicillamine challenge test was removed. The aim of this study was to determine agreement between leipzig score and modified leipzig score for diagnosis in wilson disease.
Method: This was retrospective, single centre study (2017–2024), whereby 59 genetically proven patients with wilson disease previously diagnosed using Leipzig score were reassessed with modified leipzig score.
Results: 59 genetically proven wilson disease patients (69.4% male) were enrolled at median age of disease onset 9 years (7.2–10.2 years). 61% children were compound heterozygous and remaining were homozygous for ATP7B mutation. 86% of patients had Kayser-Fleischer (KF) ring positive with median ceruloplasmin 6 (3–10), 24 hour urinary copper 529 (242–1212). 72.8% of patients had direct coomb's test (DCT) negative hemolysis with median reticulocyte count of 3 (1.56–4.36). Using JASP software for statistical analysis comparison as well difference between calculated score i.e leipzig score and modified leipzig score was performed. Results to determine agreement between two score was done using Bland Altman analysis. The mean difference between modified leipzig score and leipzig score was 0.703 (95% CI 0.565–0.841). Pearson's correlation was done, which showed significant correlation between the two scores ($p < 0.001$). Results were depicted using bland altman plot, rain cloud plot.
Conclusion: The agreement (mean difference of 0.703) and its effect size showed this difference is not clinically meaningful. And the positive correlation between the two scores is present. In resource limited areas the modified leipzig score can play an important role in the absence of genetic mutational analysis.

SAT-343
Population pharmacokinetic (PK) model describing the variability of trientine pharmacokinetics in Wilson disease patients in the UNITED study
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Background and aims: Wilson disease (WD) is an autosomal recessive disorder that is characterized by a mutation in the ATP7B gene which in turn results in an impaired copper homeostasis and subsequent copper accumulation in the body. Chelating agents like trientine dihydrochloride (TETA-2HCl) are a treatment for WD patients which helps reduce copper levels. The effects of TETA-2HCl have been demonstrated in both non-clinical and clinical studies. The aim of the present analysis was to develop a population pharmacokinetic (PK) model for trientine (TETA), based on the up-titration phase in study TR-004 ("UNITED").
Method: A population PK model was developed and fitted to data collected over the first 4 weeks of treatment from both adult and paediatric patients, including those with predominantly hepatic symptoms and those with predominantly neurological symptoms. In this period, the initial dose was set at 3 mg/kg, which was up-titrated to 8 and 13 mg/kg at biweekly intervals (visits 2, 3 and 4 respectively). The influence of patient characteristics, like weight, age, and copper parameters, on relevant model parameters, such as apparent clearance and apparent volume of drug distribution, was evaluated. Once the PK modelling and covariate analysis were finalized, the final population PK model was used to compute TETA concentrations for each individual patient and quantified by the following exposure metrics: the predicted TETA maximum concentration (Cmax), the predicted TETA trough concentration (Ctrough), and the predicted TETA area under the curve (AUC). Additionally, a model-based simulation was performed to assess the impact of dose strength on TETA exposure metrics.
Results: The final population PK model was a linear 2-compartment model with first-order absorption and intra-individual variability on the absorption rate constant (Ka) and bioavailability (F1). Exposure for visit 2 was observed to be higher than for the other visits, which was described by a higher bioavailability relative to these visits. No covariates were found to affect TETA PK. The final population PK model described plasma TETA concentrations well, as demonstrated by several numerical and graphical assessments. All parameters were estimated with good precision. Using the model and model-based

simulation, exposure metrics could be derived and compared between age groups and symptom classes, as well as between different dosing strengths.
Conclusion: Plasma TETA concentrations in both adult and paediatric WD patients enrolled in study TR-004 ("UNITED") were well described by a linear 2-CMT model with first-order absorption and a higher bioavailability at visit 2 relative to the other visits. No covariates, including age and body weight, were found to affect TETA PK. A comparison of TETA concentrations and exposures was made between different age groups, symptom classes and dose strengths.

SAT-344-YI

Long-term outcome of sinusoidal obstruction syndrome secondary to hematopoietic stem cell transplantation

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Background and aims: Sinusoidal obstruction syndrome (SOS) is a potentially life-threatening liver complication of conditioning regimens of hematopoietic stem cell transplantation (HSCT). Its long-term outcome is unknown. This study aimed to investigate the long-term liver outcomes of patients with liver biopsy-proven SOS.
Method: This study is a retrospective analysis of a prospective database of patients undergoing a liver-catheterism at our center. We included all patients with histologically proven SOS related to conditioning of HSCT between 1994–2023, and who survived 6 months or more after HSCT. Two expert pathologists reviewed all liver biopsies. Development of signs of portal hypertension (PH) and liver-related events were collected. Cumulative incidence of death was compared between groups using Gray's test.
Results: 23 patients with SOS were included. Median time between HSCT and SOS diagnosis was 18 days (IQR, 14–30). Median follow-up after SOS was 6.1 years (IQR, 2.4–8). During this period, 10 (44%) patients developed signs of PH (portosystemic collaterals n = 10; esophageal varices, n = 6; portal vein thrombosis, n = 1), and 8 (35%) of them liver-related events (ascites n = 8; spontaneous bacterial peritonitis, n = 1; hepatic encephalopathy, n = 3; variceal bleeding, n = 3), in median 1.3 years (IQR, 0.89–4.17) after SOS. Cumulative incidence of appearance of signs of PH was 50%, 60%, and 90% at 1, 3, and 10 years, respectively. Cumulative incidence of liver-related events was 30%, 60%, and 80% at 1, 3 and 10 years, respectively. Patients who developed liver-related events during follow-up received less commonly ursodeoxycholic acid (10% *vs.* 46%, p = 0.042) and defibrotide (30% *vs.* 77% (p = 0.024) than patients who did not; no other clinical feature at baseline differed between the two groups, including risk factors for liver diseases. Histological features on baseline liver biopsy associated with the development of liver-related events during follow-up included periportal fibrosis (40% vs 0%, p = 0.005) and any steatosis (30% vs 0%, p = 0.043). Out of the 10 patients who developed signs of portal hypertension during follow-up, 3 underwent a second liver biopsy 1.3 (IQR, 1.0–2.7) years after SOS diagnosis, and all biopsies showed features of porto-sinusoidal vascular disorder and 6 additional patients underwent liver-stiffness measurement showing values ranging from 6 to15 kPa (median 13 kPa). Cumulative incidence of death was significantly higher in patients who developed signs of portal hypertension than in those who did not (HR: 10.88 (1.29–91.65, p = 0.028)).
Conclusion: Development of PH and liver-related events are common following SOS secondary to HSCT, particularly when patients did not receive ursodeoxycholic acid and defibrotide, and impact patients' survival. Histologically, SOS evolves towards features consistent with portosinusoidal vascular disorder.

SAT-349

Liver disease in adults with fontan circulation: a cross-sectional study from a tertiary center in western Sweden

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Background and aims: Fontan surgery represents a series of palliative procedures performed early in life for children with complex congenital heart defects, resulting in univentricular heart circulation. However, there has been increasing reports that these patients are at risk of developing Fontan-associated liver disease (FALD), which may increase morbidity and mortality. The assessment of FALD and its predictors remains unclear. This study aimed to determine the prevalence of liver disease in adults with Fontan circulation in Western Sweden and to characterize liver-related and clinical features in those with and without significant liver disease.
Method: This single-center, cross-sectional observational cohort study, included patients with Fontan circulation attending Adult Congenital Heart Disease Center at Sahlgrenska University Hospital/Östra from 2019–2023. Participants were identified through ICD codes in an administrative database. Data were retrospectively collected from medical records, including demographics, clinical history, laboratory results, imaging findings, and cardiopulmonary assessments. Participants were divided into two groups based on liver imaging: those with radiological signs of fibrosis, cirrhosis, and/or hepatomegaly (FALD group) and those without (non-FALD group). Liver imaging modalities included ultrasound, magnetic resonance imaging and computed tomography of the abdomen.
Results: Of 99 eligible participants, 96 were included (median age 26.5 [IQR 21.5, 31.0] years; 59.4% male). Liver imaging was available for 86 individuals, 64 (74%) of whom showed findings compatible with FALD, with 42 (66%) demonstrating signs of advanced fibrosis or cirrhosis. In the FALD group median liver and spleen Shear wave elastography was 14.4 kPa [IQR 9.3, 22.3] and 27.9 kPa [22.6, 37.0], respectively. Portal hypertensive gastropathy and esophageal varices were present in 64.3% and 31% of those who underwent upper endoscopy. Ascites was more common in the FALD group (20.3% vs 4.5%). Advanced FALD (per EASL criteria) was observed in 42 individuals (66%). Significant differences between groups included higher body mass index (23.8 vs 21.7 kg/m^2, p = 0.013), spleen length (13.5 vs 11.9 cm, p = 0.008), inferior vena cava pressure (15.0 vs

10.0 mm Hg, p = 0.038), and prevalence of liver focal lesions (26 vs 2, p = 0.002), predominantly hyperechogenic vascular nodules. No cases of hepatocellular carcinoma were identified. Common laboratory abnormalities included elevated gamma-glutamyltransferas and thrombocytopenia.
Conclusion: FALD is highly prevalent in adults with Fontan circulation, with nearly two-thirds showing signs of advanced liver disease. These findings are consistent with previous studies and underscore the importance of routine liver disease screening in early adulthood for this vulnerable patient group.

SAT-350
Wilson disease: presentation, clinical course and complications in a large cohort of patients attending San Paolo hospital of Milan
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Background and aims: Wilson disease (WD) is a rare hereditary illness characterised by pathological copper accumulation due to mutation in ATPTB, a gene that transcribes a protein involved in copper metabolism. The present study was aimed at describing the clinical course and treatment strategies in a cohort of patients suffering from WD followed in our Center.
Method: We analysed the medical records of 193 patients (100 M, 93 F) suffering from WD, followed in our Center between 1972 and 2023. The mean follow-up time was 12 years (from 0 to 49 years). Patients were classified according to presentation: investigations for familiarity with WD (IFW), hepatological involvement (HEP), neuropsychiatric presentation (NP) and mixed presentation (HNP), with neuropsychiatric symptoms associated with hepatological alterations.
Results: Of the 193 patients, 17% were diagnosed after IFW, while 56% presented with HEP involvement, 22% with NP and 5% with both. The mean age at the onset of disease was 18.5 (±14) years. Patients in the HEP group were the youngest at the time of presentation, with a mean age of 14.7 years, in comparison to the NP group (22 years - *p value* = 0.001) and HNP group (38.5 years - *p value* = 0.0007).
In the study population, liver cirrhosis was present in a relevant percentage of subjects at the time of presentation (44%). Interestingly, the frequency of liver cirrhosis was elevated even in patients diagnosed after IFW, representing the 42% of patients of this group.
Among patients with cirrhosis, one third experienced at least one major complication, that is, ascites, variceal bleeding, hepatic encephalopathy and hepatobiliary neoplasms during follow-up. Incidence of hepatobiliary neoplasms was 3.85 × 1000 patient-years. Regarding survival, 8 patients performed liver transplantation, while 9 died during the observation period, 5 from causes related to WD (two for hepatobiliary neoplasms).
Between therapy options, D-Penicillamine was the most chosen drug, mostly as first line therapy. The second most used was zinc, mainly as second line therapy in patients intolerant to D-penicillamine or as maintenance therapy. Trientine, only recently available in Italy, have had a more limited use. We observed a significant occurrence of adverse events with D-Penicillamine (58/166 users), mostly dangerous needing drug interruption, and even with Zinc (24/113 users), mainly for gastrointestinal intolerance.
Conclusion: The HEP presentation was the most frequent and had the earliest onset. At the onset, a substantial proportion of patients already had advanced liver disease, regardless of the mode of presentation. Approximately one-third of cirrhotic patients developed at least one major complication of cirrhosis during follow-up, including liver tumors. Penicillamine was the most widely chosen drug as first line therapy, but potentially leading to severe adverse events. The use of Trientine was limited until the availability of its tetrahydrochloride form and may represent an alternative treatment option.

SAT-351
Biochemical and immunological markers show limited accuracy in predicting histological remission in paediatric autoimmune hepatitis: results from a multicenter study
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Background and aims: Paediatric autoimmune hepatitis (pAIH) is an immune-mediated disease that can lead to serious health implications if left untreated or inadequately controlled. Although immunosuppression achieves remission rates of 60–90%, the risk of relapse remains considerable during the course of disease and upon therapy discontinuation. Whilst ongoing histological disease activity increases the likelihood of relapse, the value of liver biopsy to decide on discontinuation remains debated. This study investigates the value of biochemical and immunological markers in predicting histological disease activity in children with pAIH.
Method: We conducted a retrospective, observational, multicenter study involving patients diagnosed with pAIH per ESPGHAN criteria between January 2000 and May 2024, at the Unit of Paediatric Hepatology, University Hospital of Padua (Italy), and the Pediatric Liver Centre, King's College Hospital, London (UK). The endpoints for pAIH treatment, evaluated using non-invasive parameters - biochemical response (BR; normal transaminases), immunological response (IR; normal immunoglobulin levels), complete biochemical response (CBR; normal transaminases and immunoglobulin levels), and serological remission (SR; negative autoantibodies) - were compared with histological remission (HR), defined as a modified hepatitis activity index (mHAI) <4. Concordance analysis using a confusion matrix was performed to assess agreement between invasive and non-invasive outcome measures in follow-up biopsies.
Results: The study included 71 patients (58% female) diagnosed with pAIH at a median age of 11 years (range 1–19), AIH-1 77%, AIH-2 21% seronegative 2%. Follow-up biopsies were performed at a median age of 14 years after an average time of 5 years after diagnosis, with evaluating HR before discontinuing immunosuppression (68%) as most common indication. Median mHAI score was 2 (range 0–14). BR and CBR were discordant with HR in 20% of cases. A confusion matrix was performed to assess the accuracy of non-invasive parameters in predicting HR. BR predicted HR in 80% of patients (accuracy 0.84, kappa test 0.64) and CBR in 81.6% of patients (accuracy 0.81, kappa test 0.6). IR and SR predicted HR in 68% and 80% of cases, but demonstrated poor concordance, with kappa values of 0.3 and 0.2, respectively.
Conclusion: BR and CBR are not reliable indicators of histological remission in pAIH, as 20% of patients with normal transaminases ± immunoglobulin levels still exhibit active histologic disease. Despite the inherent limitations of this retrospective analysis, our findings underscore the importance of follow-up liver biopsies for accurately assessing histological remission.

SAT-352

Genetic and epidemiological profile of a large brazilian cohort of acute hepatic porphyria

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Background and aims: Porphyrias constitute a rare group of inborn errors of metabolism, with a genetic etiology related to defects in the heme biosynthesis pathway, resulting in abnormal production and toxic accumulation of heme precursors. Acute Hepatic Porphyrias (AHPs) comprise a group of four diseases (Acute Intermittent Porphyria, Variegate Porphyria, Hereditary Coproporphyria, and ALA Dehydratase Deficiency Porphyria or Doss Porphyria) with worldwide distribution, affecting individuals of both sexes and all age groups, and are clinically characterized by recurrent episodic neurovisceral symptoms. Unfortunately, the porphyrias are usually underrecognized reflecting a lack of medical and disease awareness as well as few studies about natural history in large cohorts of patients. The main aim of this article is present consistent data about genetic and epidemiological profile of patients with AHPs in Brazil.
Method: We conducted a national cross-sectional registry with retrospective clinical data of Brazilian patients.
Results: A cohort of 150 patients was analysed in which 105 (70%) patients had the diagnosis of acute intermittent porphyria (AIP), 32 (21.3%) variegate porphyria (VP), 11 (7.3%) hereditary coproporphyria (CPOX) and 2 (1.3%) ALAD deficiency. In our cohort patients needed a mean of 62.04 medical visits and 9.6 years to achieve a definitive diagnosis. About AHP cohort, the most common first clinical manifestation was abdominal pain in 94 (62.6%) patients and acute muscle weakness in 38 (25.3%) with 73 (48.6%) patients presenting only one attack during disease course and 37 (24.6%) exhibiting 4 or more attacks in the last year. The most common variants were the c.973C>T (p.Arg325*) on *HMBS* gene present in 45 patients with AIP, c.503G > A (p.Arg168His) on *PPOX* in 23 patients with VP. Of note, 105 (70%) patients with AHP reported chronic manifestations between attacks.
Conclusion: Brazilian patients with AHP had a higher prevalence of chronic disabling manifestations and a and a higher proportion of patients with recurrent attacks than previously reported and a higher frequency of VP than reported worldwide.

SAT-353-YI

Management of Wilson disease across europe: an international physician-oriented survey by the ERN-RARE liver group

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Background and aims: Diagnosis and treatment of Wilson Disease (WD) is complex and highly specialized. It is crucial to understand the differences in the management of WD across the European Union, as international clinical and scientific collaboration becomes more common. We aimed to investigate differences in WD diagnosis and management as well as patient related perspectives across European centers.
Method: A 37-question questionnaire was distributed among physicians involved in the management of WD patients across European WD centers. Each physician responded on behalf of a WD center. Questions related to diagnosis, treatment, and monitoring of WD as well as questions addressing patient perspectives and background information from the respondent. Responding centers were classified as small or large by number of patients seen per year (</>30). Data was assessed in total as well as by managing specialty and center size.
Results: 58 physicians from 20 countries responded to the survey. 91% of centers adhered to international guidelines and 88% utilized Leipzig diagnostic criteria. Most centers had a wide range of diagnostic tools available, e.g. 24-hour urinary copper, slit-lamp examination and genetics (98%, 95% and 93% respectively). Some were less commonly available, e.g. liver biopsy for copper quantification, penicillamine challenge test and non-ceruloplasmin bound copper (74%, 53% and 43%).
21% of small centers did not offer trientine, cost was a limiting factor to some. Initial treatment of hepatic WD was uniform, whereas variability was observed for neurological presentations with 56% of centers using chelation therapy ± zinc. Neurological departments were more likely to offer chelation therapy (80% of centers, n = 5). Recommendations for copper restricted diet varied widely, with 48% recommending temporary low copper diet and 38% recommending it indefinitely.
Large centers were more likely to follow guidelines and offer more diagnostic tools and therapies, though overall there was little difference between small and large centers.
Conclusion: In conclusion, this physician-oriented survey shows adherence to international WD guidelines among European centers. The survey also uncovers important differences amongst centers particularly related to the initial treatment of non-hepatological WD, availability of trientine and recommendations for low copper diet. The survey highlights numerous areas in WD care in which evidence is lacking.

SAT-354

Liver and spleen stiffness measure by transient elastograghy: a promising tool for the clinical management of patients after Fontan-type surgery circulation

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Background and aims: Haemodynamic changes after Fontan palliation in infant patients with univentricular heart promote so-called Fontan-associated-liver-disease (FALD). FALD is not adequately monitored by traditional liver clinical scores (e.g. MELD-XI, VAST score) and progression risk biomarkers and non-invasive tools are missing. Liver and spleen stiffness (LSM and SSM) measured by transient elastography might be useful technique. Aim was to study

correlations between LSM-SSM and FALD stages in adult post-Fontan patients.
Method: 56 consecutive pts with compensated FALD (median age 25.1 y, 21.3–31.9 y; 14 F) were studied. We recorded liver morphology/structure by ultrasound-scan and LSM (Fibroscan®), biochemical liver tests, radiologic and/or upper endoscopic signs of portal hypertension and cardiological functional parameters. In a 33-pts sub cohort (26.8 y, 22.9–37.3 y; 8 F) SSM (Fibroscan®) was measured too.
Results: Median LSM and SSM were 17.9 (13.5–25.3) kPa and 30.4 (24.4–42.8) kPa respectively and significantly correlated (r = 0.546, p = 0.001). LSM was correlated with g-GT levels (r = 0.365, p = 0.009), total bilirubin (r = 0.403, p = 0.005), and spleen bipolar diameter (SBD, r = 0.465; p < 0.001), while SSM was associated only with SBD (r = 0.408, p = 0.023). Pts with advanced liver involvement had significantly higher LSM (p = 0.010) and SSM (p = 0.022): 24.5 and 39.1 kPa in VAST >1 vs 16.6 and 26.8 kPa in VAST 0–1 pts, respectively. LSM for VAST score >1 identified an AUROC of 0.727 (p = 0.004) and a 16.4 kPa cut off with 93% sensitivity and 48% specificity; SSM for VAST score >1 identified an AUROC of 0.776 (p = 0.009) and a 30.7 kPa cut off with 88% sensitivity and 77% specificity. Both LSM and SSM were correlated with left ventriculus disfunction in logistic regression (r = 0.298 p = 0.019 and r = 0.342 p = 0.049, respectively), and only LSM was associated with NTproBNP (r = 0.427, p = 0.002). SSM was higher in pts on diuretic (39.2 vs 26.1 kPa, p = 0.030) and betablockers therapy (34.0 vs 26.1 kPa, p = 0.020); LSM presented the same trend (21.3 vs 16.6 kPa, p = 0.037 and 21.1 vs 16.6, p = 0.064).
Conclusion: LSM and SSM appear promising tools for the clinical management of pts with Fontan circulation. LSM >16.4 kPa and SSM > 30.7 kPa predicted with high sensitivity advanced FALD. LSM and SSM are significantly higher in patients with worst cardiological function, suggesting their potential role in the prognostic stratification of this challenging population. These preliminary results prompt prospective studies on larger cohorts of pts after Fontan's surgery.

SAT-355
The HepQuant DuO test finds linkage between liver blood flow, portal-systemic shunting and cardiac hemodynamics in Fontan-associated liver disease

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Background and aims: Fontan-associated liver disease (FALD) is a common condition in single ventricle patients following Fontan palliation, but it remains inadequately characterized by existing laboratory and imaging techniques. We aim to measure afferent hepatic flow using the dual oral cholate challenge test (HepQuant DuO) and compare results with hemodynamic variables characteristic of those with FC.
Method: This was a single center cohort study of 35 adults with FC. The HepQuant DuO test involved oral dosing of isotopically-labelled d4-cholate, blood samples collected at 20 and 60 min, and quantitation by LC-MS/MS to yield portal hepatic filtration rate (HFR, clearance adjusted to body weight). Systemic HFR was derived using a model based on body size and concentrations of d4-cholate. SHUNT% is defined as systemic HFR/portal HFR. Total hepatic blood flow was calculated as systemic HFR/[(normal intrinsic hepatic extraction 0.78) × (1 – Hct)] and fractional hepatic arterial (HA) and portal venous (PV) flows were derived. Cardiac output, Fontan pressure, and oxygen saturation were obtained by cardiac catheterization and cardiac magnetic resonance imaging. Healthy individuals (n = 50) served as controls.
Results: Patients with FC (91% White, 54% female) had mean (SD) age of 31 (7) years and BMI 26 (6) kg/m^2 with platelet count 180,000 (66,000) μL^{-1}, hematocrit 44.5% (3.9%), MELD-XI 10.6 (1.4), FIB-4 1.1 (0.6), and APRI 0.44 (0.19). DuO test values were significantly worse in those with FC versus controls (all $p < 0.001$): SHUNT%, 30.6% (10.6%) vs. 20.4% (4.3%); portal HFR, 16.2 (8.7) mL/min/kg vs. 27.4 (9.0) mL/min/kg; systemic HFR, 4.3 (0.9) mL/min/kg vs. 5.3 (0.7) mL/min/kg. Higher Fontan pressure was associated with decreased PV flow ($r = 0.56$, $p = 0.013$). Patients with lower PV flow had a trend towards lower oxygen saturation ($r = 0.32$, $p = 0.058$). Cardiac output was not associated with afferent hepatic flow. Increasing SHUNT% is accompanied by reduction in PV flow and increase in HA flow.
Conclusion: HepQuant DuO demonstrated reduced cholate clearances and increased portal-systemic shunting (SHUNT%) in adults with Fontan circulation (FC). Increased Fontan pressure and desaturation, markers of Fontan circulatory failure, are associated with decreased PV inflow and compensatory increase in HA inflow as estimated by the DuO test. The HepQuant DuO test could be useful in measuring severity of hepatic impairment and shunting in FALD.

SAT-356
Porto-sinusoidal vascular disease: epidemiology, clinical features and treatments

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Background and aims: Porto-sinusoidal vascular disease (PSVD) encompasses various disorders characterized by abnormalities of the small vessels within the liver. Liver biopsy is essential for diagnosing PSVD, relying on the absence of cirrhosis and specific histological lesions or signs of portal hypertension. The aim of our study was to describe epidemiological, clinical, paraclinical, therapeutic, and prognostic aspects.
Method: This was a retrospective descriptive study conducted in a hepatogastroenterology department over a 7-year period from 2017 to 2024, involving all patients diagnosed with PSVD who underwent liver biopsy. Data were collected from patient records and during their follow-up.
Results: A total of 43 patients were diagnosed with PSVD, with a mean diagnostic age of 42.4 ± 12.6 years, with sex ratio M/F = 0.79. Clinical presentations included hemorrhagic decompensation in 12 (28%), abdominal pain in 14(32.6%), and anemic syndrome in 17 (39.5%). All patients had portal hypertension when diagnosed, with decompensation occurring in 36% of cases. This included hemorrhagic decompensation in 12(28%), while ascites was present in only 3(7%) of cases.
The most common laboratory finding was a pancytopenia in 28 (67.4%), cytolysis in 6(13.9%), cholestasis in 13(30%), hepatocellular insufficiency in 8(18.6%) of cases. On upper endoscopy, esophageal varices were found in 31(75%), gastroesophageal varices in 19.5%(8), and portal hypertensive gastropathy in 9(22.5%). Portal vein thrombosis was present in 25.6% (11) and portal cavernoma in 4 (9.3%) of cases. PSVD diagnosis was based on histological criteria in 60.5%(26), with 65.5%(17) exhibiting specific signs. 21(48.8%) patients had associated conditions, prothrombotic disease were found in 14(32.6%) of cases, 5(11.6%) of the patients had immunological disorders and 2(4.8%) blood diseases. Band ligation was performed for 30(69%) of patients, while beta-blockers were indicated in 60%. Anticoagulation was used to treat thrombosis in more than one-third of the cases. Whereas, splenectomy and splenorenal shunt was used to treat hypersplenism, in respectively 7 and 4% of the cases. Complications included hepatic decompensation in 18(42.9%) of cases and two deaths were reported due to hepatocellular failure and acute leukemia.

Conclusion: Recently, clear histological and clinical criteria for diagnosing PSVD have emerged. However, this disease is still poorly recognized because symptoms usually appear only after complications of portal hypertension occur. In our study, female sex was predominant; all patients presented with portal hypertension, decompensation occurring in one-third of cases. All patients underwent a biopsy, with 65% showing specific signs. Protein S and/or C deficiency was the most common etiology.

SAT-357

Etiological reclassification of cryptogenic cirrhosis after liver transplantation : insights and impact on outcomes

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Background and aims: Cryptogenic cirrhosis (CC) remains a significant indication for liver transplantation (LT), despite advances in diagnosing metabolic-associated steatotic liver disease (MASLD). However, systematic efforts to reclassify CC after transplantation remain limited. This study aimed to reassess CC cases transplanted over two decades, uncover hidden etiologies through a multidisciplinary approach, and evaluate their impact on graft and patient survival.

Method: We conducted a retrospective study at Paul Brousse Hospital, including patients transplanted for CC. A control group consisted of patients transplanted for cirrhosis of known etiology. Reclassification was performed in two phases: Phase 1 entailed an exhaustive review of clinical, histological, and imaging data, followed by a multidisciplinary expert panel evaluation in Phase 2. Genetic analyses employed a targeted panel of 165 genes. Post-LT survival outcomes were compared between reclassified CC patients and those with known etiologies.

Results: Among 3001 LT performed during the study period, 1355 were for cirrhosis, including 68 for CC. CC patients were younger than the control group (47.7 vs. 51, $p = 0.038$) and included a higher proportion of females (42.7% vs. 30.9%, $p = 0.041$). They also had higher mean total bilirubin levels at listing (209.5 vs. 157.3 µmol/L, $p = 0.043$), though MELD score were similar between the groups. The mean wait time on transplant list was similar (168 vs. 191 days, $p = 0.3$). Phase 1 allowed the identification of etiologies in 24 patients. In Phase 2, expert panel reviewed 33 cases, leading to a definitive diagnosis in 15 patients, a probable diagnosis in 4, and 14 cases remaining undetermined. Overall, 68.4% of CC cases were reclassified. Identified etiologies included metabolic steatohepatitis (25%), alcohol-related liver disease (21%), autoimmune diseases (14%), and rare genetic disorders. Among the 12 patients who underwent genetic sequencing, 3 received a molecular diagnosis: LPAC syndrome (ABCB4 mutation), congenital hepatic fibrosis (PKHD1 mutation), and ciliopathy with renal and hepatic involvement (TTC21B mutation). Additionally, 7 patients presented variants of interest without a definitive molecular diagnosis. Post-transplant survival rates were comparable between reclassified CC patients and those transplanted for known causes ($p = 0.3$).

Conclusion: This study demonstrates the value of systematic post-transplant reclassification of CC, combining comprehensive clinical evaluation, genetic sequencing, and expert panel review. Following the reclassification process, only 14 cases (0.47% of all the LT on the period) remained without a definitive etiological diagnosis, highlighting the effectiveness of the multidisciplinary approach in resolving CC cases. Identifying hidden etiologies provides critical insights into the underlying causes of CC and supports the development of personalized strategies to optimize long-term management for transplant recipients.

SAT-358

Dynamics and prognostic implications of splanchnic volumetry in patients withportosinusoidal vascular liver disorder

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Background and aims: Splanchnic volumetry is a valuable predictor of poor outcomes in cirrhosis. However, its prognostic impact in portosinusoidal vascular disorder (PSVD) remains unclear. This study aimed to evaluate splanchnic volumetry, its dynamics, and its influence on the prognosis of this rare disease.

Method: We conducted a retrospective, multicenter observational study, including all PSVD patients with an available CT scan from 10 centers in the VALDIG network. The volumes of Couinaud liver segments I-III (LLV) and IV-VIII (RLV), total liver volume (TLV), and total spleen volume (TSV) were measured using manual or semi-automated segmentation on CT imaging. All these volumes were normalized for height (ht). Patients were followed until death, liver

transplantation (LT), loss to follow-up, or last follow-up visit. Uni- and multivariate Cox regression analyses identified factors associated with the composite endpoint of first/further hepatic decompensation and all-cause mortality. The dynamics of splanchnic volumetry were assessed in patients who had a second CT scan performed at least one year after the baseline scan.

Results: A total of 177 PSVD patients were included (age: 51 ± 16 years, 60% male, 50% with high-risk varices, 44% decompensated, Child-Pugh score 6 ± 2 pts, MELD score 10 ± 4 pts). The mean normalized volumes were: LLV-ht 230 ± 118, RLV-ht 580 ± 242, TLV-ht 810 ± 281, and TSV-ht 843 ± 657 cc^3/m. During a median follow-up of 32 (IQR 10–57) months, 23% experienced first or further hepatic decompensation, 6% underwent LT, and 17% died with 53% of deaths being unrelated to liver disease. Patients meeting the composite endpoint had a larger TLV-ht (885 ± 290 vs. 773 ± 270; p = 0.008) driven by an increased RLV-ht (648 ± 266 vs. 546 ± 223; p = 0.013), while LLV-ht and TSV-ht were similar. Multivariable Cox regression analysis identified age, comorbidities associated with PSVD and hepatomegaly (defined as a TLV-ht > 904 cc^3/m corresponding to the 75th percentile) as independent predictors of worse survival free of first/further hepatic decompensation (adjusted hazard ratio [aHR] for hepatomegaly: 1.87 [95% CI 1.07–3.27], p = 0.028). The presence of hepatomegaly was associated to a higher proportion of at least one cardiovascular risk factor (CVRF; 68% vs 49%; p = 0.026), particularly arterial hypertension (36% vs 19%; p = 0.017), dyslipidemia (30 vs 11%; p = 0.002) and obesity (16% vs 4%; p = 0.006). A total of 76 patients had a second CT scan available, with a median interval of 32 months (IQR 18–70) between scans. Of these, 25% showed a mean increase of 19% in TLV, while 75% exhibited a mean decrease of 16%.

Conclusion: The presence of hepatomegaly is linked to worse prognosis in PSVD, potentially due to its association with a higher prevalence of CVRF. As the disease progresses, liver volume tends to decrease, similar to what is known to occur in cirrhosis.

SAT-359-YI

Counselling young adults with liver disease on alcohol use: a survey of clinical practices across Europe

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Background and aims: Alcohol is a part of young people's social interactions. This survey aimed to get an overview of how young people with chronic compensated liver disease are counselled on the use of alcohol across Europe.

Method: Within ERN Rare Liver, we designed a survey to assess how clinicians counsel about alcohol intake to patients with liver disease <25 years. The survey was distributed via mailing lists and newsletters to both paediatric service (PS) and adult service (AS).

Results: 142 clinicians (86 AS, 52 PS and 4 in both) from 27 countries responded. All but one counselled about alcohol. While 71% felt comfortable with their counselling (69% PS, 74% AS), 28% were only sometimes comfortable. Only 35% reported having enough knowledge to feel secure in their counselling (26% PS and 39% AS), with 56% reporting some knowledge gaps (63% PS, 52% AS) and 8% reporting lacking sufficient knowledge (9% PS, 8% AS). There was more variability in recommendations when liver disease is 'in remission' (34% PS, 51% AS always recommending complete abstinence; 44% PS, 18% AS never) 'mild' (51% PS, 65% AS always; 17% PS, 9% AS never) or 'without cirrhosis' (34% PS, 60% AS always; 25% PS, 9% AS never). Consensus increases when liver disease is 'active' (80% PS, 95% AS always; 3% PS, 0% AS never), 'with cirrhosis' (75% PS, 93% AS always; 7% PS, 1% AS never) or 'with advanced cirrhosis' (88% PS, 99% AS always; 2% PS, 0% AS never). Recommendations given to patients with liver disease were mostly stricter than those given to the general public (e.g. in remission 84% PS, 81% AS, with advanced cirrhosis 94% PS 91% AS). Compared to AS, PS set a specific limit more often (e.g. in remission 44% PS, 34% AS) and were less likely to advise complete abstinence (e.g. with advanced cirrhosis 88% PS, 99% AS) at all stages of liver disease. If any, the 'specific limit' that was given to patients showed a larger range in countries with higher national recommendations (e.g. in remission Denmark = 2–3 units/w, UK = 1–14 units/w). 83% of participants agreed that a position paper from the ERN in cooperation with the major scientific societies would be helpful for daily practice.

Conclusion: Across Europe, the recommendations about counselling young adults and adolescents vary greatly depending on clinician, country, and liver status, as well as pediatric or adult service. Counselling for complete abstinence increases when liver disease worsens, leading to more consensus within and between services, but is never fully reached. Moreover, PS were less likely to advise complete abstinence and more frequently counselled for a low minimum alcohol intake, possibly recognizing the social pressures and exploratory behaviours typical of this age group. The variability in recommendations may lead to confusion and inconsistencies in patient adherence and trust, especially upon transferring to a different service. Despite general confidence, many clinicians acknowledged knowledge gaps and reported that further clinical guidance, education and patient materials would be useful.

SAT-360-YI

Screening, high risk symptomatology and outcomes of Wilson's disease in 56,606 new referrals in a large tertiary psychiatric population

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Background and aims: Wilson's disease (WD) can present with purely hepatic, neurological or psychiatric symptoms and also as multiple combinations of these three. There are very limited data on the psychiatric pattern of symptoms of WD and the consideration of WD in the psychiatric assessment. South London and Maudsley NHS Foundation Trust (SLaM) is an international leader in mental health and is the largest provider of secondary mental health services in the UK receiving receive referrals from a wide and diverse catchment area. Our work investigates considerations of WD at SLaM and the pattern/overlap of symptoms at presentation of WD.

Method: We utilised the Clinical Records Interactive Search system at SLaM, which included a natural language processing algorithm (identifying 58 different psychiatric symptoms), and hospital episodes statistics data to collect new referrals from 2017 to 2019. This also allowed us to gather patient demographics, blood tests and the nature of the psychiatric presentation. Statistical analyses were conducted using Excel, R, and STATA.

Results: We identified 56,606 new referrals to SLaM over the 2 year period. 9.5% had liver function (LFT) and 0.1% had ceruloplasmin (Cp) requested, with only 27 of the abnormal LFT also having Cp requested. 81 patients were identified as diagnosed with WD on electronic records. Diagram 1 shows their top 5 combination of symptoms, which include cognitive impairment, anxiety, sleep disturbance, tearfulness, and hallucinations. 16,575 patients in our cohort had these 'higher risk' symptoms. Of these, 19% had blood tests requested, 5.4% had abnormal LFT and only 0.27% had LFT and Cp requested. The average age at referral was 32 years with a gender ratio of 44F: 37M. There were 22 deaths with mean age of 50years (range 18–89) and mean time after first referral was 83 months (range 7–204). 36 patients were referred after WD was diagnosed (mean time 5.56 years), and 21 were referred before diagnosis (mean time 6.64 years). Using generalised linear modelling, no association was found between age, gender, deprivation score, or ethnicity and the length of time to diagnosis.
Conclusion: The phenomenology of the presentation is of interest with many of the symptoms being likely linked to the subcortical nature of the disease pathology. We conclude that the psychiatric presentation in WD differs from the type of presentation seen in depressive or psychotic conditions and key differences in symptoms identified may be of use to aid diagnosis of WD. Our data indicate that WD remains under-screened among psychiatric patients, with only a small percentage (0.1%) being evaluated for the condition. It also highlights that 29% of new referrals were linked to a combination of 'higher-risk psychiatric symptoms.' We suggest that any patient with raised liver function ± a combination of 'higher risk' symptoms should be screened with Cp as minimum standard of care.

SAT-365-YI
Effectiveness of cystic fibrosis transmembrane conductance regulator modulator triple therapy in patients with advanced cystic fibrosis related liver disease
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Background and aims: Cystic Fibrosis related liver disease (CFLD) can cause focal biliary cirrhosis with bile duct plugging. Cystic fibrosis transmembrane conductance regulator (CFTR) modulators reduce disease severity, pulmonary exacerbations and the need for lung transplant. To understand their use in CFLD from a perspective of impact on liver outcomes, we analysed a UK tertiary cohort started on triple CFTR modulator therapy.
Method: Analysis of electronic records for patients on Elexacaftor/Tezacaftor/Ivacaftor therapy with CFLD since UK approval in 2020. Liver bloods, fibrosis non-invasive tests (NITs), spleen size and UKELD clinical scores were captured. A composite clinical endpoint of death, liver transplant or decompensation (ascites, variceal bleed, encephalopathy or primary liver cancer) was also assessed. A one-sample Wilcoxon test was used to assess if the median value differs from 0.
Results: 20 patients were identified from the CFLD clinic at University Hospitals Birmingham. Patients receiving liver or lung transplant prior to starting triple therapy (n = 5) were excluded, as were patients with inadequate data (n = 3) or concurrent non-CF liver disease (n = 1) leaving 11 patients for analysis. Median follow up was 44months (22–56 months), median age 26 years (15–51) and 55% male. 64% had compensated cirrhosis at treatment initiation, 100% had pancreatic insufficiency and 55% had history of CF related intestinal complications. Median ALP reduced with treatment (change from baseline −35%, IQR −47 to −20; p = 0.01), with stability of other biochemical markers. Fibrosis NITs remained stable as did spleen size. Only 1 patient progressed to the composite clinical end point, which in that case was death due to respiratory complications of CF albeit with concurrent ascites. UKELD was stabilised with treatment.
Conclusion: Treatment with CFTR modulator triple therapy in patients with advanced CFLD led to reduction in biochemical markers of liver injury. Less than 10% of patients with advanced CFLD treated progressed to liver decompensation suggesting stabilisation.

SAT-366
Relative exchangeable copper: an accurate biomarker for the diagnosis of Wilson disease
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Background and aims: Wilson disease (WD) is a rare genetic disorder affecting copper metabolism, leading to copper accumulation primarily in hepatic and cerebral tissues. WD diagnosis remains challenging and is currently based on the Leipzig score. Several new diagnostic markers have been proposed. The exchangeable copper (CuEXC) methodology quantifies the non-ceruloplasmin-bound copper fraction in serum. Relative exchangeable copper (REC), defined as the ratio of CuEXC to total serum copper (Total Cu), was proposed as a potential diagnostic biomarker for WD (El Balkhi *et al.*, 2009) with a cut-off value of > 18.5% for REC (El Balkhi *et al.*, 2011 and Guillaud *et al.*, 2017). This study aimed to validate the diagnostic performance of these biomarkers in WD.
Method: This cross-sectional study includes patients with and without WD (*total n* = 332) from two European centers (Aarhus (Denmark) and Barcelona (Spain)). CuEXC was quantified using the standardized procedure described by El Balkhi *et al.* REC, CuEXC, and Total Cu levels were determined and compared among groups: patients with newly diagnosed untreated WD (*n* = 13); treated WD (*n* = 91); non-Wilsonian hepatic disease (*n* = 206); and non-Wilsonian acute liver failure (*n* = 22). Diagnostic performance was assessed by receiver operating characteristic (ROC) analyses.
Results: Median REC was significantly elevated among patients with WD (*n* = 104) compared to the other groups combined (23.6% vs. 5.0%, p < 0.001). Median Total Cu was significantly lower in WD compared to non-WD groups (3.5 mcmol/L vs. 16.7 mcmol/L, p < 0.001), whereas median CuEXC was significantly elevated in WD compared

to non-WD groups (0.69 mcmol/L vs. 0.82 mcmol/L, p = 0.004). Both median REC and CuEXC levels were significantly elevated in newly diagnosed patients with WD compared to treated-WD (29.1% vs. 21.6%, p = 0.008 and 2.59 vs. 0.63 mcmol/L, p < 0.001, respectively). ROC analyses comparing newly diagnosed patients vs. those with non-Wilsonian hepatic disease yielded the following optimal diagnostic cut-offs: for REC, ≥13.8% (sensitivity 100% and specificity 99.6%, AUC: 0.998); for Total Cu, ≤7.1 mcmol/L (sensitivity 61.5% and specificity 99.1%, AUC: 0.911); and for CuEXC, ≥1.87 mcmol/L (sensitivity 76.9% and specificity 99.6%, AUC: 0.905).
Conclusion: Our data support the diagnostic value of REC for WD diagnosis. The more broadly available Total Cu was also found to be discriminative and may be useful in the initial diagnostic work-up. We suggest including relevant copper biomarkers in a future revision of the Leipzig score.

SAT-367

UNITED study: results of the up-titration phase of an open label, multicenter, prospective study to characterize the pharmacokinetics and pharmacodynamics of trientine dihydrochloride and to investigate the efficacy and safety in Wilson disease patients

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Background and aims: Trientine dihydrochloride (TETA-2HCl) has been used for the treatment of Wilson Disease for almost 40 years. Although its ability to chelate metal ions has been demonstrated in both non-clinical and clinical settings, no dedicated dose-response studies are available. Therefore, this study aims to investigate a possible pharmacokinetic (PK) - pharmacodynamic (PD) relationship of TETA-2HCl and further evaluate its efficacy and safety. The results of the Up-Titration Phase are presented here.
Method: This study is designed as an open label, multicenter prospective study containing PK, PD, efficacy and safety assessments to evaluate a potential dose-exposure-response relationship as well as to determine the long-term efficacy and safety of TETA-2HCl (Cufence®). The study also contains a PKPD sub-study including data of all patients who completed Visit 4 (Week 4) (i.e. the Up-Titration Phase). At baseline, treatment was initiated, and patients were up-titrated per visit [Visit 2 (3 mg/kg/day), Visit 3 (8 mg/kg/day), Visit 4 (13 mg/kg/day)]. Plasma PK as well as serum copper (Cu), serum ceruloplasmin (Cp) and 24-hour urinary copper excretion (24-hr UCE) levels were measured at each visit. Non-Ceruloplasmin Bound Copper (NCC) was determined at all visits both by calculation as well as directly in serum. This was complimented by neurological, hepatic and psychiatric assessments.
Results: A total of 51 patients were enrolled in study TR-004 "UNITED" and data was collected at 9 sites in Germany, France, Poland, Denmark and the UK. The mean (SD) age of the patients was 34.9 (17.29) years, and 32 patients [62.75%] were male. The majority presented with predominantly hepatic features (n = 34 [66.67%]). When analyzed per visit, the highest mean plasma concentrations were observed at 1 h post administration of TETA-2HCl. Overall, no clear trend towards an influence of predominant symptomatic presentation or age of the patients on mean plasma concentration could be determined. The same trends as described for TETA-2HCl could be observed for its metabolites (MAT and DAT). When looking at Cu, Cp, 24-hr UCE and NCC following TETA-2HCl administration, the strongest changes were seen for asymptomatic patients at all individual study visits. Furthermore, a trend was observed when comparing the different age groups. Also, a clear increase of 24-hr UCE could be observed for all patient groups, reaching the highest values for asymptomatic patients and in the age group ≥18 years. The liver endpoints did not show any change and no serious TEAEs or deaths were observed during the up-titration phase.
Conclusion: The results of this "UNITED" PKPD sub-study show that up-titration of TETA-2HCl in multiple bodyweight dependent steps is generally safe and well tolerated, and that there are possible indications for a relationship between the PK, PD and pre-symptomatic presentation of disease and age.

SAT-368

Outcomes in Navajo neurohepatopathy patients who have undergone liver transplant

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Background and aims: Navajo Neurohepatopathy (NNH) is a rare mitochondrial depletion syndrome, caused by a mutation in the MPV17 gene. Prognosis is poor, with progression of disease in childhood with developmental delays and regression, neurologic decline, and liver failure. Liver transplant has been controversial for patients with this diagnosis; however, the purpose of this report is to recommend against liver transplant as it has not been seen to affect long-term outcomes or patient survival.
Method: We investigated outcomes for patients with NNH who had undergone liver transplant and subsequently followed at our institution. Their growth, neurologic status, and development was monitored closely for months to years after transplant. Data for this study was exclusively collected from review of the patients' medical charts from 2002–2023, including documentation of clinic visits with Gastroenterology, Hepatology & Nutrition; Neurology; General Pediatrics and/or inpatient records.
Results: Three patients underwent liver transplant and followed in multidisciplinary clinics post-transplant. All transplanted patients, now at 4 years, 5.5 years, and 14 years post-transplant, have evidence of neurologic decline and failure to thrive, similar to progression of disease seen in non-transplanted patients.
Conclusion: In the Navajo population, a homozygous R50Q MPV17 mutation leads to a rare mitochondrial DNA depletion syndrome. This rare disease is characterized by progressive neurological decline, liver dysfunction, and liver failure. The natural course of NNH inevitably leads to irreversible neurological deterioration, with varying degrees of severity and age at onset. While liver transplant specifically addresses hepatic failure associated with NNH, it does not play a role in altering the neurological manifestations of the disease. Knowing that affected transplanted patients will inevitably develop neurologic decline due to the natural progression of the disease, it is our view that liver transplant is not a reasonable solution to offer this patient population. While this is a small cohort of patients, our approach to

patient management may be applicable to other systemic mitochondrial disorders associated with liver disease.

SAT-369-YI

Isolated metabolic syndrome is a risk factor for splanchnic venous thrombosis and recurrence of vascular event

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Background and aims: Recent non-cirrhotic, non-neoplastic portal vein thrombosis (PVT) is most commonly caused by a prothrombotic condition or a local risk factor. However, no risk factor is identified in one-third of cases. Preliminary work in our center has shown that abdominal obesity is a risk factor for PVT. The aim of this study was to assess the impact of metabolic syndrome (MetSd) on the risk of thrombotic recurrence in patients with PVT.
Method: This is a monocentric, retrospective, observational study. All patients with acute non-cirrhotic, non-neoplastic PVT not related to liver vascular disease between 2003 and 2023 were included. The inclusion date was the date of imaging at the diagnosis of PVT. Routine clinical, biological, and imaging data were collected, both at baseline and during follow-up. The search for risk factors, according to recommendations, was systematically performed. Patients were classified into three groups: patients with at least one identified recognized risk factor, patients with no identified risk factor (idiopathic group = I), and patients with isolated MetSd according to NCEP-ATPIII criteria (MetSd group = II). The thrombotic event was defined by new venous thrombosis (splanchnic or other) or an arterial event (acute coronary syndrome (ACS) or stroke). Event-free survival rates were assessed using the Kaplan-Meier method and compared by the Log-Rank test.
Results: From 2003 to 2023, 105 patients were included (58% male, mean age 50 years (±14)). At diagnosis, 98% had abdominal pain and 27% had fever. The mean waist circumference was 101.6 cm (±13.5) and the mean BMI was 28.3 kg/m² (±5.8). Median C-reactive protein level was 77 mg/L (0–350), and median factor VIII was 242% (23–523). The most frequent form (36%) was extensive thrombosis, involving portal venous trunk, superior mesenteric vein, and splenic vein. A major thrombosis risk factor was found in 30% of cases, and a minor risk factor in 80% of cases. MetSd was present in 34 patients (33%). Among these, 15 patients (14%) had MetSd as the sole risk factor (group II). 27 patients (26%) had no identified risk factor (group I), classifying their PVT as idiopathic. Anticoagulants were stopped in all patients of the group I and in 14/15 patients in group II. 21/105 patients (20%) experienced a thrombotic recurrence. Among the extra-splanchnic recurrences, 4 were arterial (3 ACS, 1 stroke) and 10 were venous (6 deep vein thromboses and 4 pulmonary embolisms). The probability of being free of recurrence at 7 years was 83% in group I vs 37% in group II (p = 0.006).
Conclusion: These results suggest that MetSd is associated with an increased risk of thrombotic recurrence after PVT further reinforcing its role as a risk factor of splanchnic vein thrombosis. The potential benefit of long-term anticoagulation should be evaluated in these patients, even in the absence of other identified risk factors.

SAT-370

Disease penetrance and survival in HFE p.C282Y/p.H63D compound heterozygous and p.H63D homozygous individuals - a population-based cohort study

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Background and aims: Hemochromatosis is a common genetic disorder characterised by iron overload. Of all common HFE genotypes, homozygosity for p.C282Y has the highest penetrance. A wide variation in disease penetrance estimates for p.C282Y/p.H63D compound heterozygosity has been reported, with low estimates in screening studies and higher penetrance in liver clinic populations. Homozygosity for p.H63D is generally not considered a disease-associated genotype. This study aims to assess age- and sex-specific risk of iron overload, cancer incidence, and life expectancy in a large cohort of HFE-genotyped individuals referred to a liver clinic.
Method: This study was conducted in Tyrol, Austria, and included 8,839 individuals referred for HFE genotyping between 1997 and 2021. Patient demographics, comorbidities, blood test results, and causes of death were extracted from health records. Demographics, laboratory parameters, and survival were analysed using health records. Penetrance, survival rates, and cancer incidence were determined from electronic patient records, health insurance and cancer registries. Outcomes were compared with a propensity score-(PPS)-matched, population-based control group.
Results: We included 507 p.C282Y/p.H63D compound heterozygous and 301 p.H63D homozygous individuals and compared them with 542 individuals homozygous for p.C282Y and PPS-matched controls. Among liver clinic referrals, the prevalence of provisional iron overload at the time of genotyping was 25.1% in p.C282Y/p.H63D compound heterozygotes, compared to 55% in p.C282Y homozygotes. Penetrance of provisional iron overload in p.H63D homozygotes was 25.3% as compared to 11.5% in individuals with normal HFE genotype. On a population level, cumulative lifetime risk for the development of provisional iron overload was significantly lower in p.C282Y/p.H63D compound heterozygotes (1.18%) and p.H63D homozygotes (0.45%) as compared to 18.83% in p.C282Y homozygous patients. Median life expectancy was sig. lower in in p.H63D and p.C282Y homozygous individuals when compared to population-matched controls. HFE p.H63D homozygotes had the greatest burden of comorbidities.
Conclusion: Lifetime penetrance for provisional iron overload is 20 times lower in p.C282Y/p.H63D compound heterozygosity and 50 times lower among p.H63D homozygotes compared to p.C282Y homozygosity. Data from the present study suggest that p.H63D has minor effects on the penetrance of provisional iron overload and the observed higher mortality is rather determined by comorbidities than by HFE genotype.

SAT-371-YI

Prognostic role of endoscopic ultrasound guided direct portal pressure gradient measurement in porto-sinusoidal vascular disorder

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Background and aims: Hepatic venous pressure gradient (HVPG) is considered the gold standard for the diagnosis of clinically significant portal hypertension (CSPH), a condition linked to the risk of developing hepatic decompensation events. However, HVPG is an indirect method to measure portal pressure and its application in pre-sinusoidal form of portal hypertension (PH), as in porto-sinusoidal

vascular disorder (PSVD), is hindered by low accuracy. Recently, endoscopic ultrasound (EUS)-guided Portal Pressure Gradient (PPG) measurement, which allows direct measurement of portal pressure, has emerged as a safe method, potentially addressing the limitations of HVPG. However, data on its application in patients with CSPH and pre-sinusoidal form of PH remain lacking. This study aims to evaluate the safety and usefulness of EUS-PPG compared to HVPG in a cohort of patients with PSVD and CSPH.

Method: In this prospective single-center study, patients with a diagnosis of PSVD who presented a clinical suspicion of CSPH underwent HVPG and EUS-guided PPG baseline measurements. A second EUS-PPG measurement was performed in patients naïve to non-selective beta-blockers (NSBBs) to evaluate hemodynamic response to therapy. The definition and severity of adverse events (AEs) was determined according to the newly introduced AGREE classification for AEs in GI endoscopy. The prognostic role of EUS-PPG was assessed in term of prediction of hepatic decompensation.

Results: Twenty patients were enrolled (mean age 54.9 ± 15.6; male 60%) and a total of 20 HVPG and 27 EUS-PPG measurements were performed, without any adverse events. Mean EUS-PPG was 18.2 ± 4.5 mmHg, significantly higher than mean HVPG value (5.9 ± 2.9 mmHg). Patients with a previous episode of hepatic decompensation had higher mean EUS-PPG values compared to those without decompensation (21.9 ± 2 vs 15.7 ± 3.9 mmHg, p = 0.001). In seven NSBB-naïve patients, the mean baseline EUS-PPG was 17.7 ± 3.8 mmHg, decreasing to 16 ± 2.7 mmHg after maximum NSBB titration. A significant hemodynamic response (>20% EUS-PPG reduction or <12 mmHg absolute value) was observed in only three patients (42.8%). At univariate logistic regression, EUS-PPG was associated with hepatic decompensation (p = 0.025).

Conclusion: EUS-PPG measurement is safe and might have a prognostic role in patients with PSVD and CSPH, outperforming HVPG.

SAT-372

Spleen stiffness in porto-sinusoidal vascular disorder: link to portal hypertension and varices

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Background and aims: Porto-sinusoidal vascular disorder (PSVD) represents a recently recognized clinical entity. Patients with PSVD commonly present presinusoidal portal hypertension along with its associated complications. In the case of PSVD, spleen stiffness measurement (SSM) could help us in identifying patients with portal hypertension (PH) and who are at high risk of developing esophageal varices and bleedings. The aim of the SPLENO-HYPE study is to prospectively follow patients with PSVD who have benefited from an assessment, by measuring liver and SSM, and to study the links between SSM and complications.

Method: Interim (6-month) analysis of our prospective monocentric study of PSVD patients defined following the recent guidelines. Data include demographic data, clinical, biological and radiological data, liver biopsies findings and liver stiffness measurements (LSM) and SSM with the FibroScan® Expert 630.

Results: During the first 6-month period, 22 patients with PSVD were included, 20 with nodular regenerative hyperplasia (NRH) and 2 with incomplete septal fibrosis on the liver biopsy. Among the 22 patients, the majority (20/22, 90.91%) exhibited clinical and biological markers of significant PH. Thrombocytopenia (platelet count <150,000/mm³) was observed in 77% of patients as well as splenomegaly with an average spleen size of 16.5 ± 2.7 cm. Oesophageal varices were present in 85% of the cohort (17/20) including 7 with grade 2 and 5 with grade 3 varices. The mean LSM was 12.6 ± 8.7 kPa. Half of the patients had values below 10 kPa, 27% had values between 10 and 15 kPa, and 23% exceeded 15 kPa. Notably, most patients with values below 10 kPa showed signs of significant PH, including thrombocytopenia, splenomegaly (8/11), and esophagogastric varices (9/11). All patients without significant PH had values under 15 kPa. The mean SSM was 65.6 ± 25.3 kPa. A weak positive correlation was observed between SSM and the grade of esophageal varices (R^2 = 0.178), while the correlation was stronger between platelet count and esophageal varices (R^2 = 0.441). Only three patients had values below 40 kPa. These patients showed no signs of significant PH. On all patients with SSM > 40 kPa, only one patient did not have evidence of significant PH. When comparing patients with SSM <40 kPa (n = 3) to those with increased SSM, there were no significant differences in terms of platelet count, spleen size, ALBI score, or LSM. However, the presence of esophageal varices differed significantly (p < 0.001).

Conclusion: Patients with PSVD commonly present with significant PH features. Elevated SSM, > 40 kPa threshold observed in cirrhosis, together with a LSM incompatible with cirrhosis indicates a diagnosis of PSVD and may serve as a useful marker for screening esophageal varices. Integrating platelet count into the assessment could further enhance screening strategies. Validation in larger cohorts is needed.

SAT-373

Epidemiology, clinical presentation and management of Wilson's disease in Portugal – data from a national registry

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Background and aims: Wilson's Disease (WD) is a rare systemic disorder with few published epidemiologic data in Portugal. We aimed to characterize WD nationwide, by estimating its prevalence

and assessing its clinical presentation, treatment and monitoring across the country.
Method: Multicentric cross-sectional study in adults living in Portugal diagnosed with WD, with an ongoing hospital follow-up and updated records by the end of December 2023 at a national liver database (Liver.pt, sponsored by the program "Hepatologia em Rede"). We collected data regarding demographic and clinical characteristics since diagnosis until the patients' last appointment. Only living patients were considered for analysis.
Results: 156 patients with WD, followed in 20 different Portuguese hospitals. 95% were Portuguese, mean-aged 44 ± 13 years (min-max. 18–80 years) with 52% males.
We estimated a WD prevalence in Portugal of 1.89 cases per 100,000 inhabitants, considering that we were able to include all patients diagnosed and none remained undiagnosed. This was calculated using the official population numbers published by our statistics national institute in 2022, reporting 8,264,506 inhabitants between 18–80 years. The mean age at WD diagnosis was 23 ± 14 years. Most patients (60%) presented exclusively with liver-related symptoms, 18% with neurological manifestations and 18% with both. Regarding the liver-related symptoms, 46% of the patients presented with elevated liver enzymes without advanced fibrosis, 20% had liver cirrhosis (LC) (Child-Pugh A in 68% and B in 32%), 9% acute liver failure and 3% acute hepatitis without liver failure. Four percent were asymptomatic and diagnosed through family screening. Around two-thirds of patients were initially treated with penicillamine, 18% with trientine and 16% with zinc. Currently, after excluding the transplanted patients, there are 45% patients under penicillamine, 33% on trientine and 21% on zinc. We registered a mean of 1.23 drugs per patient during a median follow-up of 21 years, which included 102 drug discontinuations (52 of penicillamine, 38 of zinc and 12 of trientine). The most common reasons for penicillamine withdrawal were side effects (33%) and stock rupture in 2006 (31%). Disease progression was the most frequent reason for zinc (57%) and trientine (44%) discontinuation. Intolerance was recorded in 14% with zinc, 11% with trientine and 10% with penicillamine. During follow-up, 32 patients (20%) underwent liver transplantation (LT). LC at diagnosis was associated with a 4.5 times increased risk for LT.
Conclusion: Our estimated prevalence of WD in the Portuguese population was similar to the numbers reported in the literature (1:30,000–50,000). The course of WD was characterized by multiple therapeutic regimens and therefore needs close monitoring for adhesion and side effects, since in fact one fifth of the patients finally needed LT, although under follow-up and treatment. This was the first nationwide epidemiologic study of WD in Portugal.

SAT-374-YI

Health related quality of life in patients with porto-sinusoidal vascular disorder

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Background and aims: Porto-sinusoidal vascular disorder (PSVD) is a chronic and rare liver disease leading to the development of portal hypertension. There is no data concerning health related quality of life (HRQoL) in patients with PSVD. This study aimed to assess the HRQoL in patients with PSVD with signs of portal hypertension and to identify clinical characteristics associated with impaired HRQoL.
Method: This is a French prospective, observational, multicenter study, ancillary to the APIS phase III randomized controlled trial (NCT04007289), that included patients with PSVD and signs of portal hypertension, according to VALDIG criteria. We assessed HRQoL at inclusion in the trial using the SF-36 questionnaire, a generic score, and the CLDQ questionnaire, a liver disease-specific score. Lower values of these scores indicate poorer HRQoL. We compared HRQoL to data reported in the literature for other liver diseases. We then assessed characteristics associated with impaired HRQoL using univariate analyses, followed by stepwise regression with Benjamini-Hochberg correction (q value).
Results: Between June 2019 and December 2023, 166 patients with PSVD and sign of portal hypertension were included; 143 and 157 patients filled out the SF-36 and CLDQ questionnaires, respectively. Median age was 55 years and 53% were men. 67% had porto-systemic collaterals, and 36% had high-risk varices. Median prothrombin index was 86%. The physical component summary (PCS) and even more the mental component summary (MCS) of the SF-36 score were altered (45 ± 9 and 44 ± 12, respectively), and below the normative value of 50 for healthy U.S. populations. The overall CLDQ score was 5.0 ± 1.16. As compared with data available in the literature, patients with PSVD patients reported poorer HRQoL than those with viral hepatitis, MASLD, or cholestatic liver disease, particularly concerning the mental component of the SF-36 and CLDQ scores. Conversely, HRQoL in PSVD patients was higher than that of patients with severe or decompensated cirrhosis. Comparisons with MASH and hepatocellular carcinoma were less conclusive. Lower serum albumin, lower hemoglobin levels, and a history of upper gastrointestinal bleeding were associated with trends towards lower PCS scores ($q = 0.062$ for each). HIV infection and diabetes were significantly associated with lower MCS scores ($p = 0.029$ each). Lower hemoglobin concentration was strongly associated with a reduced overall CLDQ score ($q = 0.003$).
Conclusion: Patients with PSVD and signs of portal hypertension have an impaired HRQoL, particularly in terms of mental components of the scores. Their HRQoL is poorer than that of patients with viral hepatitis, MASLD or cholestatic liver disease, and higher than that of patients with decompensated cirrhosis. Features associated with

lower HRQoL scores included lower hemoglobin concentration, diabetes, and HIV infection.

SAT-375

Frequency of ATP7B gene variants in brazilian patients with Wilson's disease

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Background and aims: Wilson's disease (WD) is a rare genetic disorder with over 900 variants identified in the *ATP7B* gene. Understanding the regional distribution of these variants can improve WD diagnosis and direct future treatments based on disease phenotype. This study aimed to evaluate the frequency of *ATP7B* variants in a Brazilian WD cohort and their association with clinical phenotypes.
Method: Genetic analysis was performed using massive parallel sequencing of the 21 exons and exon-intron junctions of *ATP7B* (Mendelics Genomic Analysis Laboratory) in patients diagnosed with WD and their first-degree relatives under investigation. Participants were recruited from two Brazilian centers. Demographic data and predominant clinical presentations were assessed.
Results: Forty-one individuals were included (58% female; mean age 26 ± 12 years): 38 with confirmed WD and 3 heterozygous relatives without clinical disease. Among WD patients, phenotypes were distributed as follows: 21/38 (55%) with isolated hepatic manifestations, 7/38 (18.5%) with hepatic and neurological symptoms, 7/38 (18.5%) with isolated neurological manifestations, and 3/38 (9.0%) asymptomatic. A total of 76 *ATP7B* variants were identified. The pathogenic variants c.3402delC, c.2123T > C, and c.3818C > T showed the highest allele frequencies at 19.8%, 14.5%, and 10.5%, respectively. Most patients (87.0%) exhibited compound heterozygosity, while 8.0% had homozygosity and 5.0% simple heterozygosity. Variants c.2145C > T, c.1552T > C, c.2866-6T > G, c.2562G > C, and c.3188C > T were classified as of undetermined significance, whereas c.2072G > T, c.3551T > C, exon 3–4 deletion, c.3694A > C, and c.3071_3072delTG were classified as likely pathogenic. Regarding the disease phenotype, patients with variants c.3402delC CG > C and c.2123T > C presented equal distribution of the isolated hepatic or hepatic plus neurological phenotype, while c.3818C > T variant was associated with predominantly hepatic phenotype. Presence of exon 2 deletion was associated with severe neurological manifestations.
Conclusion: The *ATP7B* variants c.3402delC, c.2123T > C, and c.3818C > T were the most prevalent in this Brazilian cohort. Variants of undetermined significance, such as c.2145C > T and c.3188C > T, were identified in confirmed WD cases. A high genotype heterogeneity was observed, correlating with diverse phenotypic presentations.

SAT-376-YI

Children and adults with severe alpha-1 antitrypsin deficiency present a unique histological liver phenotype (Pi*ZZ genotype)

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Background and aims: Liver disease in severe alpha-1 antitrypsin (AAT) deficiency (Pi*ZZ genotype) displays a biphasic pattern with the first peak in early childhood and the second, adult peak after the age of 40 years. Our aim was to histologically characterize the pediatric and adult liver disease.
Method: We recruited 67 adults and 48 Pi*ZZ children aged four weeks to 17 years from six countries who underwent a liver biopsy/transplantation. A blind histological scoring was performed by two histopathologists.
Results: Pediatric Pi*ZZ samples originated more often from liver transplantation (64.6 vs. 21.2%, $p < 0.0001$) and children displayed significantly higher liver enzymes than adults. Compared to adults, children presented a significantly higher fibrosis stage according to METAVIR (4.0 vs. 2.5, $p < 0.0001$). Higher liver steatosis was more prevalent in Pi*ZZ adults, while bile plugs and duct paucity were significantly more common in Pi*ZZ children (bile plugs: 43.8 vs. 10.4%, $p < 0.0001$; duct paucity 58.3 vs. 1.5%, $p < 0.0001$). No difference in AAT accumulation scores according to Clark was found. When subdividing the pediatric cohort based on age (<1 year, 1–5 years and 6–17 years), cirrhosis was more common in both older age groups than in younger children (64.7 vs. 75.0 vs. 30.8%, $p = 0.045$). There were no differences in liver steatosis, inflammation, or cholestasis parameters, but youngest children displayed less AAT accumulation and less frequently had larger aggregates.
Conclusion: Our study reveals unique histological patterns in Pi*ZZ children and adults thereby providing basis for patient counseling and further mechanistic studies.

SAT-381

Rapid liver disease progression after first hepatic decompensation in individuals with severe alpha-1 antitrypsin deficiency (Pi*ZZ genotype)

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Background and aims: Although severe alpha-1 antitrypsin deficiency (AATD, Pi*ZZ genotype) predisposes to liver disease, the role of AATD in decompensated liver cirrhosis is unclear. The aim of this study was to evaluate the impact of the Pi*ZZ genotype on the further course of liver disease after the first hepatic decompensation event.
Method: We retrospectively included 59 Pi*ZZ individuals with decompensated cirrhosis from 12 European centres and applied propensity score matching for Child-Turcotte-Pugh (CTP) score as well as age/sex to compare the natural disease course with other cirrhosis etiologies. After first decompensation as baseline event, subjects were followed until further decompensation, liver transplantation, or liver-related death.
Results: Most patients were male (75%) and had a mean age of 55 years. The most common first hepatic decompensation event was ascites (68%), followed by variceal bleeding (22%) and overt hepatic encephalopathy (10%). At first decompensation median CTP/MELD scores were 8/14 points and at listing/liver transplantation 16/20 points, respectively. Median time on transplantation list was 2.9 [IQR 1.1–7.2] months. Compared to Pi*ZZ individuals, patients with other etiologies (SHR: SLD 0.62, $p = 0.007$; abstinent ALD 0.50, $p < 0.001$; HCV 0.56, $p = 0.004$) presented with significantly lower risk of further hepatic decompensation, liver transplantation, or liver-related death. Exchanging further decompensation by ACLF yielded comparable results.
Conclusion: Our study defines the natural disease course of Pi*ZZ individuals with decompensated liver cirrhosis that was more progressive than in other etiologies thereby underlining the need for disease-specific therapies and early listing for liver transplantation after first decompensation.

SAT-382
Can drug metabolites predict outcome of Wilson disease?

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Background and aims: D-penicillamine (DP) is bound to proteins, metabolised in the liver in a Phase II reaction and excreted in urine. Its metabolites are not routinely measured for drug monitoring. We aimed to study if there is any correlation of hepatic metabolites of DP in clinical response and toxicity in Wilson disease (WD).
Method: WD children completing >1 year of therapy were prospectively assessed for DP metabolites in urine. Urine samples were collected 5 hours after the ingestion of 15–20 mg/kg of DP. Samples were processed by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. The pH dependent longitudinal ^{1}H NMR spectra of patient urine samples were recorded with pH from 4.5 to 9.0, with 0.5 increment; at 25°C with water suppression using pre-saturation single pulse experiment. The findings were validated using liquid chromatography and mass spectroscopy. The ratios of the metabolites were assessed. Response was defined as near-normalisation of liver enzymes and synthetic functions. Adequate chelation was defined as exchangeable copper <0.87 micromol/L.
Results: 61 WD children, aged 11.8 (6–19) years on 5(1.5–10) years of chelation had baseline pediatric end-stage liver disease (PELD) score of 3(−9 to 43). 77% had predominant excretion of penicillamine-disulphide (PD) and penicillamine-cysteine-disulphide (PCD) while 23% excreted S-methyl cysteine (SMC) or N-acetyl penicillamine (NAP) with median levels 54 (1.8–778), 123 (5.1–2501), 20 (0.5–556) and 7.3 (0.3–200) micromol/L respectively. 74% were responders and 47% had adequate chelation. CuEXC was lower in responders than non-responders [0.73(0.2–1.78) vs 1.08(0.44–2.73) micromol/L, $p = 0.009$], Those showing adequate chelation had higher PCD/SMC ratio as compared to SMC/NAP ratio ([5.6 (0.12–49) vs 3.2 (0.5–470, $p = 0.03$]. Non-responders had significantly higher PD/NAP as compared to other metabolite ratios. 8 (13%) patients with bone marrow toxicity had higher NAP/PCD than other metabolites. 5 patients with subnephrotic proteinuria had higher SMC [15 (6.8–49) vs 2.3 (0.12–25) micromol/L, $p = 0.03$] than patients without proteinuria.
Conclusion: Dominant metabolic pathways and the ratio of their metabolites may determine the outcome in hepatic Wilson disease.

SAT-383-YI
Non-invasive stratification of portal hypertension in patients with BCR::ABL1-negative myeloproliferative neoplasms

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Background and aims: The course of BCR::ABL1-negative myeloproliferative neoplasms (MPN) is frequently complicated by thromboembolic events in the splanchnic venous system, resulting in portal hypertension. The introduction of spleen stiffness measurement (SSM) might improve the diagnosis of portal hypertension in these patients. Therefore, the aim of this study was to evaluate the clinical utility of SSM (performed by using the 100 Hz probe) in non-invasive stratification of portal hypertension in patients with MPN.
Method: We performed a retrospective, mono-centric, cross-sectional analysis including all patients with MPN attending the haematological outpatient clinic at the Medical University of Vienna with available liver stiffness (LSM)/SSM from 10/2023 to 09/2024. LSM/SSM were linked to signs and events of portal hypertension.
Results: Fifty-nine patients were included (mean age 58.5 ± 14.0 years, 70% females, polycythaemia vera and essential thrombocythaemia as main entities). One fourth of patients had portal vein thrombosis. While 18 patients (30.5%) had specific, 29 patients (49.2%) had unspecific signs of portal hypertension. Twelve patients (20.3%) experienced portal hypertensive events prior to study inclusion. LSM/SSM adequately stratified patients with vs. without portal hypertension. SSM was independently linked to portal hypertension and showed numerically higher model characteristics compared to LSM. LSM <5/≥15 kPa as well as sequential SSM <21/≥50 kPa can adequately rule-in and -out portal hypertension with a remaining grey zone of 24%.

Conclusion: LSM/SSM were associated with portal hypertension in patients with MPN. A sequential application of easy-to-remember cut-offs for ruling-in and ruling-out of portal hypertension might improve the clinical management and decision-making in patients with MPN.

SAT-384

Antinuclear antibodies target unknown autoantigens in porto-sinusoidal vascular disorder without portal hypertension

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Background and aims: Recent evidence links porto-sinusoidal vascular disorder (PSVD) to connective tissue diseases. Antinuclear antibodies (ANA) are a hallmark of these conditions, but their prevalence and significance in patients with PSVD without portal hypertension (noPH-PSVD) remain unclear.
Method: Sera from patients with noPH-PSVD were analyzed for ANA using indirect immunofluorescence (IIF) on HEp-2 substrates (HEp-2 IIF). ANA-positive cases underwent RNA immunoprecipitation (RNA-IP) to identify autoantibodies for specific ribonuclear proteins. Patients with cytoplasmic staining on HEp-2 IIF, underwent ELISA for antimitochondrial antibodies (AMA), targeting the E2 subunit of the pyruvate dehydrogenase complex (anti-E2-PDH).
Results: Sixteen patients were enrolled, with a median age of 42 years (range 22–58), and 56% were female. Autoimmune comorbidities included thyroiditis in 4 patients, multiple sclerosis in one. PSVD diagnosis was based on histological evidence of nodular regenerative hyperplasia identified on liver biopsy performed for unexplained liver enzyme abnormalities. ANA were found in 8 out of 16 (50%) patients using HEp-2 IIF with titers ranging from 1:80 to 1:320. A cytoplasmic reticular/AMA-like pattern was observed in 4/16 (25%) patients, a speckled pattern in 1/16 (6.25%), a nucleolar pattern in 2/16 (12.5%; one co-occurring with a cytoplasmic reticular pattern) and a mitotic pattern (mitotic centrosome and NuMA-like) in 2 out of 16 (12.5%) cases. RNA-IP did not identify autoantibodies against specific ribonuclear proteins in any patient. Moreover, none of the patients with a cytoplasmic reticular/AMA-like pattern tested positive for anti-E2-PDH autoantibodies via ELISA.
Conclusion: In this noPH-PSVD cohort, ANA were detected in 50% of cases using gold-standard techniques. Despite 25% showing an AMA-like pattern, anti-E2-PDH testing by ELISA was negative, suggesting these ANA may target mitochondrial antigens distinct from those in primary biliary cholangitis. A notable proportion of ANA-positive patients showed mitotic staining, uncommon in connective tissue diseases. Although ANA prevalence was high, RNA-IP did not reveal specific autoantibodies, highlighting the need for further testing like protein immunoprecipitation or immunodiffusion.

SAT-385

The prevalence and risk factors of metabolic dysfunction - associated steatotic liver disease in patients with transfusion dependent thalassemia

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing concern in individuals with transfusion-dependent thalassemia (TDT), a disease characterized by chronic anaemia requiring lifelong blood transfusions. Limited data exist on the MASLD prevalence in this population. This study evaluates the prevalence of MASLD in patients with TDT using magnetic resonance imaging proton density fat fraction (MRI-PDFF) and identifies associated risk factors, including the adherence to the Mediterranean Diet (MD).
Method: Patients with TDT were prospectively recruited and underwent MRI-PDFF to assess hepatic fat content. Liver iron concentration (LIC) was measured using T2* calculations. Liver stiffness (LS) and Controlled Attenuation Parameter (CAP) were measured via transient elastography. Adherence to the MD was assessed using the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. Clinical and laboratory data was collected including all known cardiometabolic factors. Steatosis was staged based on MRI-PDFF as follows: grade S0 (<5.75%), grade S1 (5.75–15.5%), grade S2 (15.5–21.35%), and grade S3 (≥21.35%). MASLD was defined as the presence of hepatic steatosis (MRI-PDFF ≥5.75%) in patients without secondary causes of liver fat accumulation and the existence of ≥1 cardiometabolic factor per EASL guidelines. Individual risk factors for the development of hepatic steatosis were identified using multivariable linear regression. Patients with severe LIC (LIC >15 mg Fe/g), chronic viral hepatitis and suspected alcohol abuse were excluded.
Results: The cohort included 60 patients (53.3% women; mean age of 47.2 ± 8.1 years). Ten patients (16.7%) had steatosis ≥S1, all of whom had at least one cardiometabolic factor. The mean PDFF value was 3.77 ± 3.75%. Mean LS value was 5.6 ± 2.4 kPa and mean CAP value was 221.5 ± 36.3 dB/m. CAP values were significantly higher in patients with MASLD compared to those without the condition (251 vs 216 dB/m, $p < 0.01$). Multivariable linear regression analysis identified that factors such as BMI > 25 kg/m^2 (adjusted beta = 1.84, $p = 0.046$), homeostasis model assessment-estimated insulin resistance (HOMA-IR, adj. beta = 2.27, $p = 0.003$), poor adherence to the MD, as indicated by the MEDAS questionnaire (adj. beta = –0.32, $p = 0.099$) and LIC (adj. beta = 1.072, $p < 0.001$) constitute individual factors, which influence the MRI-PDFF value.
Conclusion: Our study is one of the first to indicate that MASLD is becoming a prevalent condition in TDT patients, due to metabolic and dietary factors and possibly related to the current greater life span of these patients. The identified risk factors underscore the need for integrated clinical strategies focusing on insulin resistance management, LIC reduction and dietary modifications, including enhanced adherence to the MD, to mitigate the risk of MASLD in this population.

SAT-386

The Alpha-1 foundation research registry: liver disease among alpha-1 antitrypsin deficiency patients in a United States cohort

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Background and aims: While Alpha-1 Antitrypsin Deficiency (AATD) is commonly known as genetic COPD, certain variants can lead to an increased susceptibility of severe liver disease. The Alpha-1 Foundation (A1F) has maintained a database of AATD patients since 2019, which collects ongoing data on the characterization of AATD across over 20 different genotypes within the United States. We aim to highlight characteristics among liver-affected patients with AATD within this longitudinal study.
Method: The Alpha-1 Foundation Research Registry (A1F Registry) enrolled over 3800 participants from all 50 states through REDCap between June 2019 to November 2024. Over 1,300 discrete data points per patient were captured. Utilizing the patient reported questionnaire, liver-affected patients were defined as A1F Registry participants who responded yes to any liver disease (MASH, liver

cirrhosis, fatty liver disease, mild/moderate/severe liver disease, cholestasis,) or have had a history of childhood jaundice, variceal bleeding, ascites, abnormal liver enzymes, or spontaneous bacterial peritonitis.

Results: Overall, among all Registry participants who responded to reasons for AATD testing (n = 2988), 10% reported AATD diagnosis due to liver symptoms, with other reasons including lung symptoms (43%), family history (32%), and incidental findings on direct-to-consumer testing (7%). Though AATD testing was reported in 10% due to liver symptoms, 46.7% reported to be liver-affected (n = 2962), of which 51.7% reported fatty liver disease, 54.5% reported abnormal liver function tests and 10.2% MASH. Liver-affected Registry participants identify largely as female (69.3%), with a mean age of 54.1 ± 16.26 years (range <1–91 years) (n = 1386). Of those reporting genotypes (n = 1349), 40% were PiZZ, 11.3% PiSZ, 28.5% PiMZ, 10.4% other rare genotypes and 9.8% unknown. Participants with liver disease reported standard of care liver assessments, such as Fibroscan (17.1%) or abdominal ultrasound (56.9%) (n = 1228). Among Registry participants who are liver-affected (n = 1386), 39.4% also reported a diagnosis of COPD or emphysema. Current augmentation therapy usage was reported in 26.2% of liver-affected patients.

Conclusion: The complete profile of liver-affected AATD patients including symptomology, diagnosis, and treatment demonstrated in the A1F Registry allows a better understanding of liver disease in this population. This longitudinal study contains clinical data beyond phenotype that can be utilized to determine liver disease burden in the community and allow for targeted recruitment efforts in clinical trials. This initiative empowers the Alpha-1 community and highlights the need to further characterize liver disease in AATD patients with a robust natural history study.

SAT-387

Trajectories of serum bile acid levels and their determinants in progressive familial intrahepatic cholestasis: insights from the NAPPED consortium

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Background and aims: Bile Salt Export Pump (BSEP) deficiency, also known as Progressive familial intrahepatic cholestasis type 2 (PFIC 2), is a rare genetic liver disease characterized by chronic cholestasis. Treatment strategies to decrease serum bile acid (sBA) levels have been shown to improve the prognosis of patients with BSEP deficiency. This study aimed to identify trajectory patterns of sBA levels in a natural history cohort of individuals with BSEP deficiency, that could help target therapeutic interventions.
Method: Data were obtained from the NAtural Course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) Registry, a leading worldwide PFIC patient database. We included individuals not treated with IBAT inhibitors, and censored their follow-up at age 18, surgical biliary diversion, or liver transplantation. A latent class mixed-effects model was used to identify classes of sBA trajectories. sBA measurements were log-transformed to address right skewness. We modelled the progression of sBA from birth to age 18 years using natural cubic splines—which allow for flexible nonlinear changes over time—with knots at the 0.05, 0.35, 0.65, and 0.95 percentiles. The optimal number of trajectory classes was determined using the Akaike and Bayesian information criteria and requiring each subgroup to include at least 10% of the total study population.
Results: We analysed data from 317 individuals with BSEP deficiency, who collectively contributed 1,224 sBA measurements. Each individual had at least one sBA measurement (median 2.0, interquartile range [IQR] 1.0–5.0), with a median follow-up duration of 2.8 years (IQR 0.9–7.8). Our analysis identified two log-sBA trajectories: (1) a high-stable trajectory (82% of the individuals) with a plateau at ~165 µM, (2) a "horizontal hockey-stick" trajectory (18%), characterized by a similar start sBA followed by a decline towards a plateau ~8 µM from around age 5 years. Among individuals who were censored because of transplantation or surgical biliary diversion, 94% and 96%, respectively, belonged to the high stable trajectory, compared to 6% and 4% in the second trajectory group.
Conclusion: This study identified two distinct sBA trajectories in BSEP deficiency, with one trajectory strongly associated with liver transplantation and surgical biliary diversion. These findings suggest heterogeneous disease progression and support the development of trajectory-specific management strategies.

SAT-388
Integrated PK-PD model relating serum copper concentrations, urinary copper clearance and trientine pharmacokinetics in Wilson disease: initial insights from the UNITED study

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Background and aims: In Wilson Disease (WD) patients, a mutation in the ATP7B gene results in an impaired copper homeostasis and copper accumulation in the body. Chelator treatment of patients with WD, including trientine dihydrochloride (TETA-2HCl) therapy, aim to reduce copper levels by its sequestration and enhanced elimination. While the effects of TETA-2HCl have been demonstrated in both non-clinical and clinical studies, no dedicated pharmacokinetic (PK) – pharmacodynamic (PD) modelling was ever performed. The aim of the present analysis was to reveal and quantify the relationships between the systemic trientine (TETA) exposure, its effect on serum copper markers and urinary copper excretion, as well as the influence of patient characteristics on these relationships in a broad WD patient population by means of PK-PD modelling, based on data collected during the up-titration phase of study TR-004 ("UNITED").
Method: A population PK-PD model was developed to describe the data collected during the first four weeks of study TR-004 ("UNITED"). The model was constructed as follows: first, a population PK model was developed and fitted to the data over the first 4 weeks of TETA-2HCl treatment. Then, the modelled individual TETA PK parameters were related to total 24 hour urinary copper excretion (24h-UCE) and serum non-ceruloplasmin bound copper (NCC) concentrations using an integrated population PK-PD model. As a main characteristic of the model, urinary exchangeable copper clearance (CUCL; L/h) was modelled, while the 24h-UCE and serum NCC concentrations were fitted to the data. CUCL was related to 24h-UCE (ug) through a modelled median serum NCC (ug/L).
Results: The final population PK-PD model described a baseline CUCL (BL), extended by a TETA-induced CUCL. Serum NCC was expressed as a balance between copper influx and copper efflux and was the driver of BL. To account for the observed relationship between serum NCC and the effect of TETA on CUCL (quantified by the slope; SL), a multiplicative model was incorporated, in which CUCL was affected by TETA in a multiplicative fashion (i.e. CUCL = BL*(1+SL*TETA)). Inter-individual variability (IIV) was included on all parameters of the model (BL, SL, and serum NCC). Covariate analysis revealed a positive relationship between baseline alanine transferase (ALT) and serum copper influx (Kin) as well as a positive relationship between body weight and SL. The model described both the 24h-UCE and serum NCC data well, as demonstrated by several numerical and graphical assessments. All parameters of the model were estimated with good precision.
Conclusion: The final population PK-PD model described the relationship between TETA and 24h-UCE well and indicated potential effects of baseline ALT and weight on urinary excretion parameters. The model may form the basis of a response-guided dosing for TETA-2HCl in WD.

SAT-389
Comparison of three methodologies to measure bioavailable copper in patients with Wilson disease

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Background and aims: Wilson disease (WD) is an inherited disease leading to dysfunction of ATP7B protein responsible for the biliary excretion of excess hepatocellular copper (Cu) and bioincorporation of 6 Cu atoms into each ceruloplasmin (Cp) molecule. In unaffected individuals, Cp bound Cu (CpCu) accounts for 90–95% of total circulating Cu, and only the remaining 5–10% is bioavailable. This bioavailable fraction is elevated in untreated WD and lowering its value is a treatment goal. Estimating bioavailable Cu by the standard formula NCC-Cal (mcrg/L) = Total Cu (mcrg/L) - 3.15 * Cp (mg/L) has recognized limitations. Newer methods that do not require Cp measurement include exchangeable Cu (NCC-Ex), based on chelation of bioavailable Cu with EDTA followed by ultrafiltration, and chromatographic protein speciation followed by measurement of Cu in the Cp peak (NCC-Sp). We compared these methodologies in WD patients on chelation therapy included in a clinical trial.
Method: This is a post-hoc analysis of data from the Chelate Study (Lancet Gas-Hep 2022;7: 1092). We examined measurements of Total Cu (by ICP-MS), Cp (enzymatic method), NCC-Ex (Anal Bioanal Chem 2009;394:1477), and NCC-Sp (Anal Bioanal Chem 2021;414:13) in serum samples from WD patients stable on penicillamine (DPA) during a 12 weeks run-in screening period (N = 77) and during further 48 weeks after randomization (N = 53) to either continued DPA dose or same dose of trientine tetrahydrochloride (TETA4).
Results: Measurement of Cp was available in 344 samples from 76 patients. In 127 (37%, 100 received DPA at time of measurement, and 27 TETA4) with Cp above the LLOQ for the assay (52 mg/L). Total Cu was available in 118 (92 DPA/27 TETA4) for calculation of NCC-Cal, and these values were compared with NCC-Sp (n = 118; 92 DPA/27 TETA4) and NCC-Ex (n = 108; 85 DPA, 20 TETA4). While the NCC-Ex/NCC-Sp ratio was 1.10 ± 0.44 (Mean ± SD), the NCC-Cal/NCC-Sp ratio was 2.36 ± 1.42 (mean ± SD), and the NCC-Cal/NCC-Ex ratio 2.32 ± 1.24. As evaluated by linear regression NCC-Cal mcrg/L = (1.26*NCC-Sp+62) mcrg/L, R^2 0.17, $p < 10^{-5}$, and NCC-Cal (mcrg/L) = (NCC-Ex*2.12+14) mcrg/L, $R^2 = 0.26$, $p < 10^{-7}$). These relations were not affected by treatment at time of blood sampling. In 2/127 samples, NCC-Cal was negative.
Conclusion: While NCC-Ex and NCC-Sp differed slightly, NCC-Cal was 2.3–2.4 times higher, adding to the known concerns about inter-laboratory variation and negative values of NCC-Cal. Treatment targets in WD should be method specific and recalibration of appropriate treatment ranges is needed. NCC-Sp and NCC-Ex should replace NCC-cal as a study and clinical endpoint as direct estimations of bioavailable copper (NCC-Sp and NCC-Ex) are not subject to the limitations of Cp measurement. Further work is needed to determine the Cu/Cp ratio in WD to explore potential differences from unaffected patients.

SAT-390-YI

First-line therapy with Zinc salts for Wilson disease patients: descriptive analysis from the spanish AEEH Wilson registry

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Background and aims: Zinc salts (Zn) constitute a well-known treatment for Wilson disease (WD) by reducing copper intestinal uptake (Munk E, 2021). Current WD guidelines (EASL 2012, AALSD 2022) advocate for the use of chelators as first-line therapy, whereas Zn is mainly reserved for asymptomatic patients or maintenance treatment. There is limited experience with Zn as first-line therapy, with some studies suggesting suboptimal outcomes (Weiss, 2011). We aimed to describe the characteristics and clinical outcomes of WD patients treated with first-line monotherapy with Zn in Spain.
Method: Descriptive analysis of patients within the Wilson AEEH Registry (27 centers involved, >500 patients) receiving Zn monotherapy as first-line therapy in Spain. Clinical and analytical data were collected at diagnosis, as well as treatment changes and hepatic outcomes. Variables were expressed as median (IQR) and n (%). Statistical analysis was performed with SPSS.
Results: One-hundred and nine WD patients from the Registry (21%) received Zn (94% acetate, 6% sulfate) as first-line therapy in Spain (59% male, 68% index cases, 54% adults). Only 43 (39%) of them were classified as "asymptomatic" and had a theoretical indication for Zn. Among symptomatic patients (61%), 90% had hepatic involvement (11% acute, 89% chronic) with 2% presenting with cirrhosis. After 6 months of Zn, adverse effects were reported in 29 (27%) patients, primarily digestive discomfort (83%), elevated transaminases (14%), and skin-related issues (3%). In these patients, a switch to chelators was required in 16 (55%), dose adjustments in 6 (21%), and no modifications were made in the remaining cases. After a median follow-up of 10 (6–16) years, 73 (67%) patients remained on Zn, whereas 36 (33%) required alternative treatments (78% D-penicillamine, 20% trientine, 2% liver transplantation). The main reasons for changing Zn therapy were lack of response (59%), adverse events (36%) or protocol guidance (5%). Patients who remained on Zn monotherapy were more frequently asymptomatic at diagnosis (51% vs. 21%, p = 0.01), had lower baseline ALT levels (64 IU/L vs. 130 IU/L, p = 0.02), and tended to have lower elastographic baseline values (6.3 KPa vs. 9.3 KPa, p = 0.66) (n = 19). At the end of follow-up, no significant differences were observed in liver disease severity between patients on Zn vs. chelators, assessed by elastography or ALT levels, although 3 new cases of cirrhosis were collected on the Zn-monotherapy group.
Conclusion: In this multicentric Spanish cohort, 21% of WD patients from the Registry received Zn as first-line therapy, despite being 61% of them symptomatic. On the long-term, a significant proportion of patients required change to chelators due to adverse events or lack of response. Patients who remained on Zn had milder clinical

phenotypes. These findings should be interpreted with caution and further investigated.

SAT-391

Switching from zinc salts to Trientine Tetrahydrochloride in Wilson disease: the ZICUP study

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Background and aims: Wilson disease (WD) is a rare genetic disorder characterized by excessive copper accumulation, primarily affecting the liver and brain, leading to hepatic and/or neurological symptoms. Lifelong treatment aims to prevent copper accumulation and its associated complications. Zinc salts (ZS) are commonly used during the maintenance phase or for asymptomatic patients but are associated with significant gastrointestinal side effects, poor adherence, and reduced efficacy over time. Trientine tetrahydrochloride (TETA4HCL), a copper chelator, offers an alternative for patients who are intolerant to or fail ZS therapy. This study evaluates the clinical and biochemical outcomes of transitioning from ZS to TETA4HCL over a two-year period in patients with Wilson disease, including those with mixed hepatic and neurological symptoms.
Method: A prospective study based on the French WD Registry assessed patients transitioning from ZS to TETA4HCL since 2019. Clinical Global Impression (CGI), treatment adherence, biochemical parameters, Unified Wilson's Disease Rating Scale (UWDRS), adverse events, and dose adjustments were analyzed. A subgroup analysis focused on patients with neurological symptoms.
Results: Twenty patients (14 with hepatic forms and 6 with mixed hepato-neurological forms) were included. The main reasons for transitioning to TETA4HCL were gastrointestinal intolerance (13 patients), loss of efficacy (6 patients), and practical considerations (1 patient). At baseline, 65% of patients presented elevated transaminases. After two years of TETA4HCL treatment, patients remained clinically stable, and adherence to therapy improved. To achieve normal transaminases and exchangeable copper levels, a 39% increase in the initial daily dose of TETA4HCL was necessary. Despite this adjustment, 45% of patients still showed slightly elevated ALT levels. A minimum daily dose of 675 mg TETA4HCL appears necessary. Among the neurological subgroup, UWDRS scores improved in four out of six patients, although brain MRI findings remained unchanged.
Conclusion: Transitioning from ZS to TETA4HCL maintains clinical stability in WD patients, improves adherence, and demonstrates a favorable safety profile. Optimizing dosing remains challenging, as a subset of patients failed to achieve complete biochemical normalization, suggesting potential underdosing. Further studies are needed to confirm optimal posology. These findings support TETA4HCL as a viable therapeutic alternative for patients intolerant to or failing ZS therapy, including those with neurological involvement, emphasizing the importance of ongoing monitoring and individualized dose optimization - Funding: Orphalan Pharma.

SAT-392

Profiling patients with Wilson's disease using a behavioral diagnostic tool (Observia SPUR™): insights into adherence challenges and personalized care strategies

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Background and aims: Adherence to therapy is critical in managing chronic disease. Non-adherence in Wilson's disease (WD) may lead to clinical deterioration, including fatal outcomes. SPUR™ [1] is a behavioural diagnostic tool that assesses the non-adherence risk in patients with chronic illnesses, and the behavioural drivers underlying this risk (Social, Psychological, Usage of treatment, and Rational). Identifying the drivers enables better interactions between patients and healthcare professionals, tailoring communication to the patient's needs. We aimed to evaluate the utility of SPUR™' in WD patients and identify behavioural profiles predictive of non-adherence in WD patients.
Method: In four hepatology clinics in French WD reference centres, patients completed SPUR™ multiple choice questionnaire using digital tablet before consultations, identifying behavioural drivers and generates a non-adherence risk (NAR) score (0–100 increasing from low to high) representing an average of the scores for the 13 behavioural drivers, and the overall dimensions of S,P,U,R. Physicians received results prior to the consultation and tailored communication based on patient response. Feedback from physicians and patients was collected on SPUR™'s utility.
Results: Data from 100 patients, 100% fully completed, were analysed (18: asymptomatic, 55: hepatic symptoms 6: neurological symptoms, 21: mixed phenotype). Treatment regimens included D-penicillamine (49), trientine salts (27 patients on TETA4HCL; 11 on TETA2HCL) and zinc salts (13). 77% of patients reported taking 2–3 doses daily, 42% admitted forgetting treatment at least twice, and 13% missed more than five doses in the past three months. The WD population had a median (range) NAR score of 15,8 [0–86] with high disparities. This is comparable to HIV population. Key risks were societal challenges (societal social drivers: 45%; immediate social drivers: 24%), highlighting isolation risks. Financial burdens (27%) also emerged despite healthcare reimbursement. Psychological and rational adherence drivers were minimal. Despite reported partial adherence in 42% of cases, healthcare professionals did not modify their approach in 68%. SPUR™ was deemed useful in 80%, aiding patient understanding, saving consultation time, and addressing identified social/ financial challenges.
Conclusion: In this cohort, 42% of patients missed at least two doses in three months, with adherence risks linked to societal and financial factors. SPUR™ provided valuable insights, particularly for new patients. Non-adherence is multifactorial; digital tools may improve identification leading to targeted interventions. https://observia-group.com/en/what-is-spur.

SAT-397-YI

Long-term clinical outcomes, efficacy, and safety of transjugular intrahepatic portosystemic shunt in Budd Chiari syndrome

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Background and aims: Budd-Chiari syndrome (BCS) is characterized by obstruction of hepatic venous outflow tract at any level between intrahepatic veins and right atrium due to thrombosis or primary disease of the venous wall. Transjugular intrahepatic portosystemic shunt (TIPSS) plays crucial therapeutic role in decompressing the congested liver in BCS. In this study, we aimed to assess the long-term outcomes and complications of TIPSS, and identify mortality and hepatic encephalopathy (HE) predictors in patients with BCS.
Method: In this single-centre retrospective analysis, we included BCS patients who underwent TIPSS between July 2011 and June 2024 at a tertiary care center in India. Clinical Response (CR) was defined using a modified version of EASL Clinical Practice Guidelines as absence of clinically detectable ascites in absence of diuretic therapy, or on low-dose diuretics (spironolactone 75 mg/d or furosemide 40 mg/d) and absence of first or recurrent portal hypertension related bleeding while on primary or secondary prophylaxis with non-selective beta blockers or with endoscopic therapy at 3 months. The outcomes assessed included rates of clinical response, ascites resolution, further decompensation, and complications of TIPSS such as hepatic encephalopathy and restenosis. Cox regression analysis was used to identify predictors of mortality and HE.
Results: Of 201 BCS-TIPSS patients, 184 were included, with a median follow-up duration of 4.3 (2.0–6.7) years. Among the 99 patients who underwent a hypercoagulable workup, 22 (22.2%) were found to have positive hypercoagulable conditions. Clinical response was observed in 147 (79.8%) patients. Complete and partial resolution of ascites was seen in 126 (78.2%) and 14 (8.6%) patients, respectively. Overt HE occurred in 30 (16.3%) patients, with a 1-, 5- and 10-year probability of 7.7%, 15.3%, and 22.1% respectively. Further decompensation occurred in 38 (20.6%) patients with a 1-, 5- and 10-year probability of 8.2%,17.0%, and 35.0% respectively. TIPSS restenosis occurred in 51 (27.7%) patients, with 1-, 5- and 10 year probability of 6.0%, 33.2%, and 41.9% respectively. During follow-up, 31 (16.8%) patients died with transplant-free survival probability at 1, 5 and 10 years of 93.9%, 81.7%, and 74.6% respectively. On multivariate analysis, non-response and diabetes mellitus at baseline were significant predictors of post-TIPSS HE. Non-response and post-TIPSS HE were significant predictors of mortality. A total of 15 (8.1%) patients experienced 17 immediate post-TIPSS complications. Bleeding complications related to anticoagulation occurred in 20 (10.8%) patients, with 28 bleeding episodes recorded, epistaxis being the most common complication (10 patients).
Conclusion: TIPSS is an effective, long-term therapy for BCS that leads to significant improvements in survival, ascites resolution, and bleeding prevention. Non-response to TIPSS and post-TIPSS hepatic encephalopathy are associated with increased mortality.

SAT-398

Prevalence and risk factors of liver function test abnormalities in celiac disease patients: Insights from the Kashmir, Pakistan

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Background and aims: Celiac disease, an autoimmune condition triggered by gluten, primarily affects the small intestine but can also involve other organ systems, including the liver. Liver function test (LFT) abnormalities are commonly observed in celiac disease, often reflecting liver involvement or complications. This study investigates the prevalence and types of LFT abnormalities in patients with celiac disease in the Kashmiri population of Mirpur, AJK.
Method: A cross-sectional study was conducted at Divisional Headquarters Teaching Hospital, Mirpur, AJK, between January and September 2024. The study included patients diagnosed with celiac disease based on serological tests (positive tissue transglutaminase antibodies) and intestinal biopsy (villous atrophy). LFT parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels, were measured. Patients were categorized according to the severity of LFT abnormalities, and various demographic, clinical, and nutritional factors were analyzed. Logistic regression was used to determine risk factors associated with abnormal LFTs.
Results: A total of 180 celiac patients (62% females, mean age: 31 ± 12 years) were included in the study. Among them, 30% exhibited abnormal LFTs, with the most common derangements being elevated ALT (22%), AST (18%), and ALP (15%). Factors significantly associated with LFT abnormalities included severe malnutrition (odds ratio [OR] = 3.2, $p = 0.02$), delayed diagnosis (OR = 2.8, $p = 0.03$), and coexisting autoimmune thyroid disease (OR = 2.5, $p = 0.04$). There was no significant difference in LFT abnormalities between rural and urban residents ($p = 0.09$).
Conclusion: Liver function test abnormalities are prevalent in patients with celiac disease in the Kashmiri population, with the most common derangements being elevated ALT and AST. Severe malnutrition, delayed diagnosis, and coexisting autoimmune thyroid disease are key risk factors. Routine monitoring of LFTs in celiac patients is essential for early detection of hepatic involvement and to prevent further complications. Future studies should explore the underlying mechanisms of liver dysfunction in celiac disease.

SAT-399-YI

Detection of rare mutations of Wilson's disease during family screening

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Background and aims: Wilson's disease (WD), a rare hereditary disorder with autosomal recessive transmission, necessitates clinical examination of family members (siblings, descendants, parents) of newly diagnosed patients. This is due to the potential for asymptomatic progression or a nonspecific clinical presentation in the early stages. Therefore, our objective was to screen the proband's family to facilitate timely diagnosis and enable early initiation of specific therapy.
Method: A retrospective and prospective study was conducted between 2015 and 2023, involving 13 Moldavian families that were clinically and genetically evaluated. The diagnosis was confirmed using the modified Leipzig score (2019). DNA sequencing by the Sanger method involved the use of the Taq DyeDeoxy Terminator Cycle sequencing kit (Applied Biosystems) with an ABI-Prism 3100 genetic analyzer (Applied Biosystems).
Results: In 6 out of 13 families, 8 new members with WD were identified (6 males and 2 females). The mean age at diagnosis was 16.25 ± 9.7 years (range 5–34 years). All patients were Caucasian, and originally from Moldova. No patient reported consanguineous relationships. The most common variants were p.H1069Q and p.G1341D, both as homozygous recessive and compound heterozygous. A rare mutation p.Phe764 = was also detected. In 5 cases there were first-degree relatives (siblings), and in 3 cases - second-degree relatives (cousins, nephews). 7 patients were asymptomatic, and 1

had neurological symptoms of unknown cause until that time. A family with the paradoxical transmission of pseudo-dominant inheritance was noted, and simultaneously a rare silent/synonymous mutation (p.Phe764 =) was identified in association with pathogenic missense and frameshift variants, in 3 of the 4 members affected by WD. In 4 families, although the parents are healthy carriers, both children developed WD, one member being diagnosed during family screening. In the case of the 6th family, the affected members were cousins. After clinical and paraclinical examination of the new members, in 6 cases the hepatic phenotype was determined, and in the other 2, a mixed phenotype was reported. All patients initiated chelator therapy.

Conclusion: Our study highlights the vital role of family screening in family members, genetic testing is a defining tool, especially in suspects with insignificant biological changes and uncertain clinical signs. Thus, the identification of the family with pseudo-dominant inheritance, the presence of WD in 100% of children in simple heterozygous partners, and the detection of rare mutations highlights the peculiarities of WD evolution in our cohort and the impact of genetic counseling in probands with this disease.

SAT-400

Estimating the diagnosis rate of alpha-1 antitrypsin deficiency: insights from population-based cohorts in the USA

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder that can lead to liver and/or lung disease and is often underdiagnosed. A single protease inhibitor (Pi)*Z variant increases the risk for liver and/or lung disease; the (Pi)*ZZ genotype is associated with the most severe disease manifestations. Robust evidence on the frequency of diagnosis (Dx) in individuals with AATD genotypes is lacking. This study leverages genetic information from large electronic medical record (EMR)-linked biobanks in the USA to quantify the rate of AATD Dx and to characterize individuals with AATD genotypes by AATD Dx status.

Method: A retrospective cohort of individuals with any AATD genotype (Pi*ZZ/MZ/SZ/SS/MS) was identified using genetic data from All of US (AOU; nationwide volunteer-based recruitment) and BioVU (consented care recipients at Vanderbilt University Medical Center). Demographic/clinical characteristics were extracted from linked EMRs (2018–2022). The proportion of individuals with ≥1 ICD-9/-10-CM Dx code for AATD in their EMR was reported overall and by AATD genotype. Standardized mean difference (SMD) was used to compare clinical features between individuals with an AATD genotype with and without an AATD Dx code in their EMR (SMD > 0.1 is considered a notable difference).

Results: From AOU and BioVU respectively, a total of 139/25,774 (0.5%) and 133/8988 (1.5%) individuals had ≥1 AATD Dx code in their EMR; 121/17,932 (0.7%) and 125/8300 (1.5%) were White, and 35/68 (51.5%) and 57/83 (68.7%) had a Pi*ZZ genotype. In AOU and BioVU respectively, for all individuals with and without an AATD Dx code in their EMR, the mean (standard deviation [SD]) age was 55.4 (17.1) and 58.9 (22.2) years, and 59.4% and 55.6% were female. Comorbidities were more frequently observed in those with an AATD Dx code than without: liver disease (AOU: 41.0% vs 9.6%, SMD 0.775; BioVU: 26.3% vs 4.2%, SMD 0.647), lung disease (AOU: 47.5% vs 7.6%, SMD 0.999; BioVU: 12.8% vs 3.1%, SMD 0.366), diabetes (AOU: 23.7% vs 12.2%, SMD 0.304; BioVU: 20.3% vs 6.4%, SMD 0.417), obesity (AOU: 30.2% vs 15.6%, SMD 0.354; BioVU: 17.3% vs 4.0%, SMD 0.443). More individuals with an AATD Dx code than without had an aspartate aminotransferase to platelet ratio (APRI) >0.5.

Conclusion: In this study, <2.0% of individuals with AATD genotypes had an AATD Dx code in their EMR. Those with a Dx had a higher prevalence of liver/lung disease and other comorbidities than those without a Dx in their EMR. Among those with a Pi*ZZ genotype, AATD Dx rate ranged from ~50–70%, which may be attributed to greater symptom manifestations associated with this genotype. These findings provide quantitative evidence to improve the current understanding of AATD underdiagnosis, highlighting that many individuals may remain undiagnosed. Study/writing funding: Takeda Development Center Americas, Inc.

SAT-401

Liver disease progression in patients with alpha-1 antitrypsin deficiency and a Pi*ZZ genotype: a retrospective natural history study

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Background and aims: Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder that manifests as liver and/or lung disease. The protease inhibitor (Pi)*ZZ genotype confers the greatest risk of AATD-associated liver disease. To systematically evaluate liver disease progression among patients (pts) with AATD and the Pi*ZZ genotype across pt registries, an umbrella protocol design was established. This study is the first to report data from these registries.

Method: Adults with a recorded diagnosis of AATD and a Pi*ZZ genotype confirmed by genetic testing were enrolled in the alpha-1 liver fibrosis/natural history study at the University of Florida (Nov 2013–Sep 2019). The date of enrolment was the index date. The baseline period was from initial contact to index date. The baseline liver fibrosis staging assessment period was from the index date to Day 90 post-index. The follow-up period for the assessment of liver disease progression (liver fibrosis advancement from baseline) was from Day 91 until the first occurrence of loss to follow-up, completion of the study, or death. A hierarchical approach was utilized to define fibrosis stage: if available, fibrosis stage was assessed by biopsy (baseline and Year 3); if unavailable, secondary fibrosis measures were utilized (elastography, aspartate aminotransferase to platelet ratio index [APRI], Fibrosis-4; annually). For each pt, matched fibrosis staging required the same staging method to have been used at both baseline and follow-up. Statistical analyses included descriptive statistics.

Results: Overall, 98 pts were included in the liver progression analysis. Baseline matched fibrosis staging (F0/1, n = 61; F2, n = 28; F3, n = 8; F4, n = 1) was based on liver biopsy (n = 49) or secondary measures (n = 49). Median pt age was 56 years, all were White, 62% were female and 28% were categorized as obese. At baseline, 6% pts self-reported comorbid metabolic dysfunction-associated steatohepatitis/metabolic dysfunction-associated steatotic liver disease, 79% self-reported chronic obstructive pulmonary disease/emphysema and 73% received concomitant alpha-1 antitrypsin augmentation therapy. Using a matched fibrosis staging method, 23 (23%) pts experienced liver disease progression by Month 42, by baseline fibrosis stage: F0/F1, 12 (20%); F2, 7 (25%); F3, 4 (50%). Of the 23 pts with liver disease progression, 13 were based on liver biopsy and 10

were from a secondary measure (n = 9 elastography, n = 1 APRI). When unmatched fibrosis staging was considered, 36 (37%) pts had liver disease progression by Month 42, by baseline fibrosis stage: F0/F1, 23/64 (36%); F2, 9/26 (35%); F3, 4/8 (50%).
Conclusion: Among pts with AATD and a Pi*ZZ genotype, almost one in four experienced liver disease progression by 3.5 years based on matched fibrosis staging methods. Pts with more advanced fibrosis may have a higher proportion of liver disease progression.
Study/writing funding: Takeda Development Center Americas, Inc.

SAT-402
Combination of pharmacological and surgical interruption of the enterohepatic circulation can treat cholestasis and pruritus in patients with progressive familial intrahepatic cholestasis types 1 and 2 who proved unresponsive to either treatment alone
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Background and aims: Patients with progressive familial intrahepatic cholestasis (PFIC) commonly suffer from pruritus and elevated serum bile acid levels. In FIC1 deficiency (PFIC1) and bile salt export pump (BSEP) deficiency (PFIC2), cholestasis can be alleviated in approximately 40% of patients by either partial external biliary diversion (PEBD) or intestinal bile acid transporter inhibitors (IBATi). While surgical and pharmacological diversion both interrupt the enterohepatic circulation of bile acids, it is unknown if combining both therapies improves therapeutic efficacy. We recently demonstrated that IBATi in PFIC2 patients increase the intestinal reabsorption of unconjugated bile acids (Gastroenterology 2023; 165:496–98). We therefore hypothesized that PEBD could provide additional therapeutic benefit over treatment with IBATi alone.
Method: We combined IBATi and PEBD in three PFIC patients (ages 3–14) with persistently elevated bile acids and pruritus after long-term treatment with either IBATi (N = 2) or PEBD (N = 1) alone.
Results: Patient A (PFIC1) received IBATi for more than two years without improvement of bile acids or pruritus. Within days of his PEBD (while continuing IBATi), he became free of itch with normal bile acid levels for a total follow-up of six months. Patient B (PFIC1) had been symptom-free for over a decade after PEBD but was evaluated for liver transplant when cholestasis and invalidating pruritus had recurred for two years. Within three months after addition of IBATi, his bile acid levels were normal and he was itch free. Patient C (PFIC2) received IBATi for more than three years with no discernable effect on cholestasis or pruritus. PEBD in combination with IBATi has changed the disease phenotype to an episodic course, characterized by prolonged periods (8–10 months) of complete symptom resolution interspersed with periods of cholestasis likely triggered by viral infections.
Conclusion: We show proof of principle that the combination of pharmacological *and* surgical interruption of the enterohepatic circulation can effectively treat cholestasis and pruritus in patients with FIC1 or BSEP deficiency who were found to be unresponsive to either therapy alone. We believe that combination therapy should be considered before committing these patients to liver transplantation.

SAT-403
Rare variants in ABCB4 in intrahepatic cholestasis of pregnancy in the national genomic research library
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Background and aims: Genetic susceptibility makes a significant contribution to the aetiology of intrahepatic cholestasis of pregnancy (ICP). We quantified the contribution of rare genetic variants of ATP-Binding Cassette Subfamily B Member 4 (ABCB4) to the heritability of ICP.
Method: We extracted coding single-nucleotide variants and indels with minor allele frequency <0.1% from the Genomics England library, annotated with one of the following: missense, in-frame insertion, in-frame deletion, start loss, stop gain, frameshift, splice donor, splice acceptor. They were filtered using a combined annotation-dependent depletion (CADD) threshold score ≥20. The scalable and accurate implementation of generalized mixed model (SAIGE-GENE) was employed to ascertain whether rare coding variation was enriched in cases on a per-gene basis exome-wide. Odds ratio and heritability were estimated.
Results: 249 women with ICP and 3,128 non-ICP controls were identified. Rare variants were observed in 4% (10/249) of the ICP cases and 0.4% (14/3128) of the controls. There was a statistically significant enrichment of rare and predicted damaging *ABCB4* variants in the ICP group ($p = 9.1 \times 10^{-7}$). Women carrying a rare and predicted damaging *ABCB4* variant had an 8.25-fold increased risk of developing ICP (95%CI 3.23–20.5, $p = 6.3 \times 10^{-6}$). Collapsing rare *ABCB4* variants account for 2.5% of the total heritability of ICP.
Conclusion: The rare *ABCB4* variants are significantly enriched in women with ICP, explaining 2.5% of the heritability of the condition. These findings highlight and quantify the contribution of these rare genetic variants to the pathogenesis of ICP. This research was made possible through access to data and findings in the National Genomic Research Library via the Genomics England Research Environment.

SAT-404
Accuracy of non-invasive tools in excluding advanced fibrosis in Wilson disease: results from the Wilson disease registry and Barcelona cohorts
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Background and aims: Fibrosis is a critical prognostic factor for chronic liver disease with liver biopsy (LB) as the gold standard for staging. Noninvasive tools (NIT) for fibrosis evaluation include serum scores (APRI, FIB-4) and elastography (TE), validated in many liver diseases but with limited use in Wilson disease (WD) (*Paternostro, 2020; Schilsky, 2023*). A recent score (Steatosis-Associated Fibrosis Estimator, SAFE; *Sripongpun, Hepatol 2023*) based on laboratory testing (AST, ALT, platelets, globulins) and clinical data (diabetes, age, BMI) accurately identified patients at risk of fibrosis progression in Metabolic-Associated Liver Disease. Its use in WD is justified as hepatic steatosis is among the earliest reported histological changes. We hypothesized that SAFE score should outperform APRI and FIB-4 for fibrosis staging in WD. Data from the Wilson Disease Registry (WDR) and Barcelona WD (BWD) cohort was reviewed.
Method: Cross-sectional assessment of WD patients from WDR and BWD with available LB and fibrosis staging (METAVIR). Serum NIT (FIB-4, APRI, SAFE) were calculated at first WDR visit or time closest to

LB for BWD; TE data were collected (n = 38). Patients were grouped according to time from LB to NIT: ≤12 months (≤12 mo), between 1 - 5 years (1–5 y) and >5 years (>5 y). The accuracy of NIT for advanced fibrosis detection [F≥3] was calculated as AUC for continuous NIT and according to previously validated cutoffs (APRI ≥1.5, FIB-4 ≥3.25, SAFE ≥100, TE ≥9.9 Kpa). Data was expressed as median (IQR)/ n (%).
Results: Patients (n = 121, 54.5% female) were median age 32 y and time from diagnosis of 7 y. Group distribution ≤12 mo; 1–5 y; >5 y was 48; 29; 44 patients, respectively. LB staged F ≥3 in 47 (39%) patients [29%; 31%; 54% in ≤12 mo; 1–5 y; >5 y groups, respectively]. Serum NIT (SAFE, APRI and FIB-4) were all significantly higher for F≥3 vs F0–2 patients ($p < 0.001$) in the whole cohort. Only SAFE and APRI were significantly higher in F ≥3 patients ≤12 mo and 1–5 y ($p < 0.05$) groups. Differences were lost for all NIT when LB was >5 y away. TE was non-significantly higher in F≥3 vs F0–2 for the whole cohort and ≤12 mo group ($p > 0.05$). AUC for F ≥3 prediction for SAFE, APRI, FIB-4 and TE were 0.72, 0.69, 0.68 and 0.66 for the whole cohort, and 0.72, 0.68, 0.64 and 0.81 for ≤12 mo group. Validated cutoffs yielded negative predictive values (NPV) for excluding F≥3 of 97% (SAFE and APRI), 100% (FIB-4) and 86% (TE).
Conclusion: Serum NIT were higher in WD patients with advanced fibrosis, with SAFE and TE performing slightly better than APRI and FIB4. All NIT evaluated provided useful information with high NPV for advanced fibrosis. Effective WD treatment likely accounted for the lower correlation between serum NIT and LB performed >5 y. Further validation is required to establish WD specific cutoffs for NIT and determine their utility in longitudinal evaluation and prognostication.

Viral Hepatitis – Experimental and pathophysiology

TOP-297
STING activation suppresses viral replication but promotes liver inflammation and fibrosis in chronic hepatitis B concurrent with metabolic dysfunction-associated steatotic liver disease

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Background and aims: Concomitant Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is common in patients with Chronic hepatitis B (CHB), but the implications on liver-related outcomes remain controversial. Stimulator of Interferon Genes (STING) plays a central role in innate immune activation. Here, we aim to investigate the role of STING in disease progression in CHB patients concurrent with MASLD.
Method: HBV transgenic mice and pAAV/HBV1.2 hydrodynamic injection mice fed with a high-fat diet (HFD) were both used to establish mouse models of CHB concurrent with MASLD. STING knockout, *Tmem173*$^{-/-}$ (*Sting*$^{-/-}$) and macrophage STING deficiency, *Tmem173*$^{f/f}$*Lyz2*$^{Cre+}$ (*Sting*$^{f/f}$*Lyz2*$^{Cre+}$) and liver-specific STING knock-in, *Alb*$^{cre+}$ *Sting-IRSE-EGFP*$^{ki/ki}$ (*Sting*$^{ki/ki}$*Alb*$^{cre+}$) mice and their controls were used in this study. THP1 and HepG2/HepG2.2.15 co-cultured cells were stimulated with palmitic acid (PA) or its control for 12 hours *in vitro*. Markers for STING, autophagy, and endoplasmic reticulum stress were assessed using Western blotting, immunohistochemistry, and immunofluorescence assays. The liver tissues obtained from patients were used for clinical validation.
Results: Compared with CHB or MASLD mice, the concurrent presence of CHB and MASLD in mice resulted in a significantly accelerated progression of liver inflammation and fibrosis, despite a decrease in HBV DNA levels observed within this group. Concomitant with disease progression, CHB mice concurrent with MASLD exhibited impaired autophagic flux and the upregulation of macrophage STING. The STING activation impaired the function of RAB7, thereby preventing STING from entering lysosomes for degradation. Damaged degradation of STING leads to its secretion via vesicles, which are subsequently captured by hepatocytes, triggering endoplasmic reticulum stress and exacerbating the progression of liver disease. Macrophage STING deficiency restored RAB7 function, enhanced autophagic flux, and consequently mitigated liver inflammation and fibrosis. The expression of STING, RAB7, and autophagy-related proteins was confirmed in liver tissue samples derived from patients.
Conclusion: The significant upregulation of macrophage STING expression in CHB concurrent with MASLD disease can inhibit HBV virus replication and exacerbate liver inflammation by activating antiviral and pro-inflammatory signals. Meanwhile, it impairs RAB7 function, impeding STING degradation and promoting its release through vesicles, which are then captured by liver cells and further exacerbate disease progression.

TOP-298-YI
Long non-coding RNA SNHG4 is regulated by hepatitis B virus and promotes hepatocarcinogenesis

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Background and aims: Hepatitis B virus (HBV) contributes to hepatocellular carcinoma (HCC), accounting for nearly 50% of cases; however, the underlying mechanisms remain largely unknown. Long non-coding RNAs (lncRNAs) are increasingly recognized for their roles in cancer and potential as biomarkers. Here, we investigated the role of HBV in regulating human lncRNAs in HCC progression.
Method: To identify HBV-regulated lncRNAs that promote HCC, we performed a comprehensive analysis of microarray datasets of liver samples from patients who were either HBV-infected or had HCC and focused on differential expression profiles. GEPIA2 was used for the interactive exploration of RNA sequencing data of tumors and normal samples from The Cancer Genome Atlas and the Genotype-Tissue Expression programs, examining prognostic values of HBV-mediated lncRNA and evaluating overall survival using the Kaplan-Meier method. *In vitro* studies employed HBV cell culture models to examine the expression of SNHG4 by HBV and its proteins using qPCR. To assess the correlation between SNHG4 expression and HBV load, qPCR was performed on liver biopsy specimens (n = 14) from HBV-infected patients. Functional studies were carried out using SNHG4 overexpression and CRISPR interference (CRISPRi)-mediated knockdown approaches. The impact of SNHG4 manipulation on cell proliferation, migration, and apoptosis was evaluated using cell-based assays.
Results: Our analysis of microarray datasets in liver samples from patients with HBV infection identified SNHG4 as an HBV-regulated lncRNA. SNHG4 is notably upregulated in liver samples from HBV-infected patients and in HCC, specifically in HBV-related HCC. Kaplan-Meier analysis revealed that higher expression of SNHG4 correlates with reduced overall survival. These findings were validated *in vitro*, showing that HBV and HBV proteins positively regulate SNHG4 in HBV cell culture models. SNHG4 shows a ~2-fold change with overexpression of HBV proteins, namely HBx and HBsAg. Furthermore, qPCR analysis reveals a significant correlation between SNHG4 expression levels and HBV load in liver biopsy specimens (n = 14) of patients infected with HBV. Next, we evaluated the oncogenic potential of SNHG4 by its overexpression and CRISPRi-based knockdown in various cell-based assays. SNHG4

overexpression in the presence of HBV promoted cell proliferation and migration while inhibiting apoptosis. SNHG4 knockdown in the presence of HBV using dCas9-KRAB-mCherry stable HepG2 cell line inhibits cell proliferation and induces apoptosis, suggesting its oncogenic potential.
Conclusion: In this work, we identify SNHG4, a clinically relevant HBV-regulated lncRNA in HCC, as a driver of hepatocarcinogenesis, thus offering novel insights into HBV-mediated HCC progression and novel avenues to target HBV-related HCC.

TOP-299
HDV infection induces cellular refractoriness to IFN-α, but not IFN-λ treatment
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Background and aims: Chronic hepatitis D, caused by the co-infection of hepatocytes with hepatitis B and D viruses (HBV, HDV), is the most aggressive form of chronic viral hepatitis. To date, no treatment achieves viral clearance in infected patients. Current therapies available in Europe include the entry inhibitor bulevirtide and pegylated interferon-alpha (peg-IFN-α). However, the efficacy of peg-IFN-α is limited, and HDV replication is only moderately impacted by exogenous IFN-α treatment both in vivo and in vitro. Previous studies suggested an inhibition of IFN-α signaling pathway in HDV-infected cells but the molecular mechanism in unclear. Furthermore, the response of HDV-infected cells to IFN-λ has not yet been explored. This study investigates the response to both IFN-α and IFN-λ treatment in HDV-infected cells to better understand the interactions between HDV infection and innate immune pathways and responses.
Method: RNA sequencing was performed to analyze transcriptomic modulations in HDV-infected differentiated HepaRG (dHepaRG) cells stimulated with IFN-α or IFN-λ1. Key findings were validated in vitro and compared across HDV infection cellular models, which exhibit varying IFN responses to HDV infection. Mechanistic studies, including gain- and loss-of-function assays, elucidated the role of host proteins in the HDV-mediated inhibition of IFN responses.
Results: HDV-infected cells displayed a reduced ISG response to IFN-α, indicating cellular refractoriness to IFN-α treatment. Using cellular models impaired for innate immune response and HDV antigen expression, we demonstrated that the refractoriness to IFN-α was due to MDA5-mediated pre-activation of the innate immune response induced by HDV replication rather than active inhibition of IFN signaling by HDV antigens. In contrast, we observed additive ISG induction in HDV-infected cells treated with the type III interferon IFN-λ1, suggesting a specific inhibition of the IFN-α signaling pathway. Notably, knocking down the expression of USP18, known to selectively impair IFN-α signaling, rescued IFN-α-mediated ISG induction in HDV-infected cells.
Conclusion: Our findings provide a comprehensive list of ISGs modulated by type I and type III IFN treatments in the context of HDV infection. We demonstrated that the cellular refractoriness to IFN-α treatment in HDV-infected cells results from the pre-activation of the innate immune response by HDV and is specific to the type I IFN pathway. In this context, USP18 acts as a negative regulator of the IFN-α response and is a key factor in HDV resistance to IFN-α treatment. Interestingly, the antiviral potential of IFN-λ remains unaffected by HDV infection. In conclusion, this study provides new insights into the mechanisms underlying the limited efficacy of peg-IFN-α in patients and paves the way to the development of improved antiviral strategies against HDV infection.

FRIDAY 09 MAY

FRI-227
Screening of different species reveals cat as a potential HBV infection model
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Background and aims: Hepatitis B virus (HBV) research is hindered by its highly restricted species tropism and the lack of suitable animal models. This study aims to investigate the susceptibility of hepatocytes from various species to HBV infection and to establish novel HBV infection models for basic and translational research.
Method: Freshly isolated or cryopreserved primary hepatocytes from monkey, pig, cat, goat, bull, dog, rabbit, guinea pig, and hamster were tested for HBV susceptibility. The repair of covalently closed circular DNA (cccDNA) from synthetic relaxed circular DNA (rcDNA) was assessed by transfection. Hepatocytes were subjected to ectopic expression of the viral receptor human sodium taurocholate cotransporting polypeptide (hNTCP), followed by HBV infection. Viral replication was evaluated through the production of viral antigens, and inhibition by Myrcludex B was tested. Primary cat hepatocytes were directly infected with HBV, and their ability to support HBV replication was assessed via time-dependent secretion of HBsAg and HBeAg, as well as cccDNA formation and transcription of HBV RNAs using Southern and Northern blotting. Antiviral drug testing included Myrcludex B, Entecavir, and poly IC. Additionally, cats with or without immunosuppressive treatment were infected with HBV to evaluate the feasibility of cats as an animal model.
Results: All tested hepatocyte types supported the repair process from rcDNA to cccDNA, as indicated by viral antigen production. Primary monkey, pig, and cat hepatocytes expressing hNTCP supported HBV replication, which was blocked by Myrcludex B. Direct HBV infection of primary cat hepatocytes resulted in time-dependent secretion of HBsAg and HBeAg. cccDNA formation and HBV RNA transcription were confirmed in cat hepatocytes. These cells were also responsive to antiviral treatments, indicating their suitability for evaluating anti-HBV drugs. While direct infection of immunosuppressed cats was unsuccessful, the ectopic expression of horse NTCP conferred susceptibility to HBV, as evidenced by increased HBsAg levels in the sera.
Conclusion: This study demonstrates for the first time that primary cat hepatocytes support HBV infection, providing a potential new platform for HBV basic and translational research. The use of cats as an animal model is being explored and may further advance HBV research and therapeutic development.

FRI-228
CD300A+CD8+T cells promote functional cure in patients with chronic hepatitis B under PEG-IFN-α
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Background and aims: $CD8^+$ T cells are crucial in viral control and pathogenesis in HBV infection. However, the critical immunological

characteristics of $CD8^+$ T cells in functional cure (FC) of chronic hepatitis B (CHB) under pegylated interferon alpha (PEG-IFN-α) remain unclear.
Method: Cross-sectional peripheral blood mononuclear cells (PBMCs) were collected from 8 CHB patients undergoing PEG-IFN-α therapy and with serum HBsAg levels <3000 IU/ml at baseline for 10X Genomics single-cell RNA sequencing (scRNA-seq). 3/8 achieved FC, and 5/8 did not after follow-up. FC was defined as sustained clearance of serum HBsAg and HBV DNA after a finite course of treatment. Through determining the transcriptional profiles of immune cells, coupled with assembled T cell receptor (TCR) sequences, we analyzed the functional properties of $CD8^+$ T cells. Relevant findings were validated by flow cytometry analysis in another longitudinal cohort, including 5 FC and 5 non-FC patients after 48 weeks of PEG-IFN-α therapy.
Results: The scRNA-seq data revealed that $CD300A^+$ $CD8^+$ T cells were enriched in FC patients and expressing higher levels of cytotoxic genes (GNLY, GZMB, and PRF-1), and genes enriched in cell migration, cytokine production, such as IL-2, TNF, and IFNγ. Moreover, the SCENIC analysis indicated that the activities of BATF and TBX21, which were associated with effector functions, predominated in $CD300A^+$ $CD8^+$ T cells. Analysis of paired scRNA and TCR sequencing data revealed that $CD300A^+$ $CD8^+$ T cells displayed more pronounced clonal expansion than $CD300A^-$ $CD8^+$ T cells and tended to exhibit high activity in TCR signaling. In addition, HBV-specific $CD8^+$ T cells predicted by GLIPH highly expressed CD300A. Flow cytometry analysis in the longitudinal cohort validated that $CD300A^+$ $CD8^+$ T cells with enhanced cytotoxic activities were enriched in FC patients before and undergoing PEG-IFN-α therapy. Remarkably, the frequency of $CD300A^+$ $CD8^+$ Tcm cells at baseline was negatively correlated with the time to achieve FC.
Conclusion: These findings suggest that $CD300A^+$ $CD8^+$ T cells may serve as new therapeutic targets and be associated with achieving higher rates of functional cure in patients with CHB.

FRI-229

Interferon-α induces robust neutralizing anti-HBs production by restoring the HBsAg-specific B cell immune response in nucleos(t)ide analogues experienced chronic hepatitis B patients

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Background and aims: Anti-HBs play an important role in HBsAg clearance and functional cure of chronic hepatitis B (CHB). In this study, we aimed to determine the biological function of anti-HBs appeared in CHB patients undergoing Pegylated-Interferon-a (Peg-IFN-a)-based treatment, and explore the underlying mechanisms by which IFN-a improves anti-HBs production by B cell.
Method: A total of 171 nucleos(t)ide analoges (NAs) experienced CHB patients undergoing a clinical trial (ANCHOR study, NCT02327416) were included and randomized to receive either Peg-IFN-a-based therapy (IFN group) or entacvir (ETV) therapy (ETV group) for 96 weeks. The neutralization activity (NAT) determined by blocking HBV infection in HepG2 cells expressing sodium taurocholate co-transporting polypeptide (NTCP) and Fc effector functions assessed by Fc γ RIIIa dimer binding assay, antibody dependent cell-mediated phagocytosis (ADCP) assay, and complement-mediated cytotoxicity (CDC) assay were performed on serum anti-HBs in CHB patients. In-vivo and ex-vivo regulation of phenotypic and functional characteristics of peripheral B cell subsets by IFN-a were evaluated by flow cytometry and The Elispot assay was employed to quantify the frequency of HBsAg-secreting B cells.
Results: The IFN group exhibited significantly higher cumulative anti-HBs positive rate and quantitative anti-HBs (qAnti-HBs) than the ETV group, obviously increased NAT but decreased Fc effector function compared to qAnti-HBs-matched healthy individuals who received vaccine immunization. IFN-a therapy and external stimulation resulted in more aboundant expression of activation markers CD86/CD95 on memory B cells and higher level of plasma cell, especially for patients with qAnti-HBs above 10 log10IU/mL at the end of treatment (EOT), as well as a close correlation between the increased proportion of plasma cell and the decreased proportion of memory B cell at week 48 and 72. Importantly, in the ex vivo culture system containing overlapping peptide pools derived from HBsAg, IFN-a was confirmed to be capable of promoting the generation of activated memory B cells, plasma cell, HBsAg-specific B cell and Anti-HBs (IgM/IgG) production.
Conclusion: IFN-a treatment could successfully reinvigorate HBsAg-specific B cells to produce robust neutralizing anti-HBs, thus contributing to functional cure of CHB.

FRI-230

Naïve C57BL/6 mice immunized with CLB-405 and CLB-505 combined with a saponin-based adjuvant TQL-1055 exhibit a dose-dependent humoral and cellular immune

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Background and aims: We have previously reported anti-viral activity of two modified Hepatitis B surface antigen (HBsAg) variants displaying clearance profile associated epitopes, CLB-405 and CLB-505, combined with a novel, semi-synthetic saponin-based adjuvant, TQL-1055 in two murine models of persistent Hepatitis B infection [AASLD 2024 posters 1305 and 1307]. These studies demonstrated that TQL-1055 adjuvant was able to invoke both a cellular and humoral antigen-specific immune response in infected mice, which may be beneficial in the situation of Chronic Hepatitis B (CHB) [Zhu, D. et al, Nat Prod Chem Res. 2016 Apr; 3(4): e113]. A dose response study was performed in naïve C57BL/6 mice to evaluate the humoral and cellular immune response of CLB-405 and CLB-505 combined with TQL-1055 with and without Alhydrogel.
Method: C57BL/6 mice were administered three injections of vaccine given on days 0, 14 and 28, containing 25 micrograms (mcg) of CLB-405 and CLB-505 antigens, adjuvanted with 20, 40, or 80 mcg of TQL-1055 adjuvant with and without 100 mcg Alhydrogel. The 40 mcg TQL-1055 dose was also evaluated at higher antigen concentration at 50 mcg of CLB-405 and CLB-505 each, with and without 100 mcg Alhydrogel. The mice were terminated 14 days post-last injection, and plasma and splenocytes were collected to assess antibody response measured as anti-CLB-405 and anti-CLB-505 endpoint titers and cellular immune response measured as IFN-gamma secreting splenocytes by ELISPOT.
Results: All mice dosed with the vaccine displayed robust anti-405 and anti-505 titers, with higher titers in the TQL-1055 adjuvanted groups compared to combination of the TQL-1055 and Alhydrogel adjuvants. All mice dosed with vaccine also displayed an increase in IFN-gamma secreting splenocytes collected on study termination, with higher response in the TQL-1055 adjuvanted groups compared to TQL-1055 and Alhydrogel adjuvanted groups. The immune titers as well as cellular immune response increased with increasing dose of TQL-1055 from 20 to 80 mcg, but no significant increase in titers was seen with increase in antigen dose from 25 to 50 mcg.
Conclusion: CLB-405 and CLB-505 combined with TQL-1055 adjuvant was highly immunogenic in naïve C57BL/6 mice with a dose-dependent increase in anti-CLB-405 and anti-CLB-505 antibodies and T cell response. This study established that there is no additional benefit of adding Alhydrogel to TQL-1055 which was used to guide the clinical vaccine presentation.

FRI-231

Inflammatory and oncogenic gene signatures in chronic hepatitis delta infection

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Background and aims: Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis due to rapid progression towards end-stage liver disease including cirrhosis and hepatocellular carcinoma (HCC). Factors driving disease acceleration need to be investigated to prevent advanced disease progression. We aimed to identify molecular signatures predicting the rapid onset of severe hepatic ailment in chronic HDV infection.
Method: We investigated peripheral blood transcriptomic profiles in chronic HBV and HDV coinfected (CHB/CHD-coinfection) patients and compared with CHB-monoinfection matched for liver fibrosis to recognize gene signatures associated with CHD-induced disease progression. Multiplex cytokine bead array and flow cytometry assays were performed to validate RNAseq and examine the markers of inflammation, fibrosis and immune exhaustion.
Results: Transcriptomic profile revealed significant upregulation of genes related to inflammation, oncogenesis, tumor growth, invasion, metastasis and inhibition of anti-tumor response such as CXCL2, 3, 8, TNFSF9, IFITM1, IL-17, IGHA2, AREG, SEMA3F, CSF1R, TREML4, ANGPTL4 and LILRB2 in CHB/CHD-coinfection than CHB-monoinfection. Interestingly, none of CHB/CHD-coinfected patients we analyzed had cirrhosis or HCC, yet these patients experienced significant elevation of inflammatory and oncogenic genes, indicating HDV triggers these genes much before the onset of cirrhosis or HCC that contributes to rapid disease acceleration towards end-stage disease. Analysis of the top canonical pathways further confirmed the association of these differentially expressed genes in severe inflammatory response and oncogenic process. ELISA further confirmed induction of inflammatory and fibrogenic cytokines (IL-17, CXCL2, CXCL13 and TGF-β) in the plasma of CHB/CHD-coinfection. Additionally, these patients experienced severe immune exhaustion in effector T cell (CD4 and CD8) compartment by displaying higher inhibitory receptors PD-1 and TIGIT, which then resulted in poor antiviral response in terms of IFN-gamma, TNF-alpha, perforin and granzyme B secretion along with impaired polyfunctional responses against HBV and HDV than CHB-moninfection alone.
Conclusion: HDV coinfection leads to a dichotomous immune response, whereby suppressing antiviral (HBV and HDV-specific) T cell immunity, while having an exaggerated inflammatory and oncogenic responses resulting in accelerated liver disease progression, cirrhosis and HCC.

FRI-232

Prolonged exposure to HBV suppresses the immunogenicity and antiviral efficacy of therapeutic vaccination

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Background and aims: Hepatitis B virus (HBV) persistence strictly correlates with scarce and dysfunctional virus-specific T-cell responses. Therapeutic vaccination is a promising strategy to activate antiviral T cells and treat chronic hepatitis B. Still, it may be limited by the long-term persistence of HBV at high titers, particularly after vertical transmission. Our clinical candidate TherVacB, a protein-prime/MVA-boost therapeutic vaccine, can efficiently break HBV-specific immunotolerance in HBV-transgenic mice and mice establishing persistent HBV-replication after infection with an adeno-associated virus carrying HBV genome (AAV-HBV). We found that high levels of HBV antigen expression in the liver negatively influence vaccine-induced immunity in both mouse models. How the duration of an HBV infection influences HBV-induced immune tolerance, however, remains open. In the present study, we aimed to determine the impact of the duration of an HBV antigen exposure on the efficacy of TherVacB.
Method: Age-matched C57BL/6 mice were transduced one or three months before TherVacB vaccination with AAV-HBV at the same dose. Both groups of mice showed comparable and persistent serum HBsAg and HBeAg levels. All mice received two prime vaccinations with adjuvanted, particulate HBs and HBcore antigens and a boost with an MVA vector expressing a range of HBV antigens.
Results: TherVacB induced anti-HBs and anti-HBe seroconversion in mice that received AAV-HBV one month before vaccination. In contrast, mice that were infected for 3 months showed no or only very low anti-HBs titers and no anti-HBe. Vaccination elicited similar numbers of HBV-specific CD8 T-cells in both groups of mice. However, HBV-specific CD8 T cells isolated from long-term HBV carrier mice showed a significantly lower expression of IFN-γ, TNF, and granzyme B than short-term HBV carriers. Interestingly, in contrast to high-level HBV carriers, there was no difference in the expression levels of checkpoint inhibitors, such as PD-1 or CTLA-4, on hepatic HBV-specific CD8 T cells, suggesting a distinct mechanism involved in suppressing the efficacy of TherVacB during long-term persistent HBV infection.
Conclusion: Prolonged exposure to HBV antigens resulted in more pronounced immune tolerance and significantly decreased the effector B- and T-cell responses induced by therapeutic vaccination without inducing a classical exhaustion phenotype.

FRI-237

Sustained off-treatment inhibition of HBV replication and HBsAg levels after long-term treatment with ABI-4334 in differentiated HepaRG cells and primary human hepatocytes

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Background and aims: ABI-4334 is a next-generation class E capsid assembly modulator (CAM-E) with improved in vitro potency against pregenomic (pg)RNA encapsidation and covalently closed circular (ccc)DNA formation compared to first-generation class E CAMs (vebicorvir). Here, we aim at assessing the effect of long-term ABI-4334 treatment on HBV replication and established cccDNA pool in an *in vitro* HBV infection model and in primary human hepatocytes (PHHs).
Method: Differentiated (d)HepaRG cells were treated from day 6 post-infection (pi) with 0.1 or 1 µM ABI-4334, 1 µM vebicorvir (VBR) or 1 µM lamivudine (3TC) for 1 month, followed by 1 month off-treatment monitoring. A similar protocol was applied to PHHs, with 2 weeks of treatment followed by 2 weeks off-treatment monitoring. Harvested cells and supernatants were analyzed for HBeAg and HBsAg secretion by ELISA, intracellular HBV biomarkers (total HBV

DNA and RNA, 3.5Kb RNA and cccDNA, HBs protein) by qPCR and Western blot, cell viability and hepatocyte differentiation markers.
Results: In dHepaRG cells, ABI-4334 treatment resulted in potent, dose-dependent inhibition of HBeAg secretion at end of treatment (EOT), which was not observed in VBR or 3TC treated cells. Secreted HBsAg levels were unaffected at EOT and then gradually declined, reaching 90% inhibition at end of follow-up (EOFU). Western blot analyses demonstrated no intracellular accumulation of HBs. Similarly, cccDNA levels were not affected at EOT, but showed 60% and 90% decreases at EOFU following treatment with 0.1 and 1 µM ABI-4334, respectively. Contrary to VBR and 3TC, stopping ABI-4334 treatment did not result in rebound of HBV replication. Similar effects were observed in PHH, where a 50% decrease in HBeAg and HBsAg was observed at EOFU following ABI-4334 treatment and no HBV replication rebound was observed after drug withdrawal in the absence of detectable cell toxicity. Profound, dose-dependent inhibition of intracellular total HBV DNA and RNA and 3.5Kb RNA was observed at EOFU in dHepaRG cells. This antiviral effect was accompanied by no signs of cytotoxicity or reduced gene expression of *bona fide* hepatocyte differentiation markers. As expected, no effects on cccDNA, HBeAg or HBsAg were detected after VBR or 3TC treatments at any time points in both infection models.
Conclusion: Durable HBsAg decreases and a lack of HBV rebound was observed after stopping long-term ABI-4334 treatment in both HepaRG cells and PHH, which could be ascribed to the depletion and/or functional inactivation of intracellular cccDNA pool in these experimental conditions.

FRI-238-YI
A recent shift in the evolutionary dynamics of hepatitis A virus
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Background and aims: Hepatitis A virus (HAV) has long been associated with humans, but successful vaccinations have significantly reduced HAV infections. While the incidence rate of HAV is strongly associated with socio-economic factors, we sought to explore the recent shifts in its epidemiology (i.e., a sudden spike in cases post-2018 with increased symptomatic infection among adults) by analysing sequential changes in all available full-length HAV genomes.
Method: To investigate whether changes in the viral genome caused the change in epidemiology, we analysed 313 full-length genomic sequences from the NCBI nucleotide database, with collection date information available, covering the period from 1957 to 2022. We used the sequence of the HM175 strain (genotype 1B, accession ID: NC_001489.1) as the reference, performed multiple sequence alignment with MAFFT v7.01, and analysed the genomic data using Biopython scripts.
Results: Our analysis reveals a sharp decline (> 50%) in the proportion of non-synonymous mutations, with an increase in synonymous mutations in HAV sequences post-2018. We identified the major amino acid changes in HAV sequences before and after 2018 and found six of them were also found in a chimpanzee that developed acute liver failure. Interestingly, post-2018, (a) the key synonymous mutations observed are linked to sub-optimal codon usage, (b) the proportion of C to T mutations and T to C mutations have increased by ~30%, suggesting an active role for host editing enzymes APOBECs and ADARs. Overall, the codon usage bias for HAV has significantly reduced post-2018 compared to that in HAV sequences before 2018 (Enc: 39 vs 47; $p < 0.0001$), suggesting gradual adaptation to humans. Of note, the median number of Zinc antiviral protein (ZAP)-motifs remains constant (n = 10/genome; lowest for any RNA virus infecting humans) both before and after 2018, indicating that ZAP-mediated editing has reached a saturation.
Conclusion: This study underscores the complex and dynamic evolutionary dynamics of HAV that may be influenced by innate immune responses and natural selection. The mutations identified in HAV post-2018 merit further investigation to understand their biological implications.

FRI-239
Detecting hepatocellular carcinoma by circulating cell-free DNA in patients with chronic hepatitis B
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Background and aims: Hepatocellular carcinoma (HCC) has become a leading cause of cancer-related deaths worldwide, including in Thailand. Emerging evidence suggests that circulating cell-free DNA (ccfDNA) is a promising marker for cancer diagnosis, including HCC. Alterations in gene expression regulation through epigenetic control, such as aberrant methylation, are well-characterized in cancer biology and could serve as candidate markers for cancer detection. This study aims to measure ccfDNA methylation of septin 9 (SEPT9), an approved biomarker in colorectal cancer, but with limited studies in HCC patients.
Method: To assess SEPT9 methylation in HCC, DNA was extracted from paired tumor and adjacent normal tissues of 19 patients with HBV-related HCC (HBV-HCC), followed by bisulfite conversion and quantification using droplet digital polymerase chain reaction (ddPCR). Methylated SEPT9 was then quantified in ccfDNA from a total of 185 patients, including 108 patients with HCC and 77 patients with chronic HBV without evidence of HCC (CHB), serving as a control group.
Results: We found that copy number of methylated SEPT9 in HBV-HCC tissue was significantly higher in tumor tissue compared to normal tissue (138 copies versus 5.6 copies, $p = 0.001$). In plasma ccfDNA, HBV-HCC patients exhibited significantly higher copy number of methylated SEPT9 and methylation abundance than HBV patients (2.96 copies versus 0.44 copies, $p = 0.001$ and 12.06% versus 0.09%, $p < 0.001$). The SEPT9 methylation ratio in tumor tissue and ccfDNA showed a strong correlation ($r = 0.78$, $p < 0.001$). Based on methylation abundance, to distinguish between HCC and CHB, methylated SEPT9 demonstrated an area under the receiver operating characteristic curve of 0.83 ($p = 0.038$, 95% CI: 0.750–0.899), with a sensitivity and specificity of 69.44% and 100%, respectively (cut-off value, 0.5%).
Conclusion: Our preliminary results indicate that methylated SEPT9 in plasma ccfDNA could serve as a diagnostic biomarker for HCC.

FRI-240
Hepatitis B surface antigen specific CD4 T cell response in hepatitis B vaccinated individuals
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Background and aims: The global implementation of prophylactic hepatitis B virus (HBV) vaccination in 1984 led to a significant decrease in HBV infections. It also offers the opportunity to study immunological mechanisms of immune memory maintenance. While most individuals develop strong antibody responses against the hepatitis B surface antigen (HBsAg) after the vaccination, these titers are not universally maintained. Although the role of CD4 T cells in supporting antibody development and maintenance is well established, they have not been thoroughly investigated in this specific context.
Method: We screened our biobank for samples from individuals carrying the HLA DRB1*0101 or DRB1*0701 alleles and having

antibodies against HBsAg (anti-HBs) excluding individuals with antibodies against hepatitis B core antigen (anti-HBc). For ex vivo detection of HBsAg-specific CD4 T cells, we used peptide-loaded MHC class II tetramers restricted to the aforementioned alleles. In addition, we performed in vitro stimulation with overlapping peptides spanning the HBsAg for 10 days followed by an intracellular cytokine staining.

Results: So far, we identified and analyzed 47 individuals. 32% (15/47) had detectable HBsAg-specific CD4 T cells directly ex vivo. The highest frequencies were observed in individuals with anti-HBs titers >100 IU/l. Phenotypic analyses for different memory subsets are currently ongoing. Following in vitro stimulation with HBsAg, we identified cytokine-producing CD4 T cells in 81% of the individuals (n = 22). This is an ongoing study and additional results will be presented at the conference.

Conclusion: Our preliminary results suggest that the frequency of HBsAg-specific CD4 T cells is associated with the anti-HBs titers in vaccinated individuals. Whether this is driven by specific memory subsets and in how far this correlates with individual vaccination history is currently being investigated.

FRI-241

Longitudinal analysis of viral profiles in chronic HBV/HDV coinfected patients

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Background and aims: Interactions between HBV and HDV in coinfected patients and the role of HDV genetic variability remain poorly understood. This study aimed to assess serum samples from HBV/HDV coinfected patients to provide a comprehensive analysis of viral profiles and HDV RNA variability.

Method: Serum samples collected over time from 43 consecutive patients (32 male, 74.4%; median age 46 years, IQR:39–59; all infected with HDV genotype 1) were analyzed. HDV RNA levels were quantified using the RoboGene HDV RNA Quantification Kit (Roboscreen), while HBsAg and HBcrAg levels were measured using the Elecsys HBsAg II quant II (Roche Diagnostics) and Lumipulse G HBcrAg assays (Fujirebio), respectively. HDV genetic variability was assessed using next-generation sequencing (NGS) on the Illumina MiSeq platform.

Results: In 10/43 patients (all on NUC therapy) with two serum samples collected over 1.8 to 5.8 years (mean 2.6 years), HBV DNA was undetectable or at very low levels (<20 IU/mL), while HDV RNA, HBsAg, and HBcrAg remained at elevated levels. Specifically, median HDV RNA levels were 158,000 IU/mL (1st sample) and 82,900 IU/mL (2nd sample; P = 0.7), HBsAg levels were 5,562 IU/mL (1st sample) and 1,861 IU/mL (2nd sample; P = 0.1), and HBcrAg levels were 3.16 kU/mL (1st sample) and 3.35 kU/mL (2nd sample; P = 0.2). NGS revealed the pairwise genetic distances between HDV consensus sequences from each patient and WHO HDV reference sequence varied from 3.4% to 26%, with the median of 14.2%. that 3/43 patients (6.3%) had high-frequency mutations in Cys211 (Cys211Ser) and Gln214 (Gln214Leu) of the CXXQ isoprenylation site of HDAg. Additionally, 41/43 patients (95%) had highly frequent mutations in the nuclear export signal (aa 198–211) and lower HBsAg levels. Notably, unedited HDV (producing a higher amount of small HDAg than large HDAg) predominated in 40/43 patients (93%). Furthermore, the analysis of genetic diversity revealed that the pairwise genetic distances between HDV consensus sequences from each patient and the WHO HDV reference sequence ranged from 3.4% to 26%, with a median of 14.2%.

Conclusion: Our findings demonstrate that HBsAg and HBcrAg are produced during HDV infection independently of HBV replication. Additionally, our results highlight the significant genetic variability of HDV. Specifically, the high frequency of mutations in key regions of HDAg and the predominance of unedited HDV genomes suggest mechanisms that may play a role in viral adaptation and persistence.

FRI-242

FXR agonists as broad-acting antivirals against HBV/HDV/HEV and other hepato(cyto)tropic viruses

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Background and aims: Chronic and acute viral infections of the liver are responsible for liver pathogenesis leading to sudden organ failure or end-stage liver diseases, including cirrhosis and HCC. If HBV and HDV induce in general rather slow evolving pathogenesis, other viruses, including HEV, YFV, as well as numerous other arbovirus (e.g. DENV, RVFV) or tick-borne viruses (CCHFV) can lead to faster liver failure. To prevent liver pathogenesis, it would be interesting to have broadly acting drugs targeting these evolutionary different viruses. In this respect, host targeting agents are of high interest. Hepatocytes are key players of metabolic regulations, and metabolism modulators are expected to alter virus/host cell interactions. This study investigates the effect of Farnesoid X receptor agonists (FXR-ago) on various hepatotropic viruses, in relevant cell-culture and mouse models.

Method: Using cell culture models, including primary human hepatocytes (PHH), differentiated HepaRG, and a novel cell line able to replicate all hepatotropic viruses, as well as a liver humanized mouse model, we have studied the replication (by PCR-based methods, western blot/immunofluorescence/ELISA analyses, and TCID assays) of eight viruses (HBV, HCV, HDV, HEV, YFV, DENV, HAZV (model of CCHFV), and TOSV (model of RVFV) and their susceptibility to FXR-ago agonists used alone or in combination with Peg-IFN-alpha. Some mechanistic studies (RNA seq, loss and gain of functions, molecular analyses (Run-On assay, etc…), and classical virological analyses) were also performed to decipher the mode of action of FXR agonists against some of the viruses studied.

Results: We generated a novel cell line derived from a Huh7.5 cells, expressing the HBV/HDV entry receptor NTCP. These cells could be partially re-differentiated into hepatocyte-like cells, as shown by transcriptomic profiling and capacity to produce VLDL. HBV, HDV, HEV could replicate in differentiated Huh7.5-NTCP, as well as in dHepaRG and PHH, and were inhibited by FXR-ago in all models. The antiviral effect of FXR-ago against HEV was also confirmed in liver-humanized mice. All other viruses could replicate in dHuh7.5-NTCP and were moderately to strongly susceptible to FXR-ago. The antiviral effect was mainly due to an alteration of the specific infectivity of viral particles, leading to an inhibition of viral spreading (nicely shown for HDV). For viruses with a nuclear episome (like HBV), additional antiviral activities came from direct transcriptional inhibition. Interestingly, an additive (likely synergistic in the case of HDV) antiviral effect of FXR-ago and Peg-IFNa was observed in vitro.

Conclusion: FXR agonists are broadly acting antivirals that could be used, in combination with other drugs (e.g. Peg-IFNa), to protect the liver from acute failure and help clearing chronically replicating viruses. Further preclinical studies are needed for the newly investigated viruses, but clinical trials could already be envisaged against HDV or HEV infections.

FRI-243-YI

VDAC1-mediated lipid droplet-mitochondria tethering promotes tumorigenesis and inhibits HBV replication in CHB patients concurrent with MASLD

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Background and aims: The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased among the general population and chronic hepatitis B (CHB) patients worldwide. The clinical impacts of MASLD on CHB progression are controversial from different studies and their interaction seem complex. We aimed to explore the impact and the underlying mechanism of concurrent MASLD in CHB pathogenesis.
Method: Spatial transcriptome sequencing were performed on liver biopsies from healthy controls and patients with MASLD, CHB, and CHB concurrent with MASLD to systematically investigate the heterogeneity and ecosystem of CHB patients with and without MASLD. rAAV8-1.3 HBV hydrodynamic injection mice fed with high-fat diet (HFD)- or high-fat methionine-restriction choline-deficient diet (HFMRCD) were used to establish CHB concurrent with MASLD models. HBV-transfected HepG2.2.15 and RIL-175 cells were stimulated with palmitic acid and oleic acid (PAOA) *in vitro*. Liquid chromatography-tandem mass spectrometry (LC–MS/MS) were used to screen proteins involved in lipid droplet-mitochondria tethering. RIL-175 cells reconstituted with wild-type rVDAC1 or rVDAC1(K161R) were injected intrahepatically into mice to assess the impact of K161R mutation on VDAC1-APOE interaction and associated downstream cascades.
Results: Spatial transcriptomic analysis revealed that patients in concurrent group exhibited markedly exacerbated mitochondrial dysfunction and aberrant immune cell infiltration. Although all enrolled CHB patients were in the immune-tolerant phase, concurrent MASLD significantly increased the infiltration of tumor-associated macrophages (TAMs) within the lesion areas. Compared with CHB or NAFLD patients, concurrent CHB and NAFLD patients presented upregulated Voltage-Dependent Anion Channel 1 (VDAC1) localized on mitochondria, accompanied by a marked increase in VDAC1 oligomerization. VDAC1 subsequently interacted with the lipid droplet protein Apolipoprotein E (APOE), resulting in lipid droplets-mitochondria tethering, oxidative stress and markedly exacerbated mitochondrial dysfunction, which developed a tumorigenic microenvironment by increasing lactate production and inhibiting apoptosis. Interfering with this cascade through blocking VDAC1-APOE interaction mitigated mitochondrial dysfunction, inhibited lactate production, promoted apoptosis and suppressed the development of a pro-tumorigenic hepatic microenvironment in mice. Meanwhile, oligomerization of VDAC1 in MASLD promoted the release of mitochondrial DNA (mtDNA), which inhibited HBV replication by activating the ISG-mediated innate immune response.
Conclusion: Concurrent MASLD promotes VDAC1-mediated lipid droplet-mitochondria tethering, which is associated with higher risk of HCC and lower HBV replication in CHB patients.

FRI-244

Analysis of intrahepatic cccDNA and HBV-DNA in patients with hepatocellular carcinoma attributed to non-HBV etiologies

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Background and aims: Hepatitis B virus (HBV) is a well-recognized oncogenic virus. In previous studies, the presence of serum anti-HBc and HBV-DNA in HBsAg-negative patients have been associated with an increased risk of hepatocellular carcinoma (HCC), particularly in Asian patients. This study aimed to evaluate the presence of intrahepatic cccDNA and HBV-DNA in a cohort of HCC patients and explore its relation with serum HBV markers.
Method: Prospective cohort of 64 HBsAg-negative HCC patients from whom paired tumor tissue, adjacent non-tumor tissue, and serum samples were collected between January 2016 and January 2024. Covalently closed circular DNA (cccDNA) and intrahepatic HBV-DNA (iHBV-DNA) in both tumor and adjacent tissues were quantified using qPCR. Serum anti-HBc antibodies and HBV-DNA levels were determined using commercial assays (Roche Diagnostics). The cohort included 84% males, with a median age of 62 years; 91% were Caucasian, and 96% had underlying liver disease (HCV 36%, ALD 17%, and MASLD 16%). Additionally, 6 HBsAg-positive patients were included for comparison.
Results: Of the 64 HBsAg-negative HCC patients, 42% (27/64) had detectable iHBV-DNA in in either tumor or adjacent liver tissue [mean (SD): 0.005 (0.008) copies/cell], and 6% (4/64) also had cccDNA [0.004 (0.004)]. Serum anti-HBc was present in 19 (30%) patients,and iHBV-DNA was detected in 5 (26%) of these in either tumor or adjacent tissue. Among the 45 anti-HBc-negative patients, 22 (49%) had detectable iHBV-DNA (8 in tumor tissue, 7 in adjacent tissue, and 7 in both); cccDNA was also detected in 4 of these cases. There were no significant differences in the proportion of patients with iHBV-DNA (26% vs. 49%, $p = 0.09$) or its concentration in tissue (0.003 (0.003) vs. 0.005 (0.008) copies/cell, $p = 0.36$) based on anti-HBc status. Notably, none of the 4 patients with cccDNA had detectable HBV-DNA in serum. All 6 HBsAg-positive (and HBeAg-) patients had iHBV-DNA in both tumor and adjacent tissues [11.74 (11.51) and 3.57 (3.89) copies/cell], while cccDNA in 100% of adjacent tissues [0.59 (0.61)] and 50% of tumor tissues [0.56 (1.22)]. The levels of iHBV-DNA in these HBsAg-positive patients were significantly higher than in HBsAg-negative patients in both tumor [11.74 (15.37) vs. 0.008 (0.011), $p < 0.001$] and adjacent tissue [3.57 (3.89) vs. 0.0023 (0.0018), $p < 0.001$]. Among the 27 HBsAg-negative patients with detectable iHBV-DNA and/or cccDNA in tissue, underlying liver disease was attributed to HCV (37%), MASLD (33.3%), and other non-HBV-related causes. There were no significant differences in iHBV-DNA concentration based on etiology.
Conclusion: Nearly half of the HBsAg-negative patients with HCC attributed to other etiologies show intrahepatic HBV DNA or cccDNA. Its detection is not related to serum anti-HBc presence, indicating high exposure to HBV. Further molecular analyses are currently ongoing.

FRI-245-YI

Hepatitis E virus entry requires the cholesterol transporter Niemann–Pick C1

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Background and aims: The hepatitis E virus (HEV) presents a significant global health concern with an estimated 20 million infections occurring annually, while no specific antiviral treatments are available. Our current understanding of the viral life cycle is limited, but it is essential for the development of novel antiviral strategies. The lysosomal cholesterol transporter NPC1 has been shown to prevent the entry of different viruses, including Ebola virus and SARS-CoV-2. However, the role of the cholesterol transporter Niemann-Pick-C1 (NPC1) during HEV infections remains unclear. Here, we investigated the role of NPC1 during the HEV infectious cycle and evaluated the antiviral potential of the clinically approved NPC1 inhibitor Itraconazole.
Methods: Using a robust HEV cell culture model, we investigated the dose-dependent effect of the two NPC1 inhibitors, Itraconazole and U18666 on the infection with (non-)enveloped HEV. In addition, we performed time-of-addition as well as subgenomic replicon assays to gain insights into the mode of action of the NPC1 inhibition. We further performed quantitative RNA fluorescence in situ hybridization (RNA-FISH) to localize HEV virions during NPC1 perturbation. The requirement of NPC1 during the HEV life cycle was further validated via siRNA-mediated knockdown and CRISPR/Cas9-mediated knockout. In addition, we evaluated the antiviral effect of the NPC1 inhibitors in primary human hepatocytes (PHH).
Results: Both NPC1 inhibitors, Itraconazole and U18666A, lowered HEV infectivity at nanomolar efficacy in hepatoma cells. Consistent with this, siRNA-mediated knockdown of NPC1 and CRISPR/Cas9-mediated knockout lowered the susceptibility to infection with (non-)enveloped HEV. Time-of-addition experiments showed that the NPC1 inhibitors exert their antiviral effect during virus entry, without affecting viral replication, as observed by replicon assay. In agreement with this, we observed cholesterol accumulation and enlargement of lysosomal compartments upon NPC1 perturbation and a blockage of RNA trafficking and productive infection. In PHH, Itraconazole exhibited a potent effect in reducing the HEV infectivity.
Conclusion: Overall, our data suggests that NPC1 plays a crucial role during the viral entry of HEV. Considering that the NPC1 inhibitor Itraconazole is clinically used in immunocompromised patients (unrelated to viral conditions), the pharmacological targeting of NPC1 might guide novel antiviral strategies against HEV infections in the future.

FRI-246

HBV cccDNA: The molecular reservoir of hepatitis B persistence and challenges in eradication

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Background and aims: Hepatocytes in patients with chronic hepatitis B harbor covalently closed circular DNA (cccDNA), which acts as a stable, long-term template for viral replication, producing viral genomes and associated proteins. This viral mini-chromosome is difficult to eliminate with current treatment regimens: nucleos(t)ide analogs and interferon, and consequently viral replication occurs after stopping therapy. Novel treatment strategies are generally given in virally suppressed individuals, but accurate markers to monitor treatment efficacy in these patients are not available. In this study, we therefore develop sensitive and specific methods to assess the intrahepatic HBV viral reservoir, particularly cccDNA and its transcriptional activity via pre-genomic RNA (pgRNA).
Method: To address this need, we employed droplet digital PCR (ddPCR), which uses water-oil emulsion droplet technology for targeted amplification and detection, enabling us to distinguish between HBV rcDNA and cccDNA. We optimized this assay using the HepG2.2.15 cell line, which harbors a persistent HBV infection and produces all viral elements, achieving detection sensitivity down to 1% of infected cells within a non-infected HepG2 cell pool. Testing patient sera, which contain rcDNA but not cccDNA, with variable HBV DNA titers up to 10^9 IU/mL, all tested samples were negative for HBV cccDNA, confirming assay specificity. Further specificity was validated in liver samples from HBV- or HCV-derived hepatitis patients, with all HCV-infected samples testing negative for HBV cccDNA. This ddPCR assay provides a sensitive and specific approach for distinguishing HBV cccDNA from other viral forms, offering a valuable tool for studying the HBV reservoir and aiding in the evaluation of therapeutic strategies aimed at HBV eradication.
Results: Currently, we are utilizing this method to determine the correlation between PEGylated-IFNα treatment response and initial intrahepatic HBV cccDNA reservoir levels. This study aims to measure the baseline intrahepatic HBV cccDNA levels in patients before they began pegylated (PEG)-IFNα treatment, to explore cccDNA as a biomarker that could help identify those likely to benefit from this therapy. We also assess the transcriptional activity of HBV cccDNA, pre-genomic RNA (pgRNA) levels, to determine if treatment outcomes are influenced by either the baseline copy number or activity of HBV cccDNA. By quantifying HBV cccDNA and pgRNA levels after treatment, we want to understand how the HBV reservoir is affected post-PEG-IFNα treatment by comparing responders with non-responders.
Conclusion: Overall, our findings could provide early biomarkers to identify likely PEG-IFNα responders and offer HBV cccDNA measurement as a useful method to evaluate the efficacy of novel HBV therapeutics.

FRI-247

In vitro characterization of elebsiran (VIR-2218), an investigational siRNA therapeutic targeting hepatitis B virus

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Background and aims: Therapeutic targeting of hepatitis B virus (HBV) with RNA interference has the potential to contribute to functional cure or chronic treatment of patients with chronic HBV infection and hepatitis Delta virus (HDV). Elebsiran is an investigational small interfering RNA (siRNA) that targets the highly conserved HBx region of the HBV genome present in all HBV transcripts. Here, the preclinical activity of elebsiran was evaluated using in vitro models of HBV infection and integration, and in silico analyses.
Method: HBsAg and HBeAg reduction were assessed following HBV infection and elebsiran treatment in HepG2 cells expressing Na+-taurocholate co-transporting polypeptide (NTCP). Pan-genotypic activity was determined using a luciferase reporter system encoding HBV genotypes A-J HBx genes, and HBV genotypes A-D 1.3-overlength genome system. Nucleotide polymorphisms in the elebsiran target sequence were identified using sequence alignments

of 7,517 sequences from the HBV database, HBVdb, and tested in vitro. Elebsiran was evaluated for HBsAg secretion inhibition in HBV-DNA integrated cells (huH1, Hep3B and PLC/PRF/5). Elebsiran knock-down of HBV transcripts and its effect on viral and host proteins expression was assessed using northern and western blot analyses of HBV-infected cells.

Results: Elebsiran showed potent reductions of HBsAg and HBeAg in HBV-infected HepG2-NTCP cells. HBx mRNA knockdown was observed for sequences from all 10 HBV genotypes, with 49–78% reduction at 50 nM of elebsiran. Treatment with elebsiran led to concentration-dependent decrease of secreted HBsAg and HBeAg in 13 isolates of HBV genotypes A-D with EC50 values 0.038–0.105 nM. Elebsiran also exhibited full inhibition (>99%) of HBsAg release in huH1 & Hep3B cells and partial inhibition (52–70%) in PLC/PRF/5 cells. Sequence analysis of PLC/PRF/5 cells revealed rare polymorphisms (<0.11% frequency based on HBVdb) in the elebsiran target site of some HBV integrants, which were associated with in vitro resistance. Finally, northern blot analysis in infected cells showed elebsiran-mediated knock-down of all HBV transcripts derived from covalently closed circular (ccc) DNA. Western blot analysis confirmed protein downregulation of all HBsAg isoforms and HBx, as well as rescue of the HBV restriction factor Smc5/6.

Conclusion: Elebsiran demonstrated potent reductions of HBV viral markers in two in vitro infection models and exhibited pan-genotypic activity. Sequence analysis revealed that target site substitutions are rare. Elebsiran showed potent antiviral activity against HBV from both integration and cccDNA. Elebsiran-mediated degradation of all HBV transcripts inhibits HBx expression and restores the HBV restriction factor Smc5/6 expression, suggesting additional downstream antiviral effects of targeting HBx.

FRI-248

Description of tenofovir levels in south african adults in the EVOLVE study: a pilot project to support therapeutic drug monitoring in HBV infection

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Background and aims: Hepatitis B virus (HBV) treatment is based on nucleos/tide analogue (NA) drugs for viral suppression, which overlap with therapy used for HIV; the first line agent is tenofovir (TFV). Therapeutic drug monitoring (TDM) has not been explored to optimize therapy in HBV. However, TDM is established in the HIV field, providing a framework to fill evidence gaps for HBV. In this pilot project, we describe the distribution of free tenofovir (TFV) and its metabolite, tenofovir-diphosphate (TFV-DP), in a South African (SA) population offered treatment for HIV monoinfection or HIV/HBV coinfection.

Method: We studied Dried Blood Spot (DBS) obtained from 100 adults from EVOLVE, a project nested within the Vukuzazi programme in the KwaZulu-Natal province (KZN) of SA. Ethics approval was obtained from the relevant jurisdictions. Samples were selected to represent 40 HIV/HBV positive (coinfected), 40 HIV (monoinfected) and 20 HIV/HBV negative (control, presumed untreated), age and sex matched, participants. We used liquid chromatography-tandem mass spectrometry (LC-MS) to measure drug levels of free drug (TFV) and drug metabolite (TFV-DP). HBV viral suppression was defined as plasma HBV Viral load (VL) below the lower limit of quantitation, LLQ (<10 IU/mL). Statistical analysis was performed using Pearsons's or Kruskal-Wallis test, or logistic regression in R.

Results: In the HIV/HBV-negative control group, 1/20 individuals had detectable TFV (1077.94 fmol/punch) and TFV-DP (753 fmol/punch) and another had quantifiable TFV-DP (31.82 fmol/punch) only. In the remaining 80 samples, TFV and TFV-DP were both detected in 77/80 (96.3%) of participants, with a median level of 787 fmol/punch (IQR 524–1111) and 610 fmol/punch (IQR 372–802) respectively. TVF and TFV-DP levels correlated significantly ($R^2 = 0.59$ and $p < 0.001$). There was no significant difference in TFV and TFV-DP levels by sex ($p > 0.05$), but levels correlated positively with age ($p < 0.05$ for all). HIV VL was suppressed in all individuals, however, among the 40 individuals with HIV/HBV coinfection, 10 (25%) had HBV VL >LLQ (median VL: 195 (14, 13154 IU/mL)). Drug levels were not significantly different between HBV VL unsuppressed and suppressed individuals, (TFV: 544 vs 930 fmol/punch and TFV-DP: 464 vs 610 fmol/punch respectively), nor did they correlate with HBV status or VL ($p > 0.05$ for all).

Conclusion: We present early data to quantify TFV and TFV-DP levels in adults from SA. Drug levels were associated with age, but not sex, HBV status or HBV VL. Two HBV/HIV negative individuals tested positive for drug levels; this could be due to use of TFV for HIV pre-exposure prophylaxis. Data on treatment duration, self-reported adherence or the time between the last dose of treatment and sample harvesting is currently not available, and future work is needed to determine the relationship between drug levels and HBV virologic control.

FRI-253

Large spatial variation of intrahepatic HDV RNA levels without association with HBV core or S RNA levels in patients with HDV induced cirrhosis

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Background and aims: Hepatitis D virus (HDV) infection is an important cause of cirrhosis and liver cancer. It occurs only as co-infection with hepatitis B virus (HBV), since it requires the surface antigen of HBV (HBsAg) to form viral particles. The aim of this study was to investigate correlations between levels of intrahepatic HDV RNA, HBV core and S RNA and serum markers.

Method: 10 pieces of tissue from each of five liver explants from patients that underwent transplantation because of HDV-induced liver disease were analyzed by digital droplet PCR.

Results: A large variation of the tissue levels of viral RNA was found between and within patients. An association was observed between tissue levels of HBV core and S RNA when values from tissue pieces from all patients were considered ($p < 0.0001$) and individually for two patients with a high core expression ($p < 0.05$, $p < 0.001$). However, no association was observed between HDV RNA and HBV core or S RNA except within one patient. Furthermore, there was no correlation between HDV RNA levels in serum and tissue. Instead, for the four patients with detectable serum HDV RNA, serum HDV RNA correlated positively with tissue levels of HBV core RNA ($p < 0.005$) and showed a trend towards correlation with tissue HBV S RNA levels. In addition, a significant correlation between the levels of HBsAg and HDV RNA in serum was observed ($p < 0.05$). A sample taken from the fifth patient five years prior to the transplantation showed the same relation between the two variables as the other patients.

Conclusion: The results suggest that HBsAg may be a limiting factor for HDV particle production, and that HBV infection is not required for cells to allow HDV genome replication. The results do not support repression of HBV replication by HDV since no negative correlation was observed between tissue levels of HDV RNA and HBV core RNA.

FRI-254-YI

Early immune responses define Peg-IFNα-mediated treatment outcome in chronic hepatitis D virus infection

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Background and aims: Infection with the hepatitis D virus (HDV) induces the most severe form of chronic viral hepatitis, with almost 70% of patients developing liver cirrhosis and hepatocellular carcinoma within 5–10 years of infection. Pegylated interferon-α (Peg-IFNα) has been used to treat HDV-infected patients over the past decades with ∼20–30% of them achieving sustained virological response rates. The immunological mechanism of Peg-IFNα-induced viral control remains incompletely understood. The current study aims to identify immunological parameters that may predict Peg-IFNα-mediated treatment outcomes.
Method: Serum and liver samples were collected from patients treated within the HIDIT II study, where patients had received treatment with Peg-IFNα with or without tenofovir disoproxil fumarate for 96 weeks. Here, we re-grouped the patients based on on-treatment HDV viral decline and classified them into responders (HDV RNA decline below the lower limit of quantitation) and non-responders (sustained high HDV RNA levels). Healthy individuals and hepatitis B mono-infected patients were used as controls. Sera were tested for anti-IFNα and inflammatory cytokines. FFPE liver biopsies underwent *in-situ* immunofluorescence staining to identify immunological markers associated with treatment response.
Results: Baseline demographics showed no significant differences in age and gender between responders and non-responders. Responders demonstrated rapid HDV RNA decline, achieving undetectable levels by treatment week 48, while HDV RNA remained high in the non-responder group. Four-plex immunofluorescence staining demonstrated increased liver-resident immune cells in responders at baseline. Anti-IFNα antibodies were found in most of the patients, with some of them having pre-existing anti-IFNα antibodies. Although the levels declined in almost all responders under treatment, we observed significantly higher anti-IFNα antibody levels in the non-responders at treatment week 2. Also, plasma IFNα2 and IP10 levels, as well as tumor necrosis factor related apoptosis inducing ligand (TRAIL) were significantly increased in responders compared to non-responders at treatment week 8.
Conclusion: This study underscores the importance of anti-IFNα antibodies, as well as liver-resident immune cells in determining the success of Peg-IFNα treatment. Our current findings suggest that adaptive immunity may contribute to Peg-IFNα-mediated treatment response during chronic HDV infection.

FRI-255

Discordance between peripheral hepatitis B surface antigen (HBsAg) titres and hepatic expression in chronic HBV infection

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Background and aims: Serological profiling of hepatitis B surface antigen (HBsAg) remains central to diagnosing HBV infection and evaluating treatment response; in addition, the primary endpoint of functional cure is defined as a reduction in HBsAg (and HBV DNA) to below the limit of serum detection. To assess the validity of this approach, we explored the relationship between peripheral HBsAg titres and hepatic HBs expression.
Method: In this retrospective study, we identified subjects with chronic HBV infection (CHB) who have recently undergone a liver biopsy at King's College Hospital (UK tertiary centre). Archived FFPE liver tissue was stained for HBs and the percentage of HBs-positive hepatocytes was determined by a consultant histopathologist. HBs topography was described as "membranous" or "cytoplasmic," and results were expressed in a semi-quantitative manner (<10%, 11–50%, >50% of hepatocytes). Paired serum samples were evaluated for the following viral markers: total HBsAg (Abbott Architect®, $\log_{10}$ IU/ml), L-HBsAg (Abbkine, U/ml), HBV DNA (Roche Cobas® 6800, $\log_{10}$ IU/ml) and HBcrAg (Fujirebio, $\log_{10}$ U/ml). Differences between groups was assessed using non-parametric tests and a two tailed p value <0.05 was considered statistically significant.
Results: All subjects were HBV mono-infected and treatment naïve at the time of liver biopsy (n = 23, median age 38). Most were in the HBeAg negative phase of infection (78.3%), and a range of HBV genotypes were represented (Genotype E 39.1%, A 17.4%, B 17.4%, Other genotypes 26.1%). Median titres of total HBsAg and HBV DNA were 4.04 $\log_{10}$ U/ml (IQR 3.41–4.35) and 4.08 $\log_{10}$ U/ml (IQR 3.16–6.12), respectively, and 52.2% of patients recorded HBcrAg >3.0 $\log_{10}$ U/ml. F3/F4 fibrosis was present in 17.4% of biopsies and median necro-inflammatory score was 3 out of 18 (Ishak grading system). Extensive membranous HBs (defined as >50% of hepatocytes staining for HBs at the plasma membrane) was demonstrated in 39.1% of biopsies (including 6/18 HBeAg negative samples) and associated with higher peripheral titres of total HBsAg (p = 0.0008) & HBV DNA (p = 0.04); conversely, there was an inverse relationship between membranous HBs and peripheral L-HBsAg (p = 0.0002). Of note, there was no association between cytoplasmic HBs and any of the peripheral biomarkers (total HBsAg, p = 0.95; L-HBsAg, p = 0.99; HBV DNA, p = 0.35; HBcrAg, p = 0.79). Neither HBs-staining patterns were associated with necro-inflammatory scores (membranous HBs, p = 0.50; cytoplasmic HBs, p = 0.99) or fibrosis grade (membranous HBs, p = 0.80; cytoplasmic HBs, p = 0.96).
Conclusion: Serum HBsAg titres were reflective of membranous, but not cytoplasmic, HBs staining. Re-assessing the merits of this peripheral biomarker in defining functional cure, as well as evaluating treatment response, may be warranted.

FRI-256

Circulating miRNAs are downregulated in hepatitis delta patients that control viral replication

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Background and aims: Only a limited percentage of the hepatitis delta patients (HDV; anti-HDAg positive) can control the viral replication (undetectable HDV RNA). However, the mechanism behind this virological control remains unknown. The microRNAs (miRNAs) are small RNAs that participate in different biological

processes, including the host response against a viral infection. The present study aims to analyze the miRNAs profiles in HDV patients to identify potential biomarkers that differentiate those who control the infection.

Method: The study was conducted in two parts. First, miRNA profiles using MicroArray (Affymetrix) in plasma samples from 30 HDV patients (anti-HDAg positive - explorative cohort), grouped based on HDV RNA detectability: 15 with detectable and 15 with undetectable levels (confirmed by at least two consecutive measurements). The selected miRNAs were then validated by digital PCR (QIacuity). The cohort consisted of three longitudinal samples from 18 untreated, anti-HDAg patients, accounting for 54 plasma samples. These included patients with undetectable HDV-RNA (group A, n = 3) and chronic hepatitis delta patients (CHD) with detectable HDV-RNA (group B, n = 15). Group B was further divided based on their ALT levels into two subgroups: B1 with ALT <50 U/L (n = 6) and B2 with high ALT (n = 9). Notably, the first longitudinal samples (T0) were HDV-RNA positive in all included patients. A group of healthy donors (n = 7) was used as controls (HD).

Results: In the first part of the study, six differentially expressed miRNAs were selected (log2FC >1, *raw* p-valor <0.05 and mean expression>2): miR-122-5p, miR-192-5p, miR-194-5p, miR-23b-3p, miR-26a-5p and miR-4530, conforming two different patterns (miR-122-5p+miR-192-5p+miR-194-5p, and miR-23b-3p+miR-26a-5p). When quantifying the miRNAs in the longitudinal samples, we observed that patients with undetectable HDV-RNA (group A) had lower levels of all the miRNAs compared to those in the other groups, even at the first sample when HDV RNA was still detectable. Of note, the miR-23b-3p and miR-26a-5p, were particularly down regulated in all the HDV-positive samples in comparison to the HD (adjusted p-value <0.05).

Conclusion: Hepatitis delta patients that control viral replication exhibit a differential miRNA's profile from those with detectable and stable HDV RNA. The most differentially expressed miRNAs were generally down regulated in this group, suggesting that they can have an impact on viral replication. Further investigation is needed to understand the mechanisms behind the dysregulation of these miRNAs and their relationship with HDV replication. Study supported by the projects PI20/01692 and PI23/01065, funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF, "A way to make Europe").

FRI-257

Next generation hepatitis B virus antisense oligonucleotides incorporating novel chemistries demonstrated significantly improved properties compared to current clinical candidates

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Background and aims: Chronic hepatitis B (CHB) patients can achieve functional cure after monotherapy with antisense oligonucleotides (ASO) targeting hepatitis B virus (HBV) RNA, e.g. GSK-836 and AHB-137. This is a better outcome compared to many other new anti-HBV agents which showed no signs of HBV S antigen (HBsAg) loss. However, the reported rates of HBsAg loss at the end of ASO treatment were only moderate and the relapse rates during the off-treatment follow up period were high. Our goal is to develop a best-in-class HBV ASO that improves the rate of functional cure. We are targeting four areas for improvement compared with current clinical candidates: 1) significantly improved RNase H-mediated activity; 2) modestly improved human Toll-like receptor 8 (hTLR8) agonist activity; 3) less off target effects; and 4) improved ASO liver to kidney concentration ratio.

Method: In vitro and in vivo RNase H mediated-activity was analyzed with an HBsAg ELISA assay in the supernatant of HepG2.2.15 cell line or in the plasma of AAV-HBV mice. HEK-Blue hTLR8 and human peripheral blood mononuclear cell (PBMC) assays were used to monitor TLR8 activity. To validate ASO hTLR8 activity in vivo, hTLR8 knock-in (KI) mice were used as wild-type mice lack a functional TLR8 protein. Toxicity derived from ASO off-target effects was measured in a HepG2 Caspase3/7 assay and an ATP assay in InSphero 3-D liver cell spheroids. ASO concentrations in the liver and kidney were monitored in both mouse and monkey.

Results: To date, more than 1150 HBV ASO sequences incorporating novel chemistries have been designed, synthesized and tested. Utilizing stabilization chemistries, we have found in vitro RNase H-mediated activity could be improved ~10-fold (1 nM EC_{50}) in the HepG2.2.15 assay, compared with parental sequences with standard chemistries. Human TLR8 activities could be improved 10–100% over that of clinical stage compounds. In vitro Caspase 3/7 activities could be reduced 10–100% from those of clinical stage compounds. For individual ASOs, the overall improvements of all three aspects were evaluated and rank-ordered to select compounds for in vivo AAV-HBV mouse and hTLR8 KI mouse model studies. A lead compound, ALG-170961 has a better safety profile and improved hTLR8 activity than clinical stage ASOs. In AAV-HBV mice, HBsAg measured in mouse plasma, following 5 doses of ALG-170961 at 25 mg/kg, declined 2.89 $\log_{10}$ IU/mL from baseline to near lower limit of quantitation (LLOQ). When compared with clinical stage ASOs at the same dose level on Day 7, ALG-170961 showed 61% and 27% deeper HBsAg reduction than clinical stage compounds #1 and #2 respectively.

Conclusion: Applying novel chemistries could improve RNase H-mediated, hTLR8 and Caspase 3/7 profiles of HBV ASOs. Among several lead ASOs, ALG-170961 exhibited the most significantly improved in vivo efficacy when compared with current clinical stage compounds.

FRI-258

No evidence for viral escape mutations in immunodominant HCV-specific CD4 T cell epitopes

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Background and aims: Hepatitis C virus (HCV) infection provides a valuable model for studying immune responses under viral persistence and clearance. Direct-acting antivirals (DAAs) clear HCV in about 95% of patients, but their impact on HCV-specific CD4 T cells remains incompletely understood. Previous studies identified an exhausted signature in HCV-specific CD8 T cells, particularly in those targeting conserved epitopes. Whether a similar signature exists in CD4 T cells and how immune escape mechanisms affect these cells is unclear. This study aimed to compare HCV-specific CD4 T cells in patients with chronic infection, after DAA therapy, and in individuals with spontaneous resolution on a single-cell level, while investigating CD4 immune escape mechanisms.

Method: HCV-specific CD4 T cells were analyzed in peripheral blood mononuclear cells (PBMCs) with MHC class II tetramers by flow cytometry and single-cell RNA sequencing (scRNAseq). Immunodominant viral epitopes were characterized through viral sequencing and mutation analysis in relation to HLA-DRB1 alleles

with Fisher's exact test. Epitope-specific CD4 T cell clones were tested for cytokine responses to mutated and non-mutated epitopes to assess mutation recognition by CD4 T cells. scRNAseq was performed on HCV-specific CD4 T cells from chronic patients (n = 4, 459 cells), post-DAA therapy (n = 2, 464 cells), and spontaneous resolvers (n = 3, 697 cells).
Results: HCV-specific CD4 T cell responses in chronic HCV patients (n = 153) were lower in frequency compared to individuals with spontaneous resolution (n = 6). HCV-specific CD4 T cells from post-DAA and spontaneously resolved patients clustered differently with higher CD127 expression and lower CD95 and PD-1 expression in spontaneous resolvers. scRNAseq revealed reduced expression of interferon-stimulated genes in HCV-specific CD4 T cells after DAA therapy compared to their chronic counterparts ($p < 0.001$). Circulating viral mutations were genotype-specific and were not associated with the corresponding HLA-DRB1 alleles. HCV-specific CD4T cell clones recognized both mutated and non-mutated epitopes equally, while artificially MHC class II anchor residue mutated epitopes were not recognized.
Conclusion: All circulating amino-acid substitutions within CD4 T cell epitopes were recognized by HCV-specific CD4 T cell clones targeting the wild-type sequence. Thus, loss of viral escape mutations of HCV-specific CD4 T cells does not appear to be a dominant mechanism of viral persistence. DAA-mediated HCV clearance is associated with a downregulation of interferon signatures on HCV-specific CD4 T cells, however, they still maintain phenotypic differences to those from spontaneous resolvers.

FRI-259-YI
Phenotypic characterization of untreated chronic hepatitis B infected individuals in an ethiopian cohort using fixed whole blood samples
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Background and aims: The immunophenotype of African patients with chronic hepatitis B virus (HBV) infection is rarely described despite the large burden of disease on the African continent. In this study we used a direct cryopreservation method and flow cytometry to investigate the immune cell phenotype of untreated, chronically HBV-infected Ethiopian patients across distinct clinical stages of infection.
Method: Untreated chronic HBV-infected patients were enrolled in Adama, Ethiopia. Patients were grouped into immune control, inflammation, cirrhosis, and grey zone based on structured medical history, clinical examination, ultrasound, elastography, ALT, HBV DNA quantification and APRI score. Whole blood samples were directly cryopreserved using Cytodelics whole blood stabiliser for deferred experimentation. Samples were thawed, stained using a 27-colour flow cytometry panel, and analysed to define immune cells including B cells, T cells, natural killer (NK) cells. Analysis was restricted to samples with more than 10,000 events in the $CD45^+$ immune cell gate (n = 302).
Results: Analysis of immune cell phenotypes within the distinct chronic HBV groups demonstrated differences in the immune cell frequencies. In detail, frequencies of CD3+ lymphocytes (defined as CD15-CD45+CD3+CD19-) were significantly lower in the cirrhosis group compared with the immune control ($p < 0.0001$), inflammation ($p = 0.01$), and the grey zone ($p = 0.01$) groups. Among T cells effector memory CD4 cells (CD45RA+CCR7-) were significantly lower in the cirrhosis group compared with both the inflammation ($p = 0.04$) and the grey zone ($p = 0.04$) groups. B cells were also notably altered in the cirrhosis population with memory B cells (IgD-CD27+) significantly lower in the cirrhosis group compared with the immune control ($p = 0.003$) and grey zone ($p = 0.009$) group. Furthermore, naïve B cells (IgD+CD27-) were significantly higher in the cirrhosis group compared to the immune control ($p = 0.014$) and grey zone ($p = 0.021$) group. In addition to changes in the adaptive immune cell compartment, we also observed changes in the distribution of innate immune cells within the distinct clinical groups with $CD56^{dim}$ NK cells (defined as CD15-CD45+CD3-CD19-$CD56^{dim}$) being significantly lower in the cirrhosis group compared to both the immune control ($p = 0.009$) and inflammation ($p = 0.01$) group.
Conclusion: Our findings indicate that untreated, chronic HBV-infected patients with cirrhosis in this Ethiopian cohort exhibit a unique immunophenotype compared to other clinical groups. They display a tendency towards a naïve rather than effector phenotype which could be contributing to ongoing tissue damage and failure to control infection. Additionally, our study underscores the effectiveness of Cytodelics as a reliable reagent for the cryopreservation of single cells from whole blood in resource-limited settings.

FRI-260
Identification of hepatitis B virus epitopes presented by human leukocyte antigen A*11:01 as potential targets for immunotherapy
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Background and aims: T cell-based therapies could play a key role in combination strategies directed towards functional cure of chronic hepatitis B (CHB). Successful drug development requires identification of viral epitopes that are prevalent in affected populations, conserved across genotypes, and abundantly expressed on hepatocytes through different disease stages. However, the database of validated HLA class I epitopes under-represents alleles in high CHB burden regions. Since human leukocyte antigen (HLA) -A*11:01 is highly prevalent (~50%) in China, we interrogated the hepatitis B virus (HBV) proteome for HLA-A*11:01-restricted epitopes using immunopeptidomics and bioinformatics, prioritizing HBV envelope (Env) due to the importance of hepatitis B surface antigen loss as a treatment goal.
Method: HLA-A*11:01-transduced PLC/PRF/5 cells containing integrated HBV DNA and HEK293 T cells transduced with both HLA-A*11:01 and HBV Env were both subjected to immunopeptidome analysis using HLA-A*11:01 immunopurification followed by liquid chromatography-tandem mass spectrometry. Predicted affinities of identified peptides for HLA-A*11:01 were determined using NetMHCpan-4.1. Variant frequencies were determined using publicly available HBV genotype B and C sequences.
Results: Five and six unique HLA-A*11:01-presented HBV Env peptides were identified from the PLC/PRF/5 and HEK293 T cells, respectively, with up to 5 variants (>5% frequency) associated with each of these peptides. Predicted affinities of these variants for HLA-A*11:01 ranged from ~5 nM to 23 µM, with 3 peptides predicted to have <500 nM affinity across genotypes B and C. Two of the three peptides were highly conserved length variants (10mer and 11mer) with a single sequence for each representing >90% of the sequences analysed. However, these peptides contain three consecutive cysteine residues which, due to complexities associated with disulphide bond formation, presents a challenge for drug development. The other peptide showed more acceptable biochemical properties for target selection despite greater genotypic variation (5 variants).

Conclusion: Our highly sensitive immunopeptidomic and bioinformatic strategy identified three HLA-A*11:01-binding HBV Env peptides as potential targets for T cell therapies. This work highlights the importance of evaluating prevalent HLA alleles in tandem with anticipated viral genotypic variation to ensure that drug development is tailored to people with CHB.

FRI-261

Persistent immune defects in innate-like CD8 T cells despite antiviral therapy in chronic hepatitis B

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Background and aims: A novel population of CD8 T cells straddling the boundary between innate and adaptive immunity, has been identified. CD56+ CD8 T cells are distinguished from other CD8 T cell subpopulations, exhibiting high expression of NK receptors (NKR's) exerting NKR mediated effector functions in a TCR-independent manner, associated with global 'bystander' activation. Previous studies have recognised the role of bystander CD8 T cells correlating with liver inflammation. Evaluating this understudied cell population may provide insights into reasons for immunological failure of novel therapies for chronic hepatitis B (CHB) cure, where these cells may contribute to immunopathology.
Method: We studied the phenotypic and functional properties of global blood-circulating CD8 T cells from treated and untreated (treatment-naïve) CHB patients compared to healthy controls (HC). The proportion of activated CD8 T cells, expression of NKRs and functional profile of these cells was analysed by multi-parameter flow cytometry. Transcriptomic analysis of CD8 T cells was performed in a subset of patients.
Results: The proportion of activated (CD38+HLA-DR+) CD8 T cells expressing CD56 was significantly greater in CHB vs HC's, with a higher expression of NKRs (NKG2A, NKp30) on innate-like T cells (CD56+ CD8+). We noted the percentage of CD56+ CD8 T cells expressing NKRs were greater in subjects with 'immune active' disease (ALT >40, HBV DNA > 2,000) compared to immune control patients, reflecting their role in immunopathology. Contrarily, CHB subjects undergoing antiviral therapy (AVT), exhibited a reduced percentage of CD56+ CD8 T cells, however, NKR expression on global CD8 T cells remained significantly higher than in treatment-naïve patients. Undertaking transcriptomic analysis on sorted CD8 T cells, we observed mRNA expression of innate-like markers (KLRK1, NCR3) was higher in treated vs. untreated immune control patients indicating innate-like immune defects are not recovered by AVT. To determine cellular effector function, stimulation was undertaken with anti-CD3/CD28 (TCR-dependent) and IL-15 (TCR-independent). We noted IFNγ production was similar on CD56+ CD8 T cells with either stimulation method, but TNFα production was greater following IL-15 stimulation, indicating the capability of a differential functional profile in a TCR-independent manner.
Conclusion: We demonstrate the increased expression of a CD56+ CD8 T cells expressing NKR's in CHB patients, signalling via a TCR-independent manner, causing bystander innate immune defects. Further work is being undertaken for an in-depth evaluation of these cells to analyse the impact of AVT in the blood and liver of CHB patients, to further guide the development of therapeutic targets in the functional cure program.

FRI-262-YI

Isogenic studies of basal-core promoter and precore mutations in hepatitis B genotype c

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Background and aims: In hepatitis B virus genotype C (HBV-C), the basal-core promoter mutation (A1762T/G1764A, BCPM) and precore mutation (G1896A, PCM) have been associated with increased risk of liver cirrhosis and liver carcinogenesis. However, the underlying mechanisms remain elusive. To facilitate study of isogenic infectious HBV mutations in human hepatocyte chimeric mice (huFNRGs), we developed a streamlined approach to launch HBV infection using direct intrahepatic injection (IHI) of synthetic, recombinant HBV covalently closed circular DNA (rcccDNA).
Method: To assess the efficiency of rcccDNA IHI, we engineered and validated silent mutant barcodes and mixed these with wild-type (WT) at ratios ranging from 1:10 to $1:10^4$ to produce infectious HBV stocks. Next, we generated isogenic virus stocks of HBV-C WT, BCPM and PCM and performed infection experiments in huFNRG mice. We also obtained human serum and liver biopsy samples from 34 patients infected with HBV-C (14 WT, 14 BCPM, 5 BCPM and PCM, 1 PCM).
Results: rcccDNA IHI is highly efficient, allowing the launch of at least 10^4 rcccDNA molecules per huFNRG mouse. rcccDNA IHI was successful across all HBV genotypes tested (A-F) with a success-rate of 89.6%. Comparative studies of HBV-C variants (WT, BCPM, PCM) revealed similar viral kinetics but distinct antigen secretion profiles. Mimicking findings in human patients, no HBe-Ag secretion was observed in PCM-infected mice, with a ~90% HBe-Ag reduction in BCPM-infected animals compared to WT. Pulse-SILAC proteomic analyses identified variant-specific changes in the hepatocyte proteome and differential responses to interferon treatment in cultured human hepatocytes. RNA-seq revealed unique variant-dependent transcriptomic profiles associated with these isogenic variants in huFNRG mice. Ongoing efforts include comparing these experimental findings with RNA-seq data from obtained patient liver biopsies.
Conclusion: We established and validated a robust IHI-based method for efficiently generating infectious HBV serum from rcccDNA in huFNRG mice, enabling detailed studies of isogenic mutants. Our investigations revealed variant-specific transcriptomic and proteomic differences in BCPM- and PCM-infected mice, with translational relevance being explored through RNA-seq comparisons with human liver biopsy samples.

FRI-263-YI

Viral N6-methyladenosine modifications regulate hepatitis E virus infections

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Background and aims: The Hepatitis E virus (HEV) is annually responsible for up to 3 million symptomatic cases and approximately 70,000 deaths worldwide, making it the leading cause of acute viral hepatitis. Current treatments, including ribavirin and, in select cases, pegylated interferon-alpha, are not universally effective and are linked to severe side effects such as anemia, organ rejection, and teratogenicity. Therefore, elucidating the HEV life cycle, particularly the virus-host interactions that facilitate viral replication, is key to developing novel antiviral strategies against HEV. Interestingly, recent studies have shown that N6-methyadenosine (m6A) modifications play a role in regulating the replication cycles of both RNA (e.g., hepatitis C virus) and DNA viruses (e.g., hepatitis B virus). This study aims to explore the roles of m6A writers, readers, and erasers in the context of HEV infection.
Method: To assess the impact of m6A RNA modifications on HEV infection, we administered the methyltransferase METTL3 inhibitor STM2457 to HEV-infected hepatoma and primary liver cells in a dose-dependent manner, with subsequent screening for virus-positive cells using fluorescence microscopy. Additionally, HEV replicon-transfected cells were treated with the inhibitor to evaluate effects on viral replication via luciferase assay. For validation, siRNA-mediated knockdown of key m6A-related proteins, including writers, was performed, followed by infection experiments. Knockout efficacy was confirmed by western blot analysis. Moreover, STM2457's antiviral activity was confirmed in primary human hepatocytes by fluorescence microscopy of infected cells, and the regulation of METTL3 expression by HEV was assessed through western blotting.
Results: Our findings indicate that inhibiting m6A methylation through the use of STM2457 disrupts infection with the human-derived HEV-3 strain Kernow-C1 p6 at an effective half-maximum concentration (EC50) of ~ 10 nM. However, viral replication remains unaffected when in vitro transcribed RNA is transfected by electroporation. Moreover, the antiviral efficacy of STM2457 was confirmed in primary human hepatocytes, demonstrating an 80% reduction in infection at a 10 µM drug concentration. These findings were further validated by siRNA knockdown experiments, which demonstrated that the depletion of the m6A writer METTL3 and METTL16 by siRNAs decreased HEV infections by 41% and 12%, respectively.
Conclusion: A comprehensive understanding of the HEV life cycle, including virus-host interactions that facilitate virus infection, is essential for developing novel antiviral strategies against HEV. Our study identified m6A methylation as a crucial component of HEV biology and suggests that it represents a promising target for future antiviral interventions.

FRI-264

Variability of the hepatitis delta virus and the role of the interferon I in a superinfected mice model

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Background and aims: The hepatitis delta virus (HDV) is the most variable among the hepatitis viruses, mainly due to the loss of fidelity of the cellular RNA polymerase. The cellular enzyme ADAR1, whose expression is regulated by the intracellular interferon (IFN) pathway, enables the edition of the viral genome and the production of the large isoform of the delta antigen (HDAg). This study aimed to inspect the HDV genetic variability and the role of the type I IFN in an *in vivo* model of hepatitis B (HBV)- transgenic mice (HBVtg) super-infected with an adeno-associated vector carrying the HDV genome (AAV-HDV) and knocked-out for the IFNα/β receptor (HBVtgxIFNAR-KO).
Method: HBVtg and HBVtgxIFNAR-KO mice were injected with 5×10^{10} AAV-HDV or control vector (AAV-luciferase) viral genomes. The intrahepatic HDV RNA quasispecies (QS) was analyzed in the *HDAG* coding region (nucleotides- nt- 912–1298 in viral genome) through next-generation sequencing (MiSeq Illumina) at 7-, 21-, and 90-days post-injection (dpi). The QS composition was evaluated dividing it in fractions based on the variants' relative frequency (QFF), whereas the QS variability was studied by analyzing the nucleotide variations (SNVs) observed in at least two animals. The edition of the viral genome was calculated by considering the frequency of the variants with the A/G change in the edition site of the HDV genome.
Results: The composition of the *HDAG* QS was similar between the HBVtgxIFNAR-KO and WT mice at 7-dpi. Differently the proportion of emergent variants (frequency between 1% and the master) shows an upward trend in the next timepoints, especially in WT mice (19.6% and 30% at 21- and 90-dpi respectively, versus 12.8% and 19.8% in KO mice). In KO mice the edition of the viral genome was delayed related to the WT mice. At 7-dpi we observed the highest number of SNVs with a dominance of C/T transitions. Differently, at 21- and 90-dpi the changes were mainly A/G (changes that may be attributed to ADAR1) and T/C transitions. Among the observed SNVs, 10 were detected in all the timepoints, including the T431C (positions considering the *HDAG* ORF), whose frequency was higher and growing especially in WT mice ($5.6 \pm 4.6\%$, $13.4 \pm 5.2\%$ and $15.5 \pm 4.8\%$ at 7-, 21- and 90-dpi respectively versus $3.1 \pm 3.8\%$, $9.3 \pm 5\%$ and $8.8 \pm 3.6\%$ in KO). When considering the SNVs not-shared between the groups, at 21- and 90-dpi the WT mice presented a higher proportion of A/G and T/C changes than KO mice.
Conclusion: The different evolution of the composition of the viral QS between WT and KO mice suggests that the IFN may contribute to the intra-hepatic HDV variability. Most of the changes identified were A/G transitions, which are typically produced by ADAR1 enzyme. The common SNVs observed during the time might be indicative of the presence of hotspot of mutations in the HDV genome. Grant PID2021-126447OB-I00 funded by MCIN/AEI/ 10.13039/501100011033 and by ERDF A way of making Europe.

FRI-269

Developing personalised treatment pathways for hepatitis B using novel assays and fine needle liver aspirates

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Background and aims: Hepatitis B is the most common blood-borne virus infection and is incurable, requiring long-term suppressive antiviral therapy. Upon treatment cessation in selected HBeAg negative patients, 50–70% will relapse with risk of disease progression, ~30% will maintain virological control, and 0–20% will clear the infection (loss of HBsAg). These outcomes are difficult to predict from peripheral biomarkers alone as viral persistence is driven by intrahepatic covalently closed circular DNA (cccDNA) and integrated DNA (iDNA) which are challenging to quantify. We have developed novel assays that can detect cccDNA and iDNA in liver fine-needle aspirates (FNA) to predict relapse or cure (loss of HBsAg). We hypothesise that lower levels of cccDNA and iDNA predict viral clearance.
Method: We will recruit 130 patients who have been on long-term antiviral treatment with HBV DNA <20 IU/ml for ≥3 years, HBeAg negative, HBsAg <1000 IU/ml and are older than 18. Before stopping treatment, we will collect liver FNAs to measure intrahepatic cccDNA, iDNA and peripheral blood to measure biomarkers (HBV DNA, HBV RNA, HBsAg, HBcAg, HBeAg, ALT and peripheral blood mononuclear cells).
Results: To date we have obtained baseline FNAs from 30 patients and the procedure was well tolerated, with mild (45%) or moderate (55%) pain reported. Average recovery time was ~48 hours with minimal post-operative care. By staining cells with fluorescently-labelled myrcludex B (a hepatocyte-specific lipopeptide), we found an average of 3.3×10^5 hepatocytes per FNA. We have confirmed that our highly sensitive PCR-based assays can quantify cccDNA and iDNA in FNAs (requiring ~50 cells as minimum input). Patients have remained well past 6 months post treatment cessation with minimal flares overall. Some have cleared HBsAg and some have had to recommence treatment due to flares. Updated results will be presented.
Conclusion: We have developed highly sensitive and specific assays that can quantify HBV cccDNA and iDNA in minimally invasive liver FNAs. We will determine how well intrahepatic cccDNA and/or iDNA predict clinical outcomes after stopping antiviral therapy. We will also assess the correlation and performance of novel blood biomarkers as surrogate markers for HBV activity and host antiviral immune response. We aim to develop an integrated clinical algorithm to inform personalised treatment pathways, by identifying those who can safely stop treatment and achieve cure.

FRI-270

T helper 17 cell differentiation and the functional cure of chronic hepatitis B: insights from proteomic analysis and microRNA expression profiling of plasma-derived exosomes

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Background and aims: Recent studies have shown that exosomes are involved in the disease process of chronic hepatitis B (CHB), but there is a lack of research on the role of exosomes in hepatitis B surface antigen (HBsAg) seroclearance. This study aims to use proteomics and microRNA (miRNA) high-throughput sequencing methods to compare the composition differences of plasma exosomes between HBsAg-positive hepatitis B e antigen (HBeAg)-negative CHB patients and CHB patients achieving HBsAg seroclearance, to provide new insights for discovering therapeutic targets in achieving a functional cure.
Method: Data-independent acquisition (DIA) mass spectrometry and small RNA sequencing were utilized to examine the dynamic profiles of exosome proteins and miRNAs in plasma exosomes extracted through ultracentrifugation (Optima XL-80 K, Beckman Coulter, United States) from treatment-naïve HBeAg-negative CHB patients (n = 10) and HBsAg seroclearance patients (n = 10). We employed three miRNA prediction tools: miRWalk (v3.0), mirDIP (v5.3.0.2), and TargetScan (v8.0) to identify the target genes of miRNAs. Bioinformatics and annotation analyses were studied using Geno ontology (GO) Enrichment Analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis and Gene set enrichment analysis (GSEA).
Results: A total of 104 differentially expressed proteins (DEPs) and 63 differentially expressed miRNAs (DE-miRNAs) were significantly altered when comparing patients achieving HBsAg seroclearance with HBsAg-positive HBeAg-negative patients, with absolute $\log_2$-(fold change) > 0.77 and > 1, respectively (all $p < 0.05$). The upregulated molecules in HBeAg-negative patients included liver-specific proteins, such as fructose-bisphosphate aldolase B (ALDOB), transcription factor (TF), and C-reactive protein (CRP), as well as miRNAs (miR-122, miR-192-5p, and miR-194-5p). GO analysis revealed a high enrichment of DEPs in multiple adaptive immune-related processes, while KEGG and GSEA analysis exhibited the involvement of the IL-17 signaling pathway ($p = 0.0002$ & 0.0004 respectively) and Th17 cell differentiation ($p = 0.003$ & 0.006 respectively). We identified several miRNAs from the let-7 family, notably let-7a-5p, which exhibited the highest expression abundance (Expr) (MeanExpr = 25825, $\log_2$(fold change) = − 1.9, $p < 0.05$) in all downregulated DE-miRNAs, with a target gene IL6R, identified to play a significant role in Th17 cell differentiation.
Conclusion: Our study for the first time described specific molecular pattern of plasma exosomes in CHB patients achieving HBsAg seroclearance. Exosomes can serve as a potential biomarker for assessing liver injury severity, with Th17 cell differentiation possibly playing an important role in HBsAg seroclearance, providing valuable diagnostic and therapeutic insights for advancing the pursuit of a functional cure.

FRI-271

Immune response patterns in HBeAg (-) chronic hepatitis B patients during NA treatment depends on the viral activity at baseline

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Background and aims: Chronic hepatitis B (CHB) persistence is linked to virus-specific adaptive immune dysregulation, mainly studied in HBeAg(+) patients. Immune reinvigoration involves reversing this exhaustion and restoring T cell function to improve immune control. However, immune responses during nucleos(t)ide analogue (NA) treatment in HBeAg(-) CHB patients remain under-explored. This study aims to analyze the T-cell response in HBeAg(-) CHB patients during NA treatment.
Method: We prospectively included 28 HBeAg(-) patients undergoing NA treatment. T-cell response was assessed by FACS on PBMCs stimulated with HBV-specific peptides, focusing on frequencies of CD3+, CD4+, CD8+, and (CD4/CD8+) IFN-γ+ T cells. Serum markers (HBV DNA, HBV RNA and HBsAg) were analyzed at baseline (BL), early therapy (≤6 months), and advanced therapy (>6 months), and correlated with T cell profiles. Based on HBV replication levels at BL patients were grouped in group A (HBV DNA >10,000 IU/ml, n = 15) and group B (HBV DNA <10,000 IU/ml, n = 13).
Results: At BL, patients in group A had significantly higher HBV RNA levels than patients in group B ($p = 0.006$), while median frequencies of CD3+, CD4+, and CD8+ T cells were similar between both groups. However, CD4+ IFN-γ+ T cells (1.0% vs. 0.43%, $p = 0.07$) and CD8+ IFN-γ + T cells (3.8% vs. 1.5%, $p = 0.08$) were higher in group A. During

treatment, CD4+ T cells increased (57.5% to 67.7%, p = 0.07), while CD8 + T cells decreased (39.5% to 28.0%, p = 0.09) from BL to early therapy in group A. Median frequencies of CD4+ IFN-γ+ and CD8+ IFN-γ+ T cells also decreased significantly from baseline (1.0% and 3.8%) to advanced therapy (0.3% and 1.0%), respectively (p = 0.001 and p = 0.005). In contrast, in group B, CD8+ IFN-γ+ T cells increased significantly from BL to early therapy (1.51% to 5.28%, p = 0.02), and a significant negative correlation was observed between CD8+ IFN-γ+ T cells and HBV DNA at BL (r = –0.712, p = 0.031).

Conclusion: Patients with lower HBV replication exhibited an increase in CD8+ IFN-γ+ T cells during NA treatment, suggesting a more robust immune response. Our findings suggest that HBV particles influence immune kinetics and treatment outcomes. Further research is needed to explore the long-term impact of these immune changes on treatment efficacy and response to NA treatment withdrawal.

FRI-272

On treatment modeling of ALT, HBVDNA and HBsAg in NUC-treated HBeAg-negative CHB patients helps to characterize the immune response and may predict clinical relapse after discontinuation

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Background and aims: Undetectable HBsAg and HBV DNA off-therapy (Functional Cure, FC) is the endpoint of chronic hepatitis (CHB) treatments. Nucleo(s)tide analogues (NUCs) have modest impact on HBsAg decline, but treatment discontinuation (DC) increases the chance of FC with limited risk of severe relapses in patients (pts) with low HBsAg at the end of therapy (EOT). We investigated by mathematical modeling the on-treatment kinetics of ALT, HBV DNA and HBsAg in HBeAg negative CHB before NUCs DC to gain insights on the mechanisms leading to FC.

Method: Model assumptions: 1) serum HBsAg is produced by cccDNA and integrated DNA (intDNA) in variable proportions, 2) cccDNA may have an intrinsic decay upon NUC blocking of HBV DNA production, 3) cccDNA is not transmitted to daughter cells by division, whereas intDNA is transmitted, 4) specific killing of HBV infected cells with cccDNA causes the release of ALT. Therefore, ALT levels at the start of treatment (SOT) provide the initial estimate of the Infected cells with cccDNA (Ic_0), and ALT decline in the first 3–6 months of therapy of their immune mediated clearance rate constant (δ_0), which tends to decrease by negative feedback according to the fraction of Ic overtime $(Ic_t/Ic_0)^k$, where k can range 0–1. NUCs antiviral effect is described by an initial block of HBV DNA production (ε) followed by a slower exponential decline, with time constant ϕ, and asymptotic value γ. Individual fitting of ALT, HBV DNA and HBsAg in 23 pts throughout treatment (19 ETV, 4 TDF) provided the final calculation of the model parameters.

Results: The model was applied in 14 pts (12 M, median age 45.5y, gt A:1, D:2, C:4, B:6) with clinical relapse (CR: ALT>2xULN and HBV DNA > 2000 IU/mL) and in 9 (8 M, median age 50.5y, gt C:3, B:6) without CR (noCR). Median NUCs duration was comparable in CR and noCR [2.8 (1.9–3.2) vs 2.1 (1.6–13.8)y, p = 0.734], same for the time of HBsAg clearance after NUCs DC [4.5 (2.2–5.5) vs 3.65 (0.3–5.6) y, p = 0.277]. Median ALT at SOT was similar in CR and noCR [167 (56–681) vs 151 (41–1563) U/L, p = 0.403], as well as Log HBV DNA [6.06 (5.04–6.74) vs 5.74 (3.42–8.05) p = 0.439], whereas Log HBsAg tended to be higher in CR [2.90 (2.20–3.95) vs 2.31 (0,89–4.42), p = 0.053]. Model computed parameters showed numerically higher Ic_0 in CR vs noCR [43.9 (10.1–62.8) vs 16.2 (4.2–94)%, p = 0.201], and longer Ic_0 half-lives [25.2 (17.9–73.6) vs 18.2 (8.9–64.50) days, p = 0.179]. The clearance rate of Ic slowed-down significantly more in CR than in noCR [k value: 0.65 (0.50–0.85) vs 0.49 (0.30–0.75), p = 0.023]. The estimated non-cytolitic decline of cccDNA was slower in CR vs noCR [0.001 (0.0001–0.005) vs 0.0001 (0–0.001) day^{-1}; p = 0.011]. The parameters describing direct antiviral effect (ε,ϕ,γ) were not significantly different.

Conclusion: Modeling the dynamics of HBV in pts with or without a clinical relapse after NUCs discontinuation, suggests that the better outcome depends on the persistence of a reactive immune response during therapy, with the contribution of non-cytolitic decline/inhibition of cccDNA.

FRI-273

Experimental HCV infection identifies ribosomal RNA 2′-O-methylation sites also affected across all etiologies and stages of chronic liver diseases

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Background and aims: Ribosomes are mandatory factors for cell translation. They exhibit important heterogeneity when considering chemical modifications of ribosomal RNAs (rRNAs), events known to quantitatively and qualitatively alter translation. 2′-O-methylation (2′-O-Me) is their most abundant alteration, present in more than a hundred positions on all rRNA types. 2′-O-Me rates in defined rRNA positions have been identified as pivotal for acute myeloid leukemia or breast cancer progression. RNA viruses completely rely on cellular ribosomes for persistence, as they are unable to code for their own. Thus, oncogenic viruses are likely relevant models for the study of 2′-O-Me, especially if hepatotropic, as the liver is considered the organ with the most active protein synthesis. In this context, we considered the mutual impacts between 2′-O-Me and the hepatitis C virus (HCV), which remains a useful tool to study hepatic pathogenesis, and of which replication intensely relies on cellular translation due to its (+) RNA status.

Method: For better clinical relevance, *in vitro* infections of Huh7.5 cells were performed using the HCV genotype 1 strain TNcc-HI. 2′-O-Me scores were measured by RiboMeth-seq, a recognized quantitative method, in a variety of *in vitro* and clinical samples, obtained from one local (Lyon U. Hospital) and one national (French Liver Biobank) chronic liver disease (CLD) cohort, spanning all main etiologies and fibrosis stages (n = 90 cases), considering normal livers (n = 16) as references. RNAi depletion of the 2′-O-methyltransferase fibrillarin (FBL) was achieved to decrease the global rate of 2′-O-Me to study the implication of 2′-O-Me in HCV replication. Results were confirmed by specifically mutating the 2′-O-Me domain of FBL.

Results: *In vitro*, we demonstrated that 2′-O-Me was decreased on two rRNA positions in HCV-infected conditions compared to controls. While the global impairment of 2′-O-Me decreased by ≈50% intracellular HCV RNA levels, it triggered a near-total collapse of HCV proteins core and NS5A, demonstrating i) the importance of 2′-O-Me for viral replication, and ii) a potential new and likely decisive layer of regulation for HCV RNA translation. Of direct interest in the understanding of CLD pathogenesis, the virally induced 2′-O-Me profile persisted after viral clearance in the clinic. Strikingly, both HCV-impacted rRNA positions *in vitro* were seemingly regulated in

human liver biopsies derived from all main etiologies and fibrosis stages. Thus, as demonstrated in other pathologies, the regulation of 2′-O-Me could be of substantial importance in hepatic pathogenesis.
Conclusion: This work highlights the potential importance of ribosome chemistry regulation in hepatic pathogenesis. It also provides preliminary grounds for the identification of processes leading to these molecular alterations through viral infection.

FRI-274

Novel, high-sensitive immunoassays for phosphorylated and non-phosphorylated HBcAg detection

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Background and aims: Current HBV guidelines for treatment eligibility are based on HBV DNA viral load levels. Specifically, for HBV infected patients with DNA levels ≥2,000 IU/ml (HBeAg-) or ≥20,000 IU/ml (HBeAg+), antiviral therapies are recommended. However, HBV molecular assays to monitor HBV DNA levels are often unavailable or unaffordable in low- and middle-income countries (LMIC). We previously developed two novel HBcAg immunoassays to specifically detect non-phosphorylated HBcAg as surrogate marker for HBV DNA-containing particles (referred as HBcAg) and phosphorylated HBcAg (referred as P-HBcAg), which represents non-HBV DNA-containing particles. HBcAg and P-HBcAg correlate best with HBV DNA as compared to HBV core-related antigen (HBcrAg). Here, we describe improved P-HBcAg/HBcAg assays with superior performance and higher sensitivity that should enable decisions to put patients on antiviral therapy.
Method: The improved P-HBcAg and HBcAg assays use specific monoclonal antibodies to capture and detect either non-phosphorylated or phosphorylated HBcAg that are secreted from HBV infected hepatocytes into the blood stream. P-HBcAg and HBcAg signals are measured as relative light units (RLUs) on an Abbott ARCHITECT. We analyzed single timepoint specimens from HBV infected patients with viral loads ranging from 10^2 to 10^8 HBV DNA IU/ml.
Results: Several factors were optimized, including new monoclonal antibodies, to increase the limit of quantification (LOQ) by ~20-fold for P-HBcAg and ~60-fold for HBcAg, respectively. Serial dilutions of specimens from HBV infected patients revealed that P-HBcAg could be detected at HBV DNA levels as low as 60 IU/ml. HBcAg, which represents infectious HBV DNA-containing particles and is the least abundant antigen, is still detectable at HBV DNA levels as low as 6,000 IU/ml.
Conclusion: The ability to specifically detect low abundant P-HBcAg/HBcAg levels at the lower limit of HBV DNA levels that qualify for treatment eligibility provides additional insights for disease staging. The assays have the potential to be made available at lower cost compared to molecular assays and are more easily deployable in low- and middle-income countries where HBV diagnosis and verification of response to therapies are most needed.

FRI-275

Characterization of antigen specificity of T cell responses and HBV neutralization activity in a cohort of patients who achieved HBV HBsAg loss

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Background and aims: The optimal therapeutic goal for chronic hepatitis B (CHB) is achieving functional cure (FC), defined as HBsAg loss with or without appearance of anti-HBs antibodies. However, the mechanism underlying HBsAg loss in patients with CHB is poorly understood. Here we characterize the HBV antigen specificity of T-cell response and neutralizing antibody responses in FC compared to the matched group of CHB patients.
Method: PBMCs from 19 FC and 22 CHB patients were analysed by ex vivo IFN-γ ELISpot assay with HBsAg, core, and polymerase (Pol) peptide pools. Greater than 45 background-subtracted IFN-γ SFC/million PBMC was considered a positive signal for each peptide pool. HBV neutralization activity was evaluated in primary human hepatocytes (PHH) infected with HBV GT A-D in the presence of serially-diluted plasma from 66 FC and 8 CHB patients. Neutralization titer for each plasma sample was defined as the fold-dilution that resulted in 50% inhibition of HBV infection. Samples from FC patients were collected at an estimated time ranging from 3 to 46 months after HBsAg loss.
Results: A higher percentage of individuals with HBsAg-specific T cell responses were observed in FC (9/19, 47%) as compared to CHB patients (3/22, 14%; $p < 0.05$, Fisher's exact test). The mean magnitude of HBsAg-specific T-cell response was higher in FC than in CHB (77 vs 21 SFC/million; $p < 0.05$, student t-test). The number of patients with T cell responses against at least one HBV antigen was also higher in FC (15/19, 79%) vs. CHB patients (12/22, 55%), as was the number of patients with T cell responses against more than one HBV antigen (7/19, 37% FC vs. 3/22, 14% CHB). HBV neutralization activity was detected in 25/66 FC (38%), with 5/66 (8%) exhibiting neutralization activity at a high titer of >500 against HBV GT A-D. No HBV neutralization activity was detected in CHB plasma (N = 8).
Conclusion: In this cohort of FC and CHB patients, FC was associated with a higher frequency of detectable peripheral HBsAg-specific T cell responses and T cell responses to more than one HBV antigen. In addition, FC is associated with the emergence of HBV-neutralizing antibodies in a subset of patients.

FRI-276-YI

Early kinetics of HBV and HDV serum and intrahepatic markers during and after liver transplantation: impact of HBIG and baseline HBsAg levels

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Background and aims: Hepatitis B virus (HBV) remains a common indication for liver transplantation (LT), with graft reinfection being universal, despite the removal of the infected explant, and the use of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NUCs). The aim of this study was to investigate HBV and hepatitis D virus (HDV) kinetics in serum and liver samples during and immediately after LT to elucidate mechanisms of graft infection.
Method: Between 2020 and 2023, 12 HBV LT recipients (5 HDV-coinfected) were prospectively enrolled. Serial serum samples were collected every 15 minutes during LT and at regular intervals up to 12 months post-LT. HBsAg and HDV-RNA kinetics were analysed using piecewise linear fitting, stratified by HDV-coinfection and HBIG

administration. A plateau in HBsAg was defined as a slope not statistically different from zero. Liver tissue was obtained from explants and grafts (at reperfusion, 3, and 12 months post-LT) to assess intrahepatic viral markers (iHBV-DNA, cccDNA, iHDV-RNA) and antigens (HBsAg, HDAg).
Results: At LT, all patients were on NUCs, and only five patients had detectable HBV-DNA. After LT, serum HBV-DNA became undetectable within 48 hours in all patients. The 7 HBV-monoinfected patients all had baseline HBsAg $<10^4$ IU/mL. During anhepatic and reperfusion phases, HBV monoinfected patients who received HBIG had a rapid HBsAg loss (HBsAg clearance 5 days, t1/2 = 4.2 hours), whereas in those who did not receive HBIG, HBsAg slope plateaued, remaining near pre-treatment levels. In HDV-coinfected patients, all of whom received HBIG, HBsAg clearance during anhepatic and reperfusion phases was primarily influenced by baseline HBsAg levels. Patients with baseline HBsAg $< 10^4$ IU/mL (n = 2) cleared HBsAg within 6 hours (t1/2 = 6–9 hours), whereas those with baseline HBsAg $> 10^4$ IU/mL (n = 3) required up to 30 days to clear HBsAg (t1/2 = 4 days). HDV-RNA kinetics paralleled HBsAg, with rapid HDV declines in patients with lower baseline HBsAg (t1/2 = 2 minutes), but plateaued in those with higher baseline HBsAg, independent of baseline HDV-RNA levels.
Total iHBV-DNA was detected in all explanted livers, while cccDNA exclusively in HBV monoinfected patients. In contrast, in reperfusion and follow-up graft biopsies, intrahepatic viral markers (iHBV-DNA, cccDNA, iHDV-RNA) were absent, except in 1 HDV-coinfected patient with low levels of iHDV-RNA and HBsAg/HDAg staining at 3 months, despite negative serum markers.
Conclusion: HBIG administration accelerates HBsAg clearance in the immediate post-LT period only in patients with low baseline HBsAg levels. Circulating HBsAg early after LT may explain HBV and/or HDV entry into the graft, as a residual portion of HBsAg may harbour complete virions. However, the absence of intrahepatic HBV replication markers after LT suggests infection of very few hepatocytes and may explain the inability of HDV to complete its viral cycle.

FRI-277

CD16+ γδ T cells are associated with antibody-dependent cellular cytotoxicity and viral control in chronic HBV infection

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Background and aims: Chronic HBV infection (CHB) remains a significant global health challenge, with the immunological mechanisms underlying functional cure still not fully understood. γδ T cells, a specialized subset of T cells abundant in the liver, are crucial for immune defense but remain poorly characterized in CHB. Our analysis identified a negative correlation between CD16-positive γδ T cells and HBcrAg, a marker of intrahepatic HBV replication, suggesting their potential role in viral control and antibody-dependent cellular cytotoxicity (ADCC); emphasizing the need for further research.
Method: Therefore, we analyzed γδ T cells in individuals with acute HBV infection (n = 13) and CHB (n = 57) using spectral flow cytometry and single-cell RNA sequencing, as well as HBV viral markers. To assess ADCC activity, isolated γδ T cells and NK cells from HBV patients (acute and chronic) or cord blood from healthy individuals were stimulated with polyclonal HBsAg-specific antibodies.".
Results: Our results revealed that $CD16^+$ γδ T cells, but not $CD16^+$ NK cells, negatively correlate with HBcrAg levels in CHB. These γδ T cells exhibited high expression of cytotoxic markers such as granzyme B, perforin, and NKG2D. Upon antibody stimulation with, they showed increased production of IFN-γ, TNF-α, and CD107a, emphasizing their ADCC functionality. *Ex vivo* staining further demonstrated that $CD16^+$ γδ T cells were strongly associated with ADCC activity in CHB and acute HBV cases. Conversely, γδ T cells from cord blood, with low CD16 expression, lacked ADCC functionality.
Conclusion: This study suggests a critical role of $CD16^+$ γδ T cells in controlling HBV through ADCC during CHB. The diminished presence or functionality of $CD16^+$ γδ T cells in cord blood may contribute to the high rates of CHB in vertical transmission, offering insights into potential therapeutic targets focused on γδ T cell-mediated ADCC.

FRI-278

Ubiquitinated hepatitis D antigen induced specific cytotoxic T lymphocyte responses inhibited HDV replication via JAK/STAT pathway in HDV infected liver organoids

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Background and aims: Hepatitis D virus (HDV) infection induces the most severe form of human viral hepatitis. Poor adaptive immune responses could result in persistent HDV infection, and virus-specific CD8+T cell response plays a significant role in the eradication of HDV. However, the impact of Ub-S-HDAg on CD8+T cells in HDV is unknown. Here, we aimed to investigate the anti-viral effect and mechanisms of Ub-S-HDAg in HDV infected liver organoids.
Method: Induced pluripotent stem cells were differentiated into hepatocyte-like cells (HLCs) and subsequently seeded onto inverted colloidal crystal (ICC) scaffolds. The HLC-ICC liver organoid system was co-infected with HBV and HDV particles. The ubiquitinated small Hepatitis D antigen (Ub-S-HDAg) recombinant lentiviral plasmid was constructed and transfected into human dendritic cells (DCs), which were then co-cultured with T cells. The levels of cytokine secretion by $CD8^+$ T cells and their antiviral efficacy were subsequently evaluated. Additionally, transcriptomic sequencing and bioinformatics analyses were conducted to elucidate the immune regulatory mechanisms of Ub-S-HDAg.
Results: In this study, we successfully established a model capable of stably expressing HDV. The results demonstrated that Ub-S-HDAg significantly promoted DC maturation, enhanced CD8+ T cell proliferation, and strengthened HDV-specific cytotoxic T lymphocyte (CTL) responses. Additionally, in the Ub-S-HDAg group, CD8+ T cells exhibited significantly elevated secretion of IFN-γ, IL-2, IL-12, and TNF-α, while HDV RNA viral load and HDAg levels were markedly reduced compared to other groups. Both KEGG pathway enrichment analysis and GSEA analysis suggested that DCs transfected with Ub-S-HDAg promote the activation of CD8+ T cells via the JAK/STAT pathway, exerting antiviral effects in liver organoids.
Conclusion: Overall, our findings indicate that Ub-S-HDAg induces DCs maturation, which in turn promotes CD8+ T cell differentiation and elicits a specific cellular immune response via the JAK/STAT pathway in HDV-infected liver organoids, thus providing a potential therapeutic approach for HDV eradication.

FRI-279

Adaptive NK cells are expanded in CMV-positive patients with chronic hepatitis B or hepatitis D and remain elevated after initiation of antiviral treatment

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Background and aims: Cytomegalovirus (CMV) infection leads to expansion of adaptive natural killer (NK) cells, characterised by expression of NKG2C or FcepsilonRIgamma. CMV infection is often associated with chronic hepatitis B virus (HBV) and chronic HBV/hepatitis D virus (HDV) infections. The aim of this study was to investigate adaptive NK cell responses in CMV positive $^{(+)}$ versus CMV negative $^{(-)}$ healthy controls (HC), HBV and HBV/HDV infected patients.
Method: We investigated the phenotype and function of adaptive NK cells in a cohort of 44 HBV-positive patients: 16 (7 CMV$^-$, 9 CMV$^+$) with chronic infection (ciHBV), 24 (8 CMV$^-$, 16CMV$^+$) with chronic hepatitis (chHBV), 4 CMV+ with liver cirrhosis (lcHBV) and 12 CMV$^+$ patients with chronic (ch) HBV/HDV hepatitis and compared with 10 HC (3 CMV$^-$, 7 CMV$^+$). Chronic infection and chronic hepatitis were defined according to EASL guidelines. Follow-up samples after initiation of antiviral therapy (Tenofovir/Entecavir for HBV mono-infected, Hepcludex for HBV/HDV coinfected) were available for eight HBV and eight HBV/HDV coinfected patients.
Results: There is an increase in adaptive NK cells, particularly in the proportion of FcepsilonRIgamma-negative $^{(-)}$ CD56dim cells in CMV$^+$ ciHBV and chHBV patients ($p < 0.0001$) compared to their CMV$^-$ counterparts. More strikingly, this expansion was further increased in CMV$^+$ HBV and HBV/HDV patients with chronic hepatitis vs. CMV$^+$ HC ($p = 0.041$) and ciHBV ($p = 0.006$). FcepsilonRIgamma$^{(-)}$ CD56dim cells have higher expression of NKG2C, CD57, CD95, CD25, ILT2 and lower expression of Siglec-7, Ki67 and CD69 ($p < 0.0001$) compared to FcepsilonRIgamma$^{(+)}$ CD56dim non-adaptive NK cells. In addition, these adaptive NK cells have a higher production of Granzyme B and Eomes, but a lower production of T-bet. The frequency of FcepsilonRIgamma$^{(-)}$ CD56^{dim} cells directly correlates with viral replication in chHBV patients ($p = 0.014$). One year after initiation of therapy in patients with chronic hepatitis (HBV and HBV/HDV), the frequency of adaptive cells does not change significantly, but the expression of activation markers (CD25) decreases. After stimulation by antibody dependent cellular cytotoxicity (ADCC), adaptive NK cells show higher CD107a degranulation ($p < 0.0001$) and IFNgamma release ($p = 0.007$) compared to non-adaptive NK cells.
Conclusion: Chronic viral hepatitis B induces high level FcepsilonRIgamma$^{(-)}$ CD56^{dim} cell expansions in CMV$^+$ individuals and this does not change after initiation of therapy with nucleoside/nucleotide inhibitors. Adaptive NK cells have an activated profile and predominantly effector functions compared to non-adaptive NK cells. We hypothesise that the higher cytotoxic activity and high CD95 expression may be involved in the development of liver fibrosis.

FRI-280

Hepatitis delta virus infection hotspots in Ethiopia: a multicenter study

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Background and aims: Individuals co-infected with hepatitis B virus (HBV) and hepatitis D virus (HDV) are at high risk of developing a much faster progression of severe liver disease, including cirrhosis, hepatocellular carcinoma and liver decompensation as compared to those with HBV mono-infection. Ethiopia is endemic for HBV; however, little is known about the HDV prevalence outside the capital city. In the present study, we investigated the HDV burden in three regions of Ethiopia. The objective was to assess the prevalence of HDV specific antibodies (IgG) among HBsAg carriers in selected three regions of Ethiopia.
Method: A cross-sectional study was conducted among 1997 adult (18 years or older) patients with chronic HBV infection from May 2022 to April 2024. The study participants were recruited at four newly established hepatitis B treatment centers located in Adama, Jimma, Jigjiga and Dubti. Serum were investigated for HDV antibodies using a novel pan-genotype specific in-house competitive enzyme-linked immunosorbent assay (ELISA). Results were confirmed with a commercial ELISA method and anti-HDV positive samples were tested for HDV RNA using a commercial real-time PCR assay. HDV genotyping was determined for RNA-positive samples by Sanger method. Mann-Whitney U tests were used to compare laboratory results between anti-HDV positive and negative individuals.
Results: The median age was 30 years old (interquartile range (IQR) 25–38) and 53.0% (1059/1997) were men. The overall HDV seroprevalence was 5.3% (105/1997), but with profound geographical variations. Dubti (Afar region) had the highest HDV-specific antibodies seroprevalence with 16.9% (84/498), followed by Jimma (Oromia region) with 2.6% (13/500), Adama (Oromia region) with 1.4% (7/499), and Jigjiga (Somali region) with 0.2% (1/500). Of all anti-HDV positive samples, 63.8% (67/105) had detectable HDV RNA with a median viral load of 3.20 log10 IU/ml (IQR 1.6–5.3). All strains were HDV genotype 1. Anti-HDV positive patients had higher median values of Alanine aminotransferase 49 vs. 26 U/L ($p < 0.001$), Aspartate aminotransferase (AST) 45 vs. 26 U/L, ($p < 0.001$) and AST to platelet ratio index (APRI) score 0.5 vs. 0.3, ($p < 0.001$), and lower HBV DNA viral load 222 vs. 720 IU/ml, ($p = 0.008$) compared to anti-HDV negative patients.
Conclusion: The overall prevalence of HDV in Ethiopia is intermediate and with marked geographic variations. Of note, the Afar region seems to be a hotspot for HDV. Whereas the neighbouring Somali region has a negligible HDV prevalence, despite sharing cultural similarities with Afar. This discrepancy underscores the need for further research into risk factors influencing HDV transmission. Such studies are important to come up with effective prevention strategies and control the spread of the disease.

FRI-285

A novel quintuplex long-amplicon droplet digital PCR assay reveals greater quantities of hepatitis B virus splice variants in people with HBV/HIV co-infection compared to HBV mono-infection

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Background and aims: In people with chronic hepatitis B (CHB), HIV increases the risk of liver failure and liver cancer. HIV also increases HBV replication but decreases response to pegylated interferon (IFN) treatment. HBV splice variants (spHBV) derived from the genomic intermediate, pregenomic RNA (pgRNA), are also associated with increased replication and resistance to IFN. Thus, spHBV may partially explain certain adverse outcomes of HIV on CHB.
Method: We developed a high dimensional long amplicon droplet digital PCR to quantify the major spHBV RNAs in serum. We applied this assay in a cross-sectional study to people with HBV/HIV co-infection (PWHHB, n = 61) and people with HBV mono-infection (PWHB, n = 86) prior to treatment in the MACS/WIHS Combined Cohort Study, directly quantifying pgRNA, sp1, sp2, sp3, sp8, and sp9. In a subset with semiannual longitudinal samples, we tracked spHBV expression in stored samples from these groups (gp): 1) PWHHB before HBV-active antiretroviral therapy (ART, n = 19), 2) PWHHB during ART (n = 19), 3) PWHB (n = 12) and PWHHB (n = 2) who lose HBV DNA without treatment (HBV recovery), 4) PWHB not on treatment (n = 9). Comparisons were made with Kruskal-Wallis tests (cross-sectional study) and generalized estimating equation modeling using the Wald test (longitudinal).
Results: In the cross-sectional analysis, PWHHB had higher median HBV DNA log10 IU/mL than PWHB (8.1 vs 7.4, p = 0.01); among PWHHB, females (n = 17) had higher levels than males (n = 44, p = 0.02). After adding up the five major spHBVs in each individual, the median log10 copies/mL was higher in PWHHB compared to PWHB (4.1 vs 3.4, p = 0.07) and similar between female and male PWHHB (4.3 vs 3.9, p = 0.59). Of total spHBV RNA, PWHHB compared to PWHB had greater median proportions of sp2 (5.2% vs 3.0%, p = 0.01), sp3 (1.1% vs 0.6%, p = 0.006), sp8 (4.7% vs 3.6%, p = 0.04), and sp9 (0.7% vs 0.4%, p = 0.08) but not sp1 (79% vs 79%, p = 0.99). In the longitudinal analysis (median 2 years) those without treatment (gp1 and 4) had spHBV quantities and proportions of total HBV RNA (pgRNA + spHBV RNAs) that remained stable (all p > 0.2). Gp2 had a pre-ART median 4.6 log10 copies/mL of spHBV that declined – 0.23/year (p < 0.05). Gp3 had a baseline median 3.6 log10 copies/mL of spHBV that declined – 0.24/year (p < 0.05). Comparing spHBV expression dynamics during the observed window of follow-up time (median 2 years), people during HBV recovery were more likely to have spHBV declines compared to PWHHB taking ART (p < 0.001).
Conclusion: PWHHB have more spHBV than PWHB, which may contribute to differences in outcome. Further, PWHHB during ART and people with HBV recovery have decreasing quantities of spHBV over time in contrast to PWHHB and PWHB not taking treatment where no significant changes over time were observed. Interestingly, PWHHB during ART and people during HBV recovery had similar baseline spHBV quantities and rates of decline, although people during recovery were more likely to have spHBV declines.

FRI-286

Pre-mRNA Processing Factor 4B kinase is associated with hepatitis B virus replication

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Background and aims: There were still no effective therapy to cure HBV. Cellular kinases are important in the life cycle of HBV. Through a kinome siRNA library screening, we identified that Pre-mRNA Processing Factor 4B (PRPF4B) was an essential gene for HBV replication. The aim of the study is to investigate the molecular mechanism of PRPF4B on HBV replication.
Method: HBV infected HepG2-hNTCP-C4 will be used in the study. siRNA mediated knock-down of PRPF4B will be done. Quantification of supernatant HBsAg and HBV DNA and cellular cccDNA will be performed. Proteiomic studies and Bioinformatics analysis will also be performed.
Results: After siRNA mediated knockdown of PRPF4B in HBV infected HepG2-hNTCP-C4 cells, supernatant HBsAg and HBV DNA and cellular cccDNA were significantly decreased. From the TCGA database we also found that PRPF4B was significantly associated with overall survival in HBV related HCC (Adjusted hazard ratio (AHR) was 2.11, 95% confidence interval (CI) was 1.08–2.51 and p-value was 0.005). Via string data bases we found several PRPF4B related candidate proteins were associated with HBV or other viruses replication. After knock-down of RPF4B with siRNA in HBV infected NTCP-HepG2 cells, the levels of the candidate proteins including SART1, CDK2, CDK9, PRPF31 and EFTUD2 were increased. In proteiomic studies we also found several proteins related to HBV replications were up and down- regulated after knockdown of PRPF4B.
Conclusion: Inhibition of PRPF-4B significantly reduced HBsAg, HBV DNA secretion and cellular cccDNA in HBV infected HepG2-hNTCP-C4 cells. Proteiomic studies and Bioinformatics analysis gave us more information. Our data is promising and PRPF-4B may be a new therapeutic target for future anti-HBV treatment.

FRI-287

Epigenetic viral footprint of chronic HDV infection in HBV co-infected chimeric mice

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Background and aims: Chronic infection with hepatitis D virus (HDV) causes the most severe form of viral hepatitis with accelerated progression of liver disease to hepatocellular carcinoma. Antiviral

therapy with bulevirtide reduces HDV load in patients with encouraging effects on liver disease parameters. However, effective chemopreventive strategies to attenuate liver disease progression and reliable biomarkers are urgently needed to improve disease management. Chronic diseases are often driven by epigenetic regulation, including histone modifications. Indeed, we have previously shown that chronic hepatitis C infection induces a pro-fibrotic transcriptional signature that is epigenetically regulated and partially persistent after antiviral therapy (Hamdane et al. Gastroenterology 2019; Juehling et al. Gut 2021). Here, we aim to determine the impact of chronic HDV infection on liver transcriptomics and epigenetics to identify molecular pathways of liver disease development and candidate biomarkers of liver disease progression.

Method: We infected human chimeric mice (FRG-NOD mice transplanted with human hepatocytes) with mock, HBV or HDV/HBV. Snap-frozen liver tissues were analyzed after 4 weeks post infection by bulk RNA-seq and ChIP-seq for histone marks associated with active transcriptional enhancers (H3K27ac and H3K4me1) and a mark for transcriptional repression (H3K27me3). In addition, we validated predicted biomarker candidates in the blood of infected chimeric mice and patients by ELISA.

Results: We identified 748 unique transcripts in the livers of HDV/HBV-infected mice compared to HBV mono- and mock-infected animals. Notably, most of these transcripts were highly upregulated by HDV infection and enriched for genes involved in HDV replication, inflammation, fibrosis, and cancer risk. Consistently, most of the genes encoding these transcripts are also associated with at least one histone mark associated with active enhancers, potentially representing a persistent viral footprint in the infected liver. Interestingly, 110 transcripts of this HDV signature potentially encode secretory proteins based on signal peptide prediction. The top candidate markers are positively correlated with transcript levels and are elevated in the blood of HDV-infected mice and patients.

Conclusion: We have uncovered an HDV-specific transcriptional signature that may be part of a persistent epigenetic viral footprint. Components of the signature are differentially secreted into the blood of infected animals and may therefore serve as risk markers for disease progression. Further work is underway to determine whether these proteins can serve as prognostic biomarkers for disease progression and/or therapeutic response, such as bulevirtide, and to predict and validate compounds capable of reversing risk-associated transcriptional signatures.

FRI-288

Synthetic interferon exhibits potent antiviral activity against HBV with the potential for an improved safety profile

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Background and aims: The type I interferon (IFN) system is a potent host innate immune defense mechanism against viral pathogens. Activation of this pathway occurs upon engagement of IFN with the host IFN alpha receptors 1 and 2 (IFNAR1/2) with subsequent signaling leading to the expression of >300 interferon stimulated genes (ISGs), many of which have direct antiviral activities. While type I IFNs and their derivatives have been utilized in patients as antiviral drugs, toxicity has limited widespread therapeutic use. Our goal is to develop synthetic interferons, SYNFERON™ molecules, that maintain the antiviral properties of type I IFN while reducing the inflammatory properties for an improved safety profile. SYNFERON molecules are bispecific antibody-derived domains comprised of one moiety that binds to IFNAR1 linked to a second moiety that binds to IFNAR2 that activate the IFN pathway with novel biological outcomes.

Method: Human PBMCs were treated with IFN or SYN1 and STAT1 phosphorylation was monitored by flow cytometry or ISG expression was measured using reverse transcription quantitative PCR (RT-qPCR). Primary human hepatocytes (PHH) were infected with HBV or co-infected with HBV and HDV and treated with IFN alpha (IFNα) or SYN1. HBsAg, HBV DNA and HDV RNA were measured. FRG liver-humanized mice were infected with HBV and treated with SYN1, pegylated IFNα or PBS. Serum HBV DNA levels, HBeAg and HBsAg levels were measured.

Results: We show that SYN1 activates IFNAR1/2 signaling as demonstrated by monitoring the phosphorylation of STAT transcription factors in cell lines and primary cells. In addition, we demonstrate that SYN1 shows reduced induction of pro-inflammatory and pro-apoptotic ISGs as compared to natural IFNs. SYN1-treated HBV-infected PHH showed dose-dependent and potent reduction of HBsAg, HBeAg and HBV DNA levels comparable to treatment with type I IFNs, with minimal impact on cell viability. Furthermore, SYN1 inhibited HDV replication in PHH co-infected with HBV and HDV. Importantly, SYN1 potently inhibited HBV replication in a mouse model of HBV infection. SYN1 also exhibited potent and broad antiviral activity against multiple virus families, including respiratory viruses, herpesviruses, and flaviviruses.

Conclusion: Our data demonstrate that SYN1 confers potent antiviral activity against HBV in vitro and in vivo with reduced inflammatory properties resulting in the potential for an improved tolerability and safety profile in the clinic.

FRI-289

Eliminating hepatitis B with a combination of the newly revised Entecavir and Birinapant

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Background and aims: Hepatitis B is a major global health issue, particularly in the Southeast Asia region. However, due to the heterogeneous nature of HBV infection, achieving a functional and chronic cure is challenging. Therefore, we designed a combination therapy using a newly revised Entecavir and Birinapant to test its effectiveness against HBV infection in mouse models. Both the revised Entecavir and Birinapant are liver-targeting compounds that selectively bind to the hepatocytes receptors while minimally affecting extrahepatic cells.

Method: We utilized hydrodynamic injection in an in vivo transfection mouse model to assess the efficacy of the revised drug, including SC-3001 (Entecavir analog) and SC-3002 (Birinapant analog), as well as their combination therapy. The control drugs included single uses of Entecavir or Birinapant and their combination therapy. We measured HBV DNA, HBs antigen (HBs Ag) and HBe antigen (HBe Ag) and anti-HBs antibody.

Results: SC-3001 significantly reduce the HBV DNA titer, demonstrating greater efficacy than Entecavir. SC-3002 significantly reduce the HBV DNA titer and HBe Ag level, showing superior efficacy compared to Birinapant. Although SC-3001 or SC-3002 did not significantly decrease the HBs Ag individually, their combined use resulted in significant elimination of HBV DNA and HBs Ag, increased production of anti-HBs antibodies and greater efficacy compared to the control drug (Entecavir + Birinapant). Furthermore, a notable side effect of the control drug is facial hair loss, which was not observed in the other groups.

Conclusion: The data indicated that the newly revised Entecavir and Birinapant can effectively eliminate HBV infection and induce the greater anti-HBs antibody production, achieving a functional cure. Therefore, their combined use may serve as a potential drug candidate for treating HBV infection.

FRI-290

NTCP intronic polymorphism rs17556915 had no impact on HDV RNA levels and bulevirtide response in patients treated with bulevirtide

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Background and aims: Bulevirtide (BLV) is an entry inhibitor that binds to the HDV entry receptor, sodium taurocholate cotransporting polypeptide (NTCP). BLV has demonstrated potent antiviral efficacy in phase 2 and 3 studies and has been approved for the treatment of compensated chronic hepatitis D (CHD) in the EU and other non-EU countries. Recently a retrospective study reported a possible influence of the NTCP intronic polymorphism rs17556915 on baseline (BL) HDV RNA levels and early response to BLV in CHD patients receiving BLV 2 mg monotherapy. Here, we evaluated the impact of this polymorphism on BL HDV RNA levels and BLV treatment outcome in patients with CHD from a phase 3 study MYR301 (NCT03852719, BLV monotherapy) and a phase 2b study MYR204 (NCT03852433, BLV with or without peginterferon alfa-2a [PegIFN]).
Method: Whole genome sequencing (WGS) was performed on whole blood samples for a total of 290 of 324 (90%) patients in MYR301 (128 of 150, 85%) and MYR204 (162 of 174, 93%) at BL, with all patients from Europe. Viral response (VR), partial response (PR), and nonresponse (NR) were defined as achieved undetectable HDV RNA or ≥2 log10 HDV RNA decline from BL, achieved ≥1 but <2 log10 HDV RNA decline from BL, achieved <1 log10 HDV RNA decline from BL, respectively. Statistical analysis was conducted using One-way ANOVA or Fisher's exact test.
Results: All samples (n = 290) were performed for WGS and the rs17556915 polymorphism data was obtained from all the tested samples. The genotype distribution (CC: 194 of 290, 66.9%; TT: 6 of 290, 2.1%; CT: 90 of 290, 31.0%) was consistent with that of the European population and met Hardy-Weinberg Equilibrium expectations. The median BL HDV RNA levels from patients with genotypes CC, TT and CT were 5.38, 5.25, 5.33 log10 IU/mL, respectively, and had no significant difference across the 3 genotype groups (p = 0.3997). Patients with CC had similar VR, PR and NR rates compared to CT or TT groups during treatment at Weeks 24, 48, 96 and 144 in BLV 2 mg (n = 42), BLV 10 mg (n = 133) monotherapy, or BLV+PegIFN combination treatment (n = 92) groups. Additionally, patients with CC had similar decline rates in HDV RNA at each individual timepoints during treatment compared to CT or TT groups in BLV 2 mg, 10 mg monotherapy or BLV+PegIFN combination treatment groups.
Conclusion: The rs17556915 genotype distribution aligned with that of the European population. NTCP rs17556915 polymorphism had no impact on BL HDV RNA levels and BLV treatment outcomes in patients receiving BLV 2 mg or 10 mg monotherapy, or BLV+PegIFN combination therapy in MYR204 and MYR301 studies.

FRI-291-YI

Targeting hepatitis E virus with an innovative CRISPR-Cas13-based therapeutic approach

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Background and aims: Viral infections are a major cause of disease, mortality and economic loss worldwide. In particular, RNA viruses cause a wide range of human diseases and represent a global health problem. To date, effective antiviral drugs are not available for a variety of clinically relevant viral pathogens, including the hepatitis E virus (HEV). Currently, therapeutic options for HEV are restricted to the off-label use of ribavirin (RBV), a broad-spectrum antiviral agent. The CRISPR/Cas13 system presents a promising approach for targeting RNA viruses. In this study, we explored the potential of the CRISPR/Cas13d system as an innovative therapeutic strategy against HEV.
Method: We developed a reporter assay to screen CRISPR RNAs (crRNAs) targeting conserved viral regions and identified functional crRNAs targeting HEV-3. Using a subgenomic replicon reporter and a robust HEV cell culture model, we investigated if the CRISPR/Cas13d system can be "programmed" to selectively target HEV replication/infection.
Results: Using our reporter assay we identified several functional crRNAs, which efficiently target different regions of the HEV-3 genome. We further demonstrate that the CRISPR/Cas13d system in combination with cRNAs targeting the ORF1 of HEV can effectively reduce HEV-3 replication and decrease the production of infectious particles in hepatoma cell lines. In addition, we show that the CRISPR/Cas13d system can be used to prevent HEV-3 infection in hepatoma cells. Using bioinformatic analysis, we further identified a minimal set of three crRNAs covering ~95% of HEV genomes with zero mismatches.
Conclusion: Overall, our findings highlight the potential of the CRISPR/Cas13d system as innovative antiviral strategy to simultaneously target different HEV variants and thereby combat viral infection.

FRI-292

Single-cell immune profiling of liver and blood reveals pretreatment signatures associated with treatment outcomes in young children with chronic hepatitis B

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Background and aims: Chronic hepatitis B virus (HBV) infection is more likely to become chronic in young children, but the cure rate following antiviral therapy is significantly higher in children compared to adults. The underlying immune mechanisms remain unclear. This study aims to explore the immune features associated with chronic HBV infection in children and adults, and how these relate to antiviral treatment outcomes in children.
Method: The study enrolled 19 untreated children aged 1–6 years with chronic HBV infection (9 of whom achieved HBsAg loss and 8 did not upon treatment), along with 11 untreated adults with chronic HBV infection. Immune characteristics of liver tissue and peripheral blood were analyzed using single-cell RNA sequencing and TCR/BCR sequencing. Differences between cured and non-cured children were assessed to identify immune features associated with treatment outcomes.
Results: Single-cell RNA sequencing revealed 8 major immune cell populations and 49 immune subpopulations in both liver tissue and peripheral blood. Children with chronic HBV (CHB) showed distinct immune characteristics compared to adults, notably with more naïve T cells and liver-resident NK cells, and fewer effector T cells and liver memory B cells. In children, the presence of CXCL13+ CD4 T cells in liver tissue and their role in germinal center B cell differentiation towards memory B cells was linked to the failure to achieve functional cure upon antiviral therapy.
Conclusion: This study provides a comprehensive analysis of the immune features in both adults and children with CHB, as well as in

cured and non-cured children. The differentiation of liver-resident memory B cells appears closely associated with the inability to achieve functional cure following antiviral therapy, providing insights into immune mechanisms that may influence treatment outcomes.

FRI-293

Peripheral helper CD4+ T cell functionality distinguishes between acute resolving and chronic hepatitis B

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Background and aims: $CD4^+$ T cells are crucial in mediating viral control and pathogenesis in HBV infection, but their phenotypical and functional characteristics remain incompletely understood in patients with both acute and chronic HBV infection.
Method: We utilized single-cell RNA sequencing (scRNA-seq), single-cell multiplex secretome analysis, and multicolor immunohistochemistry (mIHC) to analyze intrahepatic and blood $CD4^+$ T cells from HBV-infected patients at various disease phases, including immune tolerant (IT), immune activation (IA), acute resolving (AR), and chronic resolved (CR). Functional experiments were conducted to validate the phenotypes of peripheral helper $CD4^+$ T cells (Tph) and assess the impact of Ursodeoxycholic acid (UDCA) on Tph cell functionality.
Results: We identified ten distinct $CD4^+$ T cell subsets with different tissue preferences and functional profiles. Intrahepatic Tph cells were enriched in both AR and IA patients, but not in IT and CR patients. The frequency of Tph cells was positively correlated with liver inflammation. In IA, Tph cells predominantly produced TNF-α via ER stress and a BHLHE40-dependent mechanism, whereas in AR, they shifted toward producing IL-10 and IFN-γ. UDCA inhibited ER stress and corrected BHLHE40-dependent TNF-α polarization in Tph cells, enhancing IL-10 and IFN-γ production.
Conclusion: Our study indicates that Tph cell functionality differs between acute and symptomatic chronic HBV infections. UDCA treatment restores the function of Tph cells and may represent a therapeutic approach to the treatment of CHB.

WEDNESDAY 07 MAY

Viral hepatitis A-E – Clinical aspects

WED-260

Plasma exchange to treat hepatitis A related acute liver failure – a retrospective multicentre cohort study

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Background and aims: Plasma exchange (PLEX) has recently shown to improve survival in acute liver failure (ALF); there is no study specifically analyzing its utility to treat Hepatitis A virus related acute liver failure (HAV-ALF). ALF patients who are not on inotropes tolerate PLEX better (PMID: 39001974). We aimed to assess efficacy of plasma exchange (PLEX) to treat HAV-ALF.
Method: We retrospectively studied consecutive HAV-ALF patients who underwent PLEX between 2018 and 2024 in 9 centres in India. The controls were HAV-ALF patients managed with standard medical treatment (SMT) between 2011–2024. Primary study outcome was in-hospital liver transplant (LT)-free survival with PLEX versus SMT. Poor outcome was defined as death or terminal discharge.
Results: Fifty HAV-ALF patients in PLEX group (males: 35; age: 21.5 (18–27 years, median, IQR; King's college criteria fulfilled (KCC): 12 (24%)) and 32 HAV-ALF in SMT group (males: 17; age: 20.5 (17–26.8) years; KCC fulfilled: 4(12.5%)) were studied. No patient underwent LT. PLEX group patients had 2 (1–3) PLEX sessions.Overall, patients in PLEX group tended to have more severe liver failure than SMT group [MELD: 32.5(26.8–38.3) versus 31 (24.3–35.8); SOFA: 10 (6–12) versus 6 (4.5–12.5); HAV-ALFSG score ≥2 factors fulfilled: 25 (52.1%) versus 10 (35.7%); ALFA score: −0.04 (−0.84 to 0.67) versus −0.64 (−1.4 to −0.08). In-hospital survival was 68.8% in the 32 HAV-ALF patients on SMT and 70% in the PLEX treated patients (P value = 1). Survival in patients not on inotropes was better in PLEX group (31/33; 94%) vis-à-vis SMT group (19/27; 70%), independent of MELD and ALFSG (≥2 poor prognostic factors fulfilled) with adjusted HR of 0.135 (95% CI 0.017–1.06, p value: 0.05). Similarly, in patients with ALFA score >−0.7, PLEX group had better survival (18/19; 95%) vis-à-vis SMT (6/9; 67%; p-value: 0.05).Overall PLEX patients on mechanical ventilation, inotropes, with high MELD or ALFA scores or those who fulfilled ≥2 poor prognostic ALFSG criteria had poor outcome (p value <0.01).
Conclusion: PLEX improves survival with native liver in HAV-ALF patients not on inotropes.

WED-261

Cross-sectional study on clinico-pathological profile and outcomes of severe hepatitis A outbreak in India

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Background and aims: Hepatitis A virus infection (HAV) is widely believed to be a mild self-limiting illness with fulminant presentation in less than one percent cases. Recently, a resurgence of HAV epidemic unfolded in Kerala, a state with high standards of sanitation and healthcare access comparable to developed nations. Many atypical findings were reported including early renal and pulmonary involvement, development of hemophagocytic lymphohistiocytosis (HLH) and acute liver injury/failure (ALI/F) prompting a detailed analysis of such cases.

Method: We conducted a multi-centric, hospital-based study at six tertiary care hospitals. Patients with IgM HAV positivity and atypical features (a-HAV) were included in the study arm and outpatients with usual symptoms (u-HAV) were used as comparator.
Results: Total of 269 patients (u-HAV-141, a-HAV-128) were included (mean age 33.27 ± 12.24, 67% males). a-HAV cases showed a significantly higher prevalence of metabolic co-morbidities and co-infection with dengue and leptospirosis (4.7% each) and scrub typhus (3.1%). a-HAV had significantly higher incidence of continuing fever (91% vs 13, evanescent rash(12% vs 4%), hepatomegaly(60% vs 38%), splenomegaly (24% vs 14%), prolonged cholestasis (16%), ascites (29% vs 10%), encephalopathy (21%), HLH(15%), higher mean levels of total leukocyte counts, bilirubin, AST, triglycerides, ferritin (4957 vs 1137 IU), LDH (818 vs 332 IU), presence of autoantibodies (16% vs 1.4%), AKI (16%), metabolic acidosis and lower levels of albumin and platelets. a-HAV was associated with significantly higher steroid use (33% vs 5.7%), plasma exchange (22%), continuous renal replacement (12%). Also, progression to ACLF (9.3%), hospital re-admission rates (12%), mortality (12%) was significantly higher in the a-HAV group. Genotyping revealed the strain to be genotype IIIA, a common variant in India in all 56 tested samples. Independent predictors of mortality in acute HAV infection were the presence of autoantibody (OR-5.6), encephalopathy (OR-25) and AKI (OR-1.6). Further, presence of autoantibodies was associated with disease progression or ALI/ALF in all patients with acute HAV infection (OR-13.6).
Conclusion: The study provides a strong indication regarding changing clinical presentation and virulence of hepatitis A infection. Unlike previous outbreaks, our cohort showed a significant number of patients with severe and atypical manifestations. Further genetic sequencing is planned for this cohort.

WED-262
Prolonged cholestasis following hepatitis A : what lies beneath
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Background and aims: Hepatitis A virus is a common agent for acute viral hepatitis,particularly in the tropics. Prolonged cholestasis, manifested by jaundice and pruritus persisting for more than 4 weeks is encountered in a minority of HAV infection. Short course of steroids are often prescribed in prolonged cholestasis. With this background, we tried to describe the clinical course of prolonged cholestasis in HAV along with role of oral steroids in HAV cholestasis.
Method: All subjects having a serum total bilirubin more than five (5) mg /dl for a period of more than four (4)weeks, after being diagnosed of HAV related acute hepatitis,were followed up. Acute hepatitis A was diagnosed by typical symptoms of acute hepatitis, by the presence of serum IgM anti-HAV positivity, and by the exclusion of other etiologies of acute hepatitis. Liver function test and prothrombin time were done after 4 weeks of index diagnosis of HAV. Patients having florid features of cholestatic hepatitis on liver biopsies were given oral prednisolone at a dose of 0.5 mg/kg/day. Subjects who had bland cholestasis on liver biopsies were not given oral steroids and symptomatic management for pruritus was done. Follow up done for at least six months after stoppage of steroids.
Results: From January 2018 till January 2024, Sixty six (66) subjects having prolonged cholestasis of HAV were diagnosed. Males were predominant. Mean Age of the population 26 years (Range 14–48). None had underlying evidence of chronic liver disease. Mean value of peak total bilirubin 19.4 mg /dl (Range 13.3–56.8). Autoimmune markers were positive in 14 subjects. 63 subjects underwent percutaneous image guided liver biopsies. 4 subjects had bland cholestasis and were given supportive therapy for pruritus 0.18 subjects had features of autoimmune liver disease. 13 subjects diagnosed as autoimmune hepatitis, 4 subjets diagnosed as auto-immune hepatitis –primary biliary cholangitis overlap (AIH-PBC), and one subjects diagnosed as PBC. All of them were given standard medical care. Rest 41 showed features of cholestatic hepatitis. None had evidence of cirrhosis on histopathology. All, 41 subjects were given oral steroids at a starting dose of 0.5 mg/kg/day, weekly LFT and PT were monitored. Steroids were tapered at a dose of 5 mg/week if there was improvement of serum bilirubin in LFT or subjective improvement of pruritus. All of the subjects showed improvement of serum bilirubin after steroid administration. Mean time taken for normalization of serum bilirubin 42 days (range 14–63). 4 subjects who had bland cholestasis, mean time taken for normalization of serum bilirubin 98 days (range 56–140).
Conclusion: Prolonged cholestasis is not an uncommon complication of HAV infection. Short course of oral steroids offer an excellent therapy in a selected subset of patients and reduces morbidity. Underlying autoimmune liver disease can be present in them.

WED-263
Hepatitis E virus persistence in cerebrospinal fluid: a rare phenomenon observed in immunosuppressed patients beyond 18 months post-viremia clearance under Ribavirin therapy
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Background and aims: This study aims to determine the duration of hepatitis E virus (HEV) persistence in the central nervous system (CNS) and to evaluate the prevalence of current HEV infections among neurological inpatients.
Method: Cerebrospinal fluid (CSF) samples were obtained from 326 patients undergoing lumbar puncture at the University Medical Center Hamburg-Eppendorf for various clinical indications. Additionally, 146 unselected neurological inpatients were included and compared to 1,000 healthy blood donors. HEV testing included PCR and detection of anti-HEV IgG and IgM antibodies.
Results: HEV was detected in the CSF of 1/326 patients (0.3%) but not in their blood samples. This individual, a stem cell transplant recipient, had cleared a chronic HEV infection more than 18 months prior following prolonged ribavirin therapy. Anti-HEV IgG antibodies were detected in 28.2% of CSF patients, 29.4% of neurological inpatients, and 16.8% of blood donors ($p = 0.002$ for both patient cohorts vs. blood donors). Anti-HEV IgG-positive patients were significantly older compared to anti-HEV IgG-negative patients (mean age 62 vs. mean age 68; $p = <0.001$) but did not differ significantly regarding the distribution of sex ($p = ns$). Anti-HEV IgM was detected in 1.2% of CSF patients, 2.7% of neurological inpatients, and 1% of blood donors ($p = ns$). Only one patient's anti-HEV IgM positivity was confirmed by immunoblot.
Conclusion: Although 92 patients undergoing CSF puncture showed evidence of previous HEV exposure, HEV persistence in CSF was identified in only one immunosuppressed patient, suggesting that CNS persistence beyond the blood-brain barrier is possible but uncommon. However, in cases of chronic HEV infection in immuno-suppressed individuals, HEV can persist in the CSF for more than a year despite the clearance of viremia. The higher anti-HEV IgG seroprevalence among neurological patients appears to be an age-related phenomenon, as these patients were older than the blood donors.

Viral hepatitis B and D – Clinical aspects

TOP-281

The impact of HBV genotypic diversity and temporal variations on hepatocellular carcinoma risk in chronic HBV infected patients

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Background and aims: Hepatocellular carcinoma (HCC) is a leading causes of cancer-related deaths worldwide. Chronic hepatitis B virus (HBV) infection is a major risk factor, with viral load, specific HBV genotypes, and mutants significantly associated with its progression. HBV, a diverse DNA virus with 10 genotypes (A to J), is predominantly represented by genotypes B and C in Asia, where co-infection with multiple HBV genotypes is common. While previous studies have focused on primary genotypes, most relied on single time-point analyses, leaving the impact of other genotypes and HBV diversity changes over time largely unexplored. This study investigated the relationship between HBV diversity proportions, their variation over time, and HCC risk using refined techniques for sub-genotype detection.
Method: Data from a longitudinal cohort of 439 chronic HBV carriers (REVEAL-HBV) in seven Taiwanese communities were analyzed. Full-length HBV DNA sequences, averaging ~5,000 reads per subject, were obtained using PacBio technology and compared with 35 NCBI reference sequences. Participants were classified into 3 categories based on primary genotype proportion: Class 1 (100%), Class 2 (100% > proportion ≥99.89%), and Class 3 (<99.89%). Class 1 and Class 2 formed the "Low HBV Diversity Group," while Class 3 comprised the "High HBV Diversity Group." Of the 439 participants, 250 underwent follow-up phase, and data from both phases were analyzed to evaluate changes over time. Cox and time-dependent Cox regression models assessed associations between HBV diversity and HCC risk, adjusted for gender, age, DNA levels, and primary genotypes.
Results: At baseline, over 80% of participants (n = 359) had more than two HBV genotypes, and approximately 50% (n = 216) were classified in the "High HBV Diversity Group." Individuals with primary genotype C2 had a higher HCC risk than those with genotype B2, based on baseline (HR = 3.40, 95% CI = 2.08–5.55) and follow-up data (HR = 2.77, 95% CI = 1.52–5.05). The "High HBV Diversity Group" exhibited higher HCC risk than the "Low HBV Diversity Group" in baseline data (HR = 1.78, 95% CI = 1.23–2.56), but this association was absent in follow-up data (HR = 1.15, 95% CI = 0.73–1.81). Time-dependent Cox regression revealed that a decrease in HBV class was linked to significantly elevated HCC risk (HR = 3.19, 95% CI = 1.78–5.72). All analyses adjusted for baseline HBV class, gender, age, DNA levels, and primary genotype.
Conclusion: This study underscores the predictive value of primary HBV genotypes for HCC risk, with genotype C2 conferring a higher risk than genotype B2, regardless of baseline or follow-up data. HBV diversity proportions reliably predict long-term HCC risk but are less effective in short-term. Patients co-infected with multiple HBV genotypes at baseline had higher HCC risk than those with singular infections; but this association diminished during follow-up. Changes in HBV class strongly predicted HCC risk, with a decrease linked to significantly elevated risk over time.

TOP-282

Clinicial ulility of novel HBV serological marker HBcrAg and immunological markers in the second trimester of pregnancy for predicting post-delivery ALT flares

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Background and aims: Chronic Hepatitis B (CHB) changes in context of pregnancy - while pregnancy induces immune tolerance, post-delivery immune reconstitution manifests as ALT flares in 20% patients within 1 year post-partum. HBeAg+ status and high viral load were predictive of post-delivery flares. A novel marker of cccDNA transcriptional activity – hepatitis B core-related antigen (HBcrAg) is useful in predicting HBV mother-to-child-transmission (MTCT) risk, reflects HBeAg status and correlates with HBV DNA levels, but data on its utility to predict post-delivery ALT flares are lacking. Soluble markers of immune system activity chemokines CXCL10 (IP10) and soluble PD1 (sPD1) demonstrated ability to delineate CHB phases (infection vs hepatitis) and might be useful in predicting post-delivery flares. We aimed to assess ability of pregnancy (2nd trimester) plasma levels of immunological markers (CXCL10 and sPD1) and serological/virological markers (HBeAg status, HBV DNA, HBsAg and HBcrAg) to predict post-delivery ALT flares in single centre cohort.
Method: Plasma samples from the 2nd trimester (median gestation 23 wks) of 853 HBsAg+ pregnant patients with post-partum follow-up >1 year were collected between 1.1.2012–31.12.2022. We measured levels of HBV DNA by TaqMan PCR [IU/ml], HBeAg & HBsAg by Abbot Architect® [IU/ml], HBcrAg by CLEIA Fujirebio [log_{10}U/ml] and CXCL10 & sPD1 [both pg/ml] by ELISA (R&D Systems). The results were compared according to the presence/absence of ALT flares defined as (ALT > 38 IU/l and 2-fold increase from pregnancy level) within 1 year post-delivery (every 3 months follow-up) and according to treatment status.
Results: From enrolled 853 patients (median age 29 yrs): 668 (78%) patients were aware of HBV infection before pregnancy with 165 (19%) already treated with tenofovir and continued on therapy post-delivery vs 688 patients not on therapy. No case of MTCT was reported. Post-delivery ALT flares occurred in 170 (20%) patients and were more frequent in treated vs untreated patients (53 patients (32%) vs 117 patients (17%), $p < 0.05$). Untreated: All HBeAg negative, but patients with flares had higher levels for all tested markers when compared to non-flare patients (HBV DNA: 3450 vs 391 IU/ml, HBsAg: 8755 vs 4010 IU/ml, HBcrAg 3.8 vs 2.5 log_{10}U/ml, CXCL10: 215 vs 108 pg/ml and sPD1 189 vs 88 pg/ml, all medians, all $p < 0.05$). Treated: All patients had HBV DNA <10 IU/ml during pregnancy & post-delivery, 24 (14%) patients were HBeAg+ and had more frequent flares (75% HBeAg positive vs 25% HBeAg negative). While HBsAg levels were similar (9010 vs 8756 IU/ml), flare patients had higher levels of HBcrAg (4.9 vs 3.5 log_{10}U/ml), CXCL10 (273 vs 112 pg/ml) and sPD1 (205 vs 94 pg/ml).
Conclusion: The combination of levels of HBcrAg with immunological markers (CXCL10 & sPD-1) during pregnancy refined prediction of post-delivery ALT flares. Larger studies validating these markers to confirm their prognostic clinical significance are needed to enable personalised delivery of care post-partum.

TOP-283-YI

Transition of immune tolerant to immune active chronic hepatitis B and potential implications for monitoring and treatment

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Background and aims: The role of antiviral therapy (AVT) in immune tolerant (IT; HBeAg-positive chronic infection) chronic hepatitis B (CHB) patients remains controversial. Although current guidelines mostly recommend AVT once patients transition to immune active (IA) disease, there is a growing trend to expand treatment criteria. We studied the risk of transitioning to IA disease in strictly defined IT patients with CHB.
Method: This is a multi-centre international cohort study from the RADICAL-consortium, which includes data from a large cohort of mono-infected CHB patients from 12 sites in North America, Europe and Asia. Baseline refers to the first clinic visit at the investigational site. The IT-phase was strictly defined as persistently (1) HBeAg-positive, (2) ALT ≤40 U/L, and 3) HBV DNA ≥5 log IU/ml during the first year after baseline. Transition to IA disease was defined as ALT ≥60 U/L or ALT > 40 U/L at 2 consecutive visits or leading to AVT initiation.
Results: In total, 480 IT patients were included with a median age of 31 (IQR 24.5–39.4), 32% were male and 96% were of Asian ethnicity. Median ALT and HBV DNA at baseline were 25 (IQR 20–31) U/L and 8.36 (IQR 8.03–8.83) log IU/mL. Patients were followed for a median of 117 (IQR 77–182) months.
During follow-up, 219 (46%) patients developed IA disease, 42% defined by ALT > 40 at 2 consecutive visits, 39% ALT > 60 and 19% ALT > 40 at start of AVT. A total of 263 (55%) IT patients started on AVT during follow-up, of whom 64% after development of IA disease. The cumulative incidence of spontaneous HBeAg loss at 3-, 5- and 10-year was 3%, 7% and 19%. The 3-, 5-, 10- and 15-year cumulative incidences of transition from IT phase to IA disease were 17%, 34%, 63%, 76% in the overall population. Transition to IA disease was more likely in patients with a higher ALT (aHR 1.06, 95% CI 1.04–1.08, p < 0.001) at baseline. Age, sex and HBV DNA at baseline were not related to transition to IA disease. Also, no association was found when age categories were investigated (<30, 30–40, > 40). Notably, the 3-, 5-, and 10-year cumulative incidence of transition to IA disease was highest in patients with a baseline ALT > 30 (29%, 49%, 74%) compared to patients with an ALT > 20 and ≤30 (16%, 36%, 69%) and an ALT ≤20 (7%, 16%, 44%) at baseline (p < 0.001). Findings were consistent in multivariable analysis (aHR for ALT > 20 and ≤30: 2.21, 95% CI 1.49–3.29; aHR for ALT > 30: 3.10, 95% CI 2.02–4.75, p < 0.001). Similar results were found in patients with a persistent HBV DNA ≥7 log IU/ml during the first year after baseline.
Conclusion: One-third of the IT patients transition to IA disease within 5 years of follow-up. An ALT ≥30 at baseline was associated with significantly higher rates of transition which occurred in almost half of them. This suggests that these patients may be good candidates for strict monitoring or even pre-emptive AVT.

TOP-284
Accelerated HBsAg reduction rate and increased proportion of HBsAg <100 IU/mL through repeated finite Nuc therapy in HBeAg-negative chronic hepatitis B patients

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Background and aims: Finite therapy is known to increase HBsAg loss rates, but its impact on HBsAg kinetics and reduction among HBeAg-negative chronic hepatitis B (CHB) patients who experience off-Nuc clinical relapse and are retreated with finite therapy remains unclear.
Method: This analysis included treatment-naïve HBeAg-negative CHB patients who underwent retreatment due to clinical relapse and received at least one additional course of finite Nuc therapy. Nuc cessation adhered to the APASL stopping rule, requiring at least one year of undetectable HBV DNA before stopping. Clinical relapse was defined as ALT > 2 times the upper limit of normal with HBV DNA > 2000 IU/mL. HBsAg levels were assessed at key time points: start (SOT) and end (EOT) of the 1st treatment, 2nd (1st retreatment: retx_SOT, retx_EOT), and 3rd (2nd retreatment: retx2_SOT, retx2_EOT) treatments, and the last follow-up, using the Elecsys HBsAg II Quantitative Assay (Roche). The annual HBsAg reduction velocity ($\log_{10}$ IU/mL/year) was calculated as HBsAg log reduction divided by treatment duration. The primary outcome was the proportion of patients achieving HBsAg <100 IU/mL by the end of follow-up.
Results: A total of 88 HBeAg-negative treatment naïve CHB patients were recruited. The mean age at the 1st treatment was 54.5 ± 9.1 years; 86.4% were male, and 34.1% were cirrhotic. During the first treatment, 70 patients used Entecavir, 8 used Tenofovir, and 10 used other Nucs (LAM, LdT). During the second treatment, 65 patients used Entecavir, and 35 used Tenofovir. The median follow-up duration was 13.4 (12.2–14.6) years. Sixty-six patients experienced relapse after the 1st retreatment, and 64 were retreated. Clinical relapse after repeat finite therapy was mostly observed in the first year and declined thereafter (1st, 2nd, 3rd, and 4th years from retx_EOT: 50.3%, 19%, 3.5%, and 2.6%, respectively). Median HBsAg levels (IU/mL) at SOT, EOT, retx_SOT, retx_EOT, retx2_SOT, retx2_EOT, and last follow-up were 1405, 507, 953, 224, 964, 144, and 76, respectively. Annual HBsAg reduction rates during the 1st, 2nd, and 3rd treatments were −0.091, −0.171, and −0.282 $\log_{10}$ IU/mL/year, respectively (P < 0.001). The proportion achieving HBsAg <100 IU/mL increased from 2.3% (SOT) to 5.7% (EOT), 11.4% (retx_SOT), 29.6% (retx_EOT), and 53.4% (last follow-up). Three patients (2 cirrhotic) developed HCC during follow-up, resulting in an annual HCC incidence of 0.33%. No liver-related mortality was observed.
Conclusion: Repeat finite therapy accelerates HBsAg reduction, significantly increases the proportion achieving HBsAg <100 IU/mL, with low HCC incidence, making it a considerable option for patients failing to achieve sustained response or functional cure after Nuc discontinuation.

SATURDAY 10 MAY

SAT-243

Analysis of liver pathological characteristics and influencing factors in patients with an inactive HBsAg carrier status

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Background and aims: The purpose of this study was to analyze the liver pathological characteristics and influencing factors in patients with an inactive hepatitis B surface antigen (HBsAg) carrier status (IHCs) and to explore the need for antiviral treatment in newly defined IHC patients according to liver tissue inflammation and fibrosis.
Method: This multicenter, retrospective and cross-sectional study included 231 IHC patients who underwent histopathological examination via liver biopsy at eight hospitals, including Beijing Youan Hospital Affiliated with Capital Medical University, from January 2018 to December 2023. Patient general information, biochemical indicators, HBV DNA and HBsAg levels, liver ultrasound findings, FibroScan results, and other examination results were collected. IHC patients were grouped on the basis of HBV DNA negativity. Differences in liver pathological inflammation activity (G) and liver fibrosis stage (S) of the patients in the two groups were analyzed. Factors affecting the degree of inflammation and fibrosis in the patients were identified with univariable and multivariable analyses, and the subsequently established multivariable prediction model was evaluated via receiver operating characteristic (ROC) curve analysis. The significance level was set to $\alpha = 0.05$.
Results: The median age of the 231 chronic hepatitis B patients was 43 years, among 95.2% (220/231) were aged ≥30 years, and men accounted for 95.2% (220/231). The median HBV DNA concentration was 94 IU/ml; a total of 35.9% (83) of the patients were negative for HBV DNA (<20 IU/ml). Patients with G≥2 accounted for 16.5% (38 patients) of the cohort, those with S≥2 accounted for 29% (67 patients), and those with evident hepatic injury (EHI), that is, those with G≥2 and/or S≥2, accounted for 35.9% (83 patients). In HBV DNA-negative IHC patients, the percentage of liver tissues with S≥2 was 42.2%, significantly greater than that in DNA-negative IHC patients (21.6%; $\chi^2 = 10.9$, $P < 0.001$). This significant difference occurred mainly in the population over 30 years of age (44.9% vs. 31%, $\chi^2 = 4.22$, $P = 0.04$). Multivariable analysis indicated that sex, HBV DNA, and the LSM were independent predictors of the liver tissue S value among IHC patients over 30 years of age. The area under the ROC curve (AUC) of the prediction model established from the independent factors was 0.855.
Conclusion: Despite presenting with HBV DNA negativity, 42.2% of patients exhibited significant liver fibrosis, and the percentage of patients with S ≥2 gradually increased with age. Male IHC patients over 30 years of age with negative HBV DNA should undergo comprehensive assessments including LSMs and platelet counts, as well as liver biopsy as appropriate. Selection of appropriate antiviral treatment can improve the chance of clinical cure and minimize the risk of long-term adverse outcomes.

SAT-244

Impact of HDV RNA levels on the risk of liver-related outcomes in patients with CHD: a european multicenter validation cohort study

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Background and aims: In a previous multicenter study in patients with chronic hepatitis D (CHD), we have shown that the levels of HDV RNA correlated with the development of clinical events (Palom A et al. J Hepatol 2023 #1810). In this study, we aim to validate the relationship between HDV RNA concentrations and the risk of developing clinical events in two independent cohorts of Italian patients with CHD.
Method: A multicenter retrospective study that includes three cohorts of untreated adults with detectable and quantified HDV RNA levels and a clinical follow-up of >1 year. In the previous analysis cohort (cohort A), HDV RNA was quantified using an in-house RT-PCR (LOD = 57.5 IU/mL). In the two Italian validation cohorts, Milano (cohort M) and multicenter one (cohort MU) HDV RNA was quantified by Robogene HDV Quantification Kit 2.0 (LOD = 6 IU/mL). Clinical endpoints (liver decompensation, HCC, liver transplant or liver-related death) were evaluated every 6 months during the follow-up.
Results: A total of 260 subjects were included and monitored during a median follow-up of 4.1 years (IQR 2–6). The analysis cohort (cohort A) included 98 patients: median age 44 (IQR 36–51) years, 59% male, 81% Caucasian, HDV RNA 5.3 (IQR 4.2–6.1) log IU/mL, ALT 71 (IQR 44–126) IU/mL, 30 (30.6%) cirrhosis and the median follow-up was 6 (IQR 3–9) years. Clinical events were observed in 12% (2/17), 22% (4/18), 18% (6/34) and 35% (10/29) of the patients according to the respective HDV RNA levels (6–6,000, >6,000–60,000, >60,000–600,000, >600,000 IU/mL) ($p = 0.103$). The two validation cohorts (cohort M: 100 patients, and cohort MU: 62 patients) were similar in gender ($p = 0.929$) and ALT levels ($p = 0.421$) but not in patient's age ($p < 0.001$), proportion of cirrhosis ($p < 0.001$) and qHDV RNA levels ($p = 0.013$). In the 119 non-cirrhotic patients, clinical events occurred in 0% (0/13), 15% (2/13), 9% (2/23), 21% (4/19) according to previous levels of viremia in the analysis cohort, and in a similar proportion in the validation cohorts: 0% (0/4), 0% (0/4), 0% (0/10), 9% (1/11) in cohort M

(p = 0.239), and 0% (0/6), 20% (1/5), 22% (2/9), 50% (1/2) in cohort MU (p = 0.164) (overall p = 0.166). In the 141 cirrhotic patients, clinical events occurred in 50% (2/4), 40% (2/5), 36% (4/11), 60% (6/10) in the analysis cohort and in a similar proportion in both validation cohorts: 41% (7/17), 25% (3/12), 40% (8/20), 50% (11/22) in cohort M (p = 0.415), and 50% (5/10), 40% (2/5), 53% (10/19), 0% (0/6) in cohort MU (p = 0.890) (overall p = 0.743).
Conclusion: In untreated patients with CHD, low levels of HDV RNA were associated with less clinical outcomes in patients without liver cirrhosis. These results were validated and confirmed in two external cohorts.

SAT-245
Treatment duration, adherence and persistence in patients with chronic hepatitis B virus infection treated with long-term nucleos (t)ide analogues in Germany
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Background and aims: Chronic Hepatitis B virus (HBV) infection poses a significant threat to global health. Nucleos(t)ide analogs (NAs) are the current standard of care for chronic HBV infection. Adherence to long-term NA therapy is vital to maintain HBV-DNA suppression. Knowledge of NA treatment patterns in prevalent chronic HBV infection as well as the duration of treatment is important to understand adherence and persistence and to describe the real-world use of these therapies.
Method: We conducted a retrospective, observational claims data analysis, which examined and described the characteristics of treatment duration and adherence to single-drug formulation second-generation NAs in adult patients with chronic HBV infection in Germany. Data from the Institute for Applied Health Research Berlin GmbH (InGef) Research Database were used. Adult patients who initiated single-drug formulation second-generation NA treatment (entecavir, telbivudine, tenofovir disoproxil fumarate, and tenofovir alafenamide) between January 1, 2015–August 31, 2022, and had a recorded diagnosis for chronic HBV infection in the year prior to their initial NA prescription, were selected. Patients with co-infections such as HIV, Hepatitis delta-virus, and Hepatitis C virus were excluded.
Results: We identified 489 adult patients with chronic HBV infection who initiated single-drug formulation second-generation NA treatment in the study period (average age [SD] 53.0 [14.7] years, females 41.5%). During follow-up (average [SD] 3.3 [2.1] years), NA treatment discontinuation was observed in more than half of the patients (n = 273, 55.8%), with a median (95% CI) time to discontinuation of 743 (560, 1,107) days (24.4 [18.4, 36.4] months). A total of 216 (44.2%) patients continued treatment throughout follow-up and 128 (46.9%) patients who discontinued NA treatment eventually restarted their therapy. Less than 10% of patients switched NA treatment (n = 41, 8.4%). Adherence was significantly worse in females (HR = 1.31, p = 0.032) versus males and better in patients living in urban regions (HR = 0.73, p = 0.044) versus rural areas. Average adherence, defined as proportion of days covered, was 0.94 ± 0.09 at the end of follow-up, and remained constant for different follow-up lengths (0.94 after 12, 24 and 36 months; 0.93 at 48 and 60 months). Adherence was positively influenced by age (OR = 1.02, p = 0.041).
Conclusion: Treatment discontinuation remains a key challenge in the management of chronic HBV infection. This study highlights the unmet need for additional support to help patients persist with NA treatment. These results also underscore the critical need for alternative therapies for chronic HBV infection with shorter and finite treatment durations with a reduced need for rigid monitoring to mitigate the high discontinuation rate while ensuring optimal clinical outcomes.
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SAT-246
Long-term perspectives on treating or observing immune-tolerant chronic hepatitis B
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Background and aims: The management of immune-tolerant (IT) chronic hepatitis B (HBV) remains debatable. While guidelines do not recommend treatment, expanding treatment to IT and "grey zone" patients is gaining support due to concerns about high viremia and liver disease risk. we aim to study the impact of treatment in IT and "grey zone" patients over the long term.
Method: This retrospective study included HBeAg-positive chronic hepatitis B patients (2000–2024) at the Toronto Centre for Liver Disease with HBV DNA > 6 log IU/mL, ALT <75 U/L, and minimal fibrosis (F0–1) assessed by biopsy or non-invasive methods. Patients treated during pregnancy for vertical transmission prevention were excluded. Groups included untreated IT (ALT <45 U/L), treated IT (ALT <45 U/L), and treated mildly active (MA) (ALT 45–75 U/L). Baseline was defined as the first clinic visit for untreated IT or treatment initiation for treated IT and MA groups. Data were analyzed using chi-squared, Kruskal-Wallis, and Kaplan-Meier methods (p < 0.05).
Results: The study included 161 patients: 107 untreated IT, 27 treated IT, and 27 treated MA. Treated IT patients most commonly received TDF (32.1%), ETV/IFN (28.6%), and TAF (21.4%), while treated MA patients primarily received TDF (53.6%) and IFN (17.9%). Of the total population, 63.5% (n = 102) were female, and 90% (n = 146) were Asian. The mean baseline age was 31 years in the untreated IT group, 35 years in the treated IT group, and 40 years in the treated MA group (P < 0.05). The mean follow-up duration was 9.6 years for the untreated IT group, 4.5 years for the treated IT group, and 8.3 years for the treated MA group. The mean ALT levels were 52 U/L in the treated MA group, 26 U/L in the untreated IT group, and 27 U/L in the treated IT group. Viral suppression (HBV DNA <10 IU/mL) was achieved in 44% of the treated IT group, 63% of the treated MA group, and 4% of the untreated group (P < 0.05). HBV DNA suppression probability reached 87% at 4 years and 100% at 10 years in the treated IT group, compared to 56% at 4 years and 95% at 10 years in the treated MA group (P < 0.05). However, 56% of treated IT and 37% of treated MA patients did not achieve suppression despite long-term therapy. HBeAg loss occurred in 11% of the treated IT group, 15% of the treated MA group, and 19% of the untreated group (P > 0.05), with 10-year probabilities of 55%, 21%, and 36%, respectively (P > 0.05). None of the patients developed cirrhosis or hepatocellular carcinoma (HCC) during the follow-up period.
Conclusion: Our findings suggest that HBeAg loss is uncommon among immune-tolerant and mildly active patients undergoing prolonged antiviral therapy. Antiviral treatment was safe, but achieving HBV DNA undetectability required extended durations of therapy for most patients. Notably, high HBV DNA in immune-tolerant patients was not associated with hepatocellular carcinoma (HCC) over a decade of follow-up.

SAT-247

Molecular epidemiology of chronic HDV infection in Italy: HDV genotypes and subgenotypes distribution in the HDV describe study cohort

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Background and aims: HDV Describe is an observational study in which consecutive HBsAg-positive carriers with antibodies to HDV, referred to 32 Italian centers, were prospectively enrolled from August 2022 to July 2024. We aimed to conduct a phylogenetic analysis to identify the HDV genotypes (Gts) and subgenotypes (Sgts) in this study cohort.

Method: HDV Gts were determined by sequence analysis of a viral genome region spanning nucleotides 908–1265. After PCR amplification, Sanger-based sequencing (BMR-GENOMICS, Padova, Italy) was performed; obtained sequences were compared to reference sequences of the eight HDV Gts retrieved from GenBank, using Basic Local Alignment Search Tool (BLAST). The identification of Sgts was performed by phylogenetic analysis using MEGA11 software considering an intrasubgenotype percentage of difference <10%.

Results: Gts and Sgts were determined in 370 HDV RNA-positive patients. Overall, 366 patients were Gt-1 and 4 were Gt-5. All patients with HDV Gt-5 were migrants from Sub-Saharan Africa regions. Among patients carrying Gt-1, we identified the following Sgts: 3 (0.8%) Sgt-1a, 3 (0.8%) Sgt-1b, 153 (42%) Sgt-1c, 7 (1.9%) Sgt-1d, 194 (53%) Sgt-1e; it was not possible to assign the Sgt in 6 (1.6%) patients. Among native Italians (n = 221), the prevalent Sgt was 1e (145/221; 65.6%), while foreign-born (n = 149) were mostly infected with HDV Sgt-1c (88/149; 59.1%) ($p < 0.001$). Most foreign-born patients were from East Europe (135/149; 90.6%); Sgt-1c was prevalent in patients from Eastern European Countries (Moldova, Albania, Ukraine, Georgia, and Russia), except those from Romania where the prevalence of Sgt-1c and 1e was equal (both 49.2%). Considering the Italian patients' sequences, the overall mean genetic distance was

0.076 ± 0.01. Among patients successfully genotyped for HBV (n = 57), most of them (47/57; 82.5%) were infected with HBV Gt-D; in such patients, HDV Sgt-1e and 1c were equally distributed (23/47, 48.9% vs. 21/47, 44.7%). Finally, Sgt-1e was associated with lower HBsAg (3.55, IQR 2.45–3.96 Log IU/mL vs 3.73, IQR 2.91–4.09 Log IU/mL; p < 0.037) and HBcrAg levels (3.30, IQR 2.6–4.3 Log U/mL vs 3.70, IQR 2.8–4.6 Log UI/ml; p < 0.020) compared to patients infected with other HDV Sgts. No further associations were found with available clinical, biochemical, and virological parameters.

Conclusion: In Italy, the most frequently observed HDV Sgts are 1c and 1e. The former is prevalent among foreign-born patients while the latter is prevalent among native Italians. The association between HDV Sgt-1e and lower levels of HBV antigens may reflect a peculiar interplay between these two viruses.

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SAT-248-YI

End of treatment anti-HBc IgG and HBcrAg predict severe flares after nucleos(t)ide analogue withdrawal in CHB – interim analysis from the multicenter prospective COIN-B trial

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Background and aims: Nucleos(t)ide analogue (NUC) withdrawal in chronic hepatitis B has been proposed as a strategy to increase functional cure rates, but the possibility of severe flares necessitates close off-treatment monitoring. Baseline predictors to identify patients at risk for such flares would improve the safety. We thus investigated several biomarkers for the prediction of flares within 24 weeks after NUC cessation in a multicenter prospective clinical trial (COIN-B, NCT04779970).

Method: End of treatment (EOT) samples of 85 start of treatment HBeAg negative, non-cirrhotic (<F3), long-term (>3 years) NUC suppressed chronic HBV patients were analyzed. Patients were monitored every 2–4 weeks. Hepatitis B surface antigen (HBsAg) (Limit of Detection (LOD) 0.05 IU/mL) and HBV RNA (LOD 3 cp/mL; Limit of Quantification (LOQ) 10 cp/mL) were analyzed on the Cobas (Roche) analyzer. Hepatitis B core related antigen (HBcrAg) (LOD 2 logU/mL; LOQ 3 logU/mL) and hepatitis B core IgG antibodies (anti-HBc IgG) (LOD 0.5 IU/mL; LOQ 0.8 IU/mL) were analyzed on the Lumipulse (Fujirebio) G600 platform.

Results: Majority of patients were male (72.9%) with a median (IQR) age of 47 (13) years. 63/85 (74.1%) were treated with tenofovir and the median (IQR) duration of last NUC treatment was 7.2 (4.8) years. Severe virological (SVF) (HBV DNA >5 log IU/mL) and severe biochemical flares (SBF) (ALT > 10×ULN) were observed in 34 (40.0%) and 19 (22.4%) patients respectively. There is an increased odd for having a viral flare (HBV DNA > 2000 IU/mL, n = 77/85) per log increase of HBsAg at EOT (OR 2.41, 95% CI 1.22–5.36, p = 0.01). 25 (30.1%) patients had HBV RNA > LOD at baseline, 13 (52.0%) of those were > LOQ. HBV RNA > LOD is not associated with any type of flare. HBcrAg was >LOD in 51 patients (60.0%), of which 29 (56.9%) were >LOQ. SVF (p = 0.006) and SBF (p = 0.03) were more frequently observed in patients with HBcrAg >LOD at baseline. Patients with HBcrAg >LOD had an OR 4.34 (95% CI 1.67–12.48, p = 0.004) and OR 4.72 (95% CI 1.41–21.70, p = 0.02) for a SVF and SBF respectively. The respective negative predictive value (NPV) to identify SVF and SBF based on HBcrAg >LOD are 79.4% and 91.1%. There is a significant decrease in the odds for having a SVF (OR 0.46, 95% CI 0.21–0.93, p = 0.04) and SBF (OR 0.20, 95% CI 0.07–0.50, p = 0.001) per log increase of anti-HBc IgG. An EOT anti-HBc IgG of ≤475 IU/mL allowed the identification of SVF and SBF with a NPV of 74.3% and 97.1% respectively. Multivariate logistic regression including HBcrAg and anti-HBc IgG pointed towards HBcrAg >LOD as an independent predictor for SVF (aOR 4.57, 95% CI 1.66–14.17, p = 0.005) and SBF (aOR 6.18, 95% CI 1.46–43.14, p = 0.03) and lower anti-HBc IgG for SBF (aOR 0.21, 95% CI 0.06–0.55, p = 0.004).

Conclusion: EOT serum anti-HBc IgG and HBcrAg but not HBV RNA nor HBsAg are associated with severe flares after NUC cessation in a multicenter prospective trial. Anti-HBc IgG and HBcrAg show promise to identify the patients at highest risk for adverse outcomes and may guide future treatment cessation strategies.

SAT-253

DM type 2 is a significant risk factor for HCC and decompensation of liver disease in HBV s Ag positive patients

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Background and aims: Hepatitis B virus (HBV) infection is a significant cause of liver disease, liver transplantation, and hepatocellular carcinoma (HCC). Various factors contribute to liver outcomes and mortality in HBV patients. However, there is limited data on the influence of metabolic factors, such as type 2 diabetes mellitus (T2DM), which is closely associated with the development of metabolic-associated steatotic liver disease (MASLD), on liver outcomes in patients with HBV.

This study aim to analyze the factors influencing liver outcomes and mortality in HBsAg-positive patients in Israel

Method: Clalit Health Services (CHS), the largest Health Maintenance Organization (HMO) in Israel, serves over 4.5 million people. We conducted a retrospective big data study analyzing all patients who

tested positive for HBsAg from January 1, 2000, to June 1, 2022. Data collection included demographics, medical history, liver outcome diagnoses (cirrhosis, ascites, esophageal varices, portal hypertension, encephalopathy, and HCC), liver transplantation (LT), and mortality. Multinomial logistic regression analysis was performed to identify factors related to outcomes. Data was extracted from CHS using Clalit's data-sharing platform powered by MDClone (https://www.mdclone.com).

Results: From January 1, 2000, to June 1, 2022, 1,749,414 patients underwent HBsAg testing, with 25,013 positive results (1.4%). After excluding 783 patients with HBV core IgM antibodies, 24,230 patients were included in the analysis. Demographic and clinical data showed that 57.6% were males, the mean age at diagnosis was 42.6 years, 47.3% had low socio-economic status, 2.4% were positive for HDV antibodies, 2.9% for HCV antibodies, and 11.4% had T2DM. Significant factors for cirrhosis complications, HCC, LT, and mortality included no antiviral treatment (OR: 7.26, 7.29, 30.4, and 3.25, respectively), platelet count <120 K (OR: 9.49, 3.77, 10.32, and 3.25, respectively), and T2DM (OR: 3.13, 2.29, 3.01, and 1.95, respectively). Smoking, co-infection with HCV, and co-infection with HDV were also significant. Female gender had a significant influence on cirrhosis complications, HCC, and mortality but not on LT.

Conclusion: In addition to factors related to viral infection and co-infection with HDV and HCV, T2DM strongly influences liver outcomes, HCC, and mortality in HBsAg-positive patients, underscoring the importance of metabolic factors in disease progression.

SAT-254

Healthcare resource utilisation and costs associated with hepatitis delta virus infection compared with hepatitis B virus monoinfection prior to death among adults in Spain

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Background and aims: Concurrent hepatitis delta virus (HDV) and hepatitis B virus (HBV) infection results in higher morbidity and mortality than HBV monoinfection (HBV only). This retrospective study compared healthcare resource utilisation (HCRU) and costs for patients with HDV vs HBV only in the 12 months before death among adults in Spain.

Method: The Spanish National Health System's Hospital Discharge Records Database (Conjunto Mínimo Básico de Datos) was screened for patients aged ≥18 years with ≥1 *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification* diagnosis code for HDV or HBV between 01/2000–12/2019 (study period). Patients with an initial HDV or HBV only diagnosis in the identification period (01/2001–12/2018) and continuous enrolment for ≥12 months before and after first diagnosis were selected; patients with HBV only had no HDV claim in the study period. Baseline characteristics and clinical comorbidities were recorded from the year before first diagnosis. The mean per-patient all-cause and disease-specific HCRU and costs between patients with HDV vs HBV only who died in the study period were evaluated in the 12 months before death. All p values were calculated using McNemar chi-square tests and generalised linear models with gamma distribution (log link).

Results: Of 10,994 patients diagnosed with HDV or HBV only during the identification period, 159 with HDV and 2,920 with HBV only were included. Patients with HDV vs HBV only had a mean age of 47 and 52 years, respectively, and were mostly male (73% and 73%, respectively). In the 12 months before death, all-cause HCRU and costs were significantly higher for patients with HDV (n = 64) vs HBV only (n = 1,168). Among patients with HDV vs HBV only, the all-cause mean number of inpatient (2.9 vs 1.9) and outpatient (2.7 vs 1.6) visits, length of inpatient stay (38.2 vs 31.7 days), number of pharmacy claims (3.5 vs 2.8), and per-patient total cost (€ 12,823 vs € 9,746), inpatient cost (€ 4,668 vs € 3,294), and outpatient cost (€ 4,796 vs € 3,148) in the 12 months before death were higher for patients with HDV ($p < 0.05$ each). These differences were also observed for disease-specific HCRU and costs (HDV, n = 54; HBV only, n = 992): in the 12 months before death, the disease-specific mean number of inpatient (3.1 vs 2.1) and outpatient visits (2.9 vs 1.8), length of inpatient stay (39.5 vs 30.8 days), number of pharmacy claims (3.6 vs 3.0), and per-patient total cost (€ 14,139 vs € 11,289), inpatient cost (€ 5,146 vs € 3,812) and outpatient cost (€ 5,288 vs € 3,649) were higher for patients with HDV ($p < 0.05$ each).

Conclusion: For adult patients in Spain, inpatient length of stay, HCRU and costs from liver-related morbidities were significantly greater in the 12 months prior to death for patients with HDV vs HBV only. These findings underscore the need to reduce the costs and disease burden associated with HDV infection in Spain.

SAT-255

Performance evaluation of the Elecsys anti-HBc II quant assay

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Background and aims: Anti-hepatitis core antibodies (anti-HBc) correlate well with the phases of hepatitis B virus (HBV) infection; therefore, anti-HBc provide an indication of past and present HBV infection and disease progression. The Elecsys Anti-HBc II quant immunoassay enables *in vitro* quantification of anti-HBc in human serum and plasma. The aim of this study was to evaluate the assay's clinical performance in terms of diagnostic sensitivity and specificity at the Medical Decision Point (MDP).

Method: Leftover anonymised serum and plasma samples from HBV-infected people, collected from two external sites, were used for diagnostic sensitivity and specificity at MDP analyses. Sensitivity was assessed in samples from participants with present acute or chronic HBV infection (with or without necroinflammatory activity), while specificity was assessed in samples from participants with past HBV infection (recovered). The MDP to distinguish between present and past infection was 180 IU/mL (based on established Roche internal MDP). Seroconversion sensitivity was compared against the qualitative Elecsys® Anti-HBc II [Roche] test across eight anti-HBc seroconversion panels. Correlative analysis between nominal anti-HBc titers of a serial dilution (0–50 IU/L) of the anti-HBc World Health Organization (WHO) Standard (95/522) and Elecsys Anti-HBc II quant-measured titers was also conducted.

Results: In the overall sensitivity analysis cohort (n = 518), 484 samples had an anti-HBc titer ≥180 IU/mL yielding a sensitivity at MDP of 93.44% (95% confidence interval [CI]: 90.95–95.41). In the overall specificity analysis cohort (n = 393), 377 samples had an anti-HBc titer <180 IU/mL yielding a specificity at MDP of 95.93% (95% CI: 93.47–97.66). Furthermore, the assay significantly differentiated past and present infection samples based on mean anti-HBc titers (44.9 vs. 6002.1 IU/mL, respectively; Wilcoxon test, $p < 0.0001$). Similar seroconversion sensitivity was achieved compared with the Elecsys Anti-HBc II test. The Elecsys Anti-HBc II quant showed good linearity ($r^2 = 0.9$), with low deviation from nominal titer (0 to 11%), over the anti-HBc WHO Standard (95/522) quantification range.

Conclusion: The Elecsys Anti-HBc II quant assay demonstrated good overall diagnostic sensitivity (>93%) and specificity (>95%) at MDP for distinguishing past and present hepatitis B infections. Seroconversion sensitivity was broadly similar compared with the

Elecsys Anti-HBc II qualitative assay. Good linearity and accuracy was also shown against the anti-HBc WHO Standard (95/522).

SAT-256

Role of HBV RNA in predicting nucleos(t)ide analogues initiation and risk of relapse after cessation

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Background and aims: The safe cessation of nucleos(t)ide analogues (NUCs) remains challenging in patients with chronic hepatitis B (CHB). We aimed to investigate the potential role of novel biomarkers in predicting risk of NUCs initiation and off-therapy relapse.
Method: From November 2020 to September 2023, we prospectively enrolled 133 CHB patients who did not receive NUCs as cohort 1, and 45 CHB patients who received NUCs and met cessation criteria as cohort 2. The correlation of novel biomarkers including quantitative hepatitis B surface antigen (qHBsAg), hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA (HBV-RNA) was studied. Risk factors associated with suitability for National Health Insurance (NHI)-indicated antiviral therapy (cohort 1) and off-NUCs relapse (cohort 2) were also analyzed.
Results: The mean ages of cohort 1 and 2 were 53.4 and 58.9 years, respectively. 132 of 133 (99.2%) CHB patients were HBeAg-negative in cohort 1, and 13 of 45 (28.9%) CHB patients were HBeAg-positive in cohort 2. Hepatitis B virus DNA (HBV-DNA) and HBV-RNA were highly correlated ($r = 0.795$, $p < 0.001$), while qHBsAg and HBV-RNA were moderately correlated ($r = 0.485$, $p < 0.001$) in patients without antiviral therapy. During a median follow-up period of 37.8 months, 18 (13.6%) HBeAg-negative CHB patients in cohort 1 were eligible for NHI antiviral therapy. Baseline HBV-RNA ≥3 log (copies/mL) was associated with the risk of further antiviral therapy (HR = 2.910, $p = 0.047$). During a median follow-up of 21.2 months, 36 (80%) patients experienced virological relapse, and 31 (68.9%) patients experienced clinical relapse after discontinuation of NUCs in cohort 2. HBV-RNA ≥3 log at end of treatment (EOT) (HR = 2.258, $p = 0.025$) and off-treatment month 3 (HR = 2.227, $p = 0.021$), and HBcrAg ≥4 log (U/mL) at month 3 (HR = 2.558, $p = 0.009$) were associated with virological relapse. In contrast, HBcrAg ≥4 log at EOT (HR = 4.494, $p < 0.001$) and month 3 (HR = 9.349, $p < 0.001$) were factors associated with clinical relapse. The combination of HBV-RNA and HBcrAg levels significantly differentiated the risk of relapse after treatment, and the prognostic power of the prediction model at month 3 was better than that at EOT. Lastly, we found that kinetics changes in novel biomarkers after cessation of NUCs differed significantly between patients with or without off-treatment relapse.
Conclusion: HBV-RNA levels predict risk of NUCs initiation or relapse after treatment. The combination of HBV-RNA and HBcrAg can be used to identify patients who can safely discontinue NUCs therapy.

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The correlation of P62 expression in predicting outcomes of HBV-related HCC after surgical resection

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Background and aims: P62, an autophagy adaptor and signaling hub, plays a critical role in hepatic carcinogenesis in patients with chronic hepatitis B virus (HBV) infection. However, its prognostic significance in HBV-related hepatocellular carcinoma (HCC) remains unclear. This study aimed to assess the impact of P62 expression levels on outcomes, including overall survival (OS) and recurrence-free survival (RFS), in patients undergoing surgical resection for HBV-related HCC.
Method: This retrospective study included 150 patients with HBV-related HCC who underwent surgical resection, collected from the Taiwan Liver Cancer Network (TLCN). Baseline demographics, serum biochemistry and pathological data from hepatectomy specimens were analyzed. P62 expression levels were determined using immunohistochemistry (IHC) staining, with a cutoff of 40% cytoplasmic staining. Prognostic factors for OS and RFS were identified using Cox proportional hazards models, and Kaplan-Meier survival analyses were employed for group comparisons.
Results: Among the 61 patients with high P62 expression, liver cirrhosis in non-tumor specimens was significantly more prevalent compared to those with low P62 expression (45.9% vs. 25.8%, $P = 0.011$). After a median follow-up of 123.5 months (interquartile range: 64–150 months), 65 patients had died, and 92 experienced HCC recurrence. The 5-year OS rates were 91.9% for patients with low P62 expression versus 77.3% for those with high P62 expression ($P < 0.001$), confirmed by multivariate analysis (hazard ratio HR 4.191, 95% confidence interval CI: 1.737–10.115, $P = 0.001$). Similarly, the 5-year RFS rates were 65.8% for low P62 expression and 28.8% for high P62 expression ($P = 0.002$). Multivariate analysis identified high P62 expression as an independent predictor of recurrence (HR 2.717, 95% CI: 1.688–4.372, $P < 0.001$).
Conclusion: In HBV-related HCC patients, high P62 expression is associated with poorer outcomes, significantly impacting both OS and RFS following surgical resection. P62 may serve as a valuable prognostic biomarker for this patient population.

SAT-258

Efficacy and safety of Tenofovir Amibufenamide and Tenofovir Alafenamide in patients with hepatitis B cirrhosis: a retro-prospective observational study

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Background and aims: Tenofovir amibufenamide (TMF) has shown potent antiviral efficacy in randomized clinical studies for chronic hepatits B (CHB). However, its efficacy and safety profile in patients with hepatitis B virus (HBV)-related cirrhosis is not well-established. This study aimed to assess the effectiveness and safety of TMF in the real world and compared compare its outcomes with those of tenofovir alafenamide (TAF).
Method: In this retro-prospective study, TMF-treated patients with hepatitis B cirrhosis were divided into treatment-naive (TN) and treatment experienced (TE) groups with low-level viremia. Using the propensity score matching method (PSM), TAF-treated patients were enrolled. A total of 606 subjects meeting the inclusion criteria were divided into two groups: TMF group (n = 304) and TAF group (n = 302). The virologic response (VR, HBV DNA < 10 IU/mL) rate, alanine transaminase (ALT) normalization rate, liver stiffness measurement (LSM), renal function parameters and blood lipid profiles during 48 weeks of treatment were evaluated. The fibrosis 4 score was also calculated in both groups.

Results: At week 24 and week 48, the VR rates in the TMF group were 63.2% and 85.7% respectively, compared to 59.3% and 82.4% in the TAF group ($P > 0.05$). Similar VR rates were observed in both groups among TN and TE patients with low-level viremia. ALT normalization rates were 86.8% (264/304) in the TMF group and 84.1% (254/302) in the TAF group ($P = 0.26$). In the TAF group, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels showed a slight increase ($P = 0.15$), which was not observed in the TMF group. Renal function parameters, including serum creatinine and estimated glomerular filtration rate, were no significant changes from baseline to week 48 in the two groups. LSM and fibrosis 4 score reduced significantly in both groups.
Conclusion: Both TMF and TAF have profound antiviral effectiveness and improvement of liver fibrosis among patients with hepatitis B cirrhosis. The effects on blood lipids are mild and regular monitoring of blood lipid profiles is recommended.

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Long-term outcomes of 'Grey Zone' (GZ) individuals living with HBeAg-negative chronic hepatitis B in a tertiary UK centre

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Background and aims: Hepatitis B 'e' antigen (HBeAg) negative chronic infection is a well-defined hepatitis B disease phase. However, owing to the dynamic nature of chronic hepatitis B (CHB), the natural history of individuals considered to be in the 'Grey Zone' (GZ) is less clear. Given the recent changes in international (WHO and Chinese) treatment guidelines, we aimed to evaluate baseline characteristics and long-term outcomes in people living with hepatitis B (PLWHB) designated to be in the GZ and excluded from treatment based on historical guidelines (EASL 2017). We report our findings from a Tertiary UK Centre.
Method: All PLWHB with HBeAg-negative CHB who first visited our Centre between 2010 and 2019 were included, if they either had baseline HBV DNA between 2,000 IU/mL and 20,000 IU/ml, or >20,000 and ALT ≤2×ULN. Individuals with co-infection, hepatocellular carcinoma (HCC) at baseline, alcohol misuse, on immunosuppression, or only one clinic visit were excluded. GZ individuals were defined by baseline HBV DNA ≥2,000 IU/ml and ALT > ULN, or HBV DNA >20,000 IU/mL and ALT ≤2×ULN. Treatment was initiated as per 2017 EASL criteria: a) ALT>×2ULN ± HBV DNA >20,000 IU/mL, b) presence of advanced fibrosis or cirrhosis, or c) Age>30 and persistently high HBV DNA levels.
Results: Out of 4,233 PLWHB, 1,635 were HBeAg-negative treatment-naïve at baseline, of whom 172 (10.5%) were designated GZ. The median follow-up for GZ individuals was 4.3 years (1.8–6.8). They were predominantly female (54.1%), mainly of White (39%), Black (31%) or Asian (21%) ethnicity and an average age of 43 ± 8 (NB 164 with Age > 30). During the follow-up period, 28 (16.3%) were initiated on treatment due to cirrhosis (n = 7), advanced fibrosis (n = 2), ALT > ×2ULN and HBV DNA > 20,000 (n = 6) or persistently high HBV DNA (n = 13). GZ individuals who required treatment were older than their peers (48 vs 41 years, p < 0.0001), predominantly male (60.3% vs 42.4%) and primarily of White origin or ethnicity (43% vs 35%). They also had higher baseline ALT (32.75 vs 26.9 u/L, p = 0.03) and liver stiffness measurement (7.3 vs 5.6 kPa, p = 0.002). Their HBV DNA level was also higher at baseline, but did not reach statistical significance (10,500 vs 5099 IU/mL, p = 0.39).
Conclusion: Some PLWHB designated as GZ are at risk of disease progression and are likely to require treatment. They share some distinguishing demographic and laboratory characteristics. These individuals can benefit from earlier treatment initiation to mitigate the risk of liver-related complications. Further prospective studies are deemed necessary to confirm these findings.

SAT-260

Autoimmunity in chronic hepatitis D: results from the HDV describe study cohort

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Background and aims: Chronic liver disease induced by hepatitis D virus (HDV) infection is associated with autoimmune manifestations. We aimed to investigate the prevalence of autoantibodies (auto-ab) and their association with clinical and virologic features in patients with chronic HDV infection.
Method: We studied 494 patients with chronic HDV infection from the HDV Describe study cohort. Non-organ-specific auto-ab (e.g., anti-nuclear auto-ab [ANA], anti-smooth muscle auto-ab [ASMA], anti-mitochondrial auto-ab [AMA], and anti-liver-kidney microsomal auto-ab [LKM]) were tested in diluted serum samples (1:80) by indirect immunofluorescence (IIF) on rat kidney/stomach/liver tissue slides (Euroimmun, Germany). Selected serum samples were analysed by immunoblot (IB) (Euroimmun, Germany) to detect antigen-specific auto-ab.
Results: The prevalence of ANA, ASMA, AMA, and LKM by IIF was 9.9% (n = 49), 12.3% (n = 61), 2.0% (n = 10), and 1.8% (n = 9), respectively. Among LKM+ patients, only one patient was LKM-1+ at IB. A high proportion of patients had anti-brush border auto-ab (n = 99; 20.0%); 9 patients were anti-parietal cells auto-ab+, 1 was anti-reticulin auto-ab+, and 1 was anti-lysosome auto-ab+. Patients who underwent previous interferon-based treatment showed a higher prevalence of ANA+ (14.6% vs. 8.3%; p = 0.046). ASMA+ was associated with liver cirrhosis (OR = 2.00, 1.08–3.70) and HDV RNA > 3 Log IU/mL (OR = 1.91, 1.03–3.52), whereas no association was observed between ASMA + and ALT > 40 U/L (OR = 1.12, 0.65–1.93). At multivariate analysis, ASMA+ results were significantly associated with liver cirrhosis (OR = 1.89, 1.01–3.51) independently from HDV RNA (OR = 1.57, 1.01–2.42) and ALT (OR = 1.22, 0.79–1.87).
Conclusion: In patients with chronic HDV infection, non-organ-specific auto-abs are often detected as epiphenomena of chronic viral infection. The assessment of circulating auto-ab might help to identify patients with high HDV replication and advanced liver disease. This research was supported by Gilead Sciences, Inc (study ID: IN-IT-980-6382).

SAT-261

Field evaluation of a novel hepatitis B core-related antigen rapid test (HBcrAg-RDT) for the identification of highly viremic pregnant women, the Gambia: preliminary results from a prospective diagnostic accuracy study

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Background and aims: Mother-to-child transmission (MTCT) represents the main route of transmission of hepatitis B virus (HBV) and identification of highly viremic pregnant women (HBV DNA level ≥200,000 IU/mL) for peripartum antiviral prophylaxis remains challenging in sub-Saharan Africa (SSA). We evaluated the performance of a novel RDT for hepatitis B core-related antigen (HBcrAg-RDT) using capillary blood and plasma to identify HBsAg-positive pregnant women with high viral loads in The Gambia.
Method: We prospectively recruited pregnant women at four health facilities in The Gambia during their first antenatal visit. We tested a total of 116 HBsAg-positive pregnant for the index serological tests (HBcrAg-RDT using capillary blood and plasma) and the reference molecular test (PCR, Xpert HBV Viral Load, Cepheid, using plasma). Our primary outcomes were the sensitivity and specificity of the HBcrAg-RDT using either capillary blood or using plasma at the laboratory to detect pregnant women with viral loads ≥200,000 IU/mL, quantified by RT-PCR (Xpert) as a reference.
Results: From March 18, 2024, to October 21, 2024, 116 treatment-naive HBV-infected pregnant women were enrolled in this study. Participants had a median age of 30 years (IQR 25–34), median HBV DNA of 100 IU/mL (10–1,445), 8/116 (6.9%) of participants with a high viral load. The sensitivity and specificity of the HBcrAg RDT using capillary blood and plasma were 0.88 (95% CI: 0.53–0.98) & 0.99 (0.94–1.00), and 0.88 (0.53–0.98) & 0.97 (0.92–0.99), respectively.
Conclusion: The HBcrAg RDT showed high diagnostic performance to identify pregnant women at risk of HBV MTCT who should receive peripartum antiviral prophylaxis. This could be a valuable tool for identifying high-risk pregnant women in decentralized antenatal care settings in resource-limited countries.

SAT-262

The asymmetry of the liver and spleen stiffness measures between patients with chronic hepatitis B and D reflects clinic-pathologic differences

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Background and aims: Chronic Hepatits D (CHD) infection causes an additional pathologic burden in patients (pts) with chronic Hepatitis B Virus (CHB) infection that accounts worsening clinical outcome. We studied the relative differences in liver (LSM) and spleen stiffness measurements (SSM) in pts with CHB and CHD, in order to point out potential added values of the SSM in this clinical setting.
Method: We studied 119 HBsAg+ pts, 71 CHB and 48 CHD undergoing regular follow-up at the Hepatology Unit of Pisa University Hospital. Physical examination, ultrasound scan, LSM and SSM (FibroScan®, Echosens,France) were performed on the same day, liver biochemistry and virological assays within one week.
Results: CHD pts were younger (median age: 47.8 vs 58.9 years, $p < 0.001$), with higher prevalence of female gender (43.8% vs 23.9%, $p = 0.038$) and mostly non-italian native (62.5% vs 26.8%, $p < 0.001$). Cirrhosis prevalence was similar between CHB and CHD pts [30 (42.3%) vs 27 (56.3%), $p = 0.189$]. CHD pts showed higher median HBsAg serum levels (3.65 vs 2.61 log UI/ml, $p < 0.001$), AST (28 vs 24 U/L, $p = 0.014$) and ALT (27 VS 19 U/L, $p = 0.001$). Median LSM was lower in CHB than in CHD pts [6.2 (2.8–71) vs 8.1 (2.8–33.1) kPa ($p = 0.004$)], whereas SSM was similar [25.6 (9.3–87.6) vs 26.8 (4.8–100) kPa, ($p = 0.569$)]; accordingly, median SSM/LSM-ratio was lower in CHD than in CHB [2.98 (1.00–9.64) vs 3.88 (1.09–16.25), $p = 0.003$). Median spleen diameter (SD) was 11.0 (7.0–18.0) cm in CHB and 12.0 (6.5–23.0) cm in CHD ($p = 0.079$). CHD showed a significantly lower SD/LSM ratio [1.33 (0.36–3.89) vs 1.78 (0.21–4.08), $p = 0.007$], but similar SD/SSM ratio [0.44 (0.14–2.06) vs 0.43 (0.14–1.07), $p = 0.688$]. Also in cirrhotic pts, median LSM was significantly lower in CHB than in CHD [9.7 (3.7–71) vs 13.3 (5.6–33.1) kPa, $p = 0.022$], whereas SSM was similar [34.0 (9.9–87.6) vs 33.3 (14.5–100) kPa, $p = 0.842$]. The SD/LSM ratio showed a trend to be lower in cirrhotic CHD [0.92 (0.36–2.09) vs 1.20 (0.21–2.89); $p = 0.054$]. In CHD, as compared to CHB pts, SSM correlated better with LSM, overall ($\rho = 0.761$ vs $\rho = 0.465$) and in cirrhotics ($\rho = 0.799$ vs $\rho = 0.432$); with SD overall ($\rho = 0.643$ vs $\rho = 0.489$) and in cirrhotics ($\rho = 0.647$ vs $\rho = 0.524$) and with platelets count overall ($\rho = -0.617$ vs $\rho = -0.498$) and in cirrhotics ($\rho = -0.726$ vs $\rho = -0.638$).
Conclusion: Combining LSM and SMM provides a useful differential clinic pathologic characterization of liver disease in patients with CHB and CHD. The significantly lower SD/LSM ratio found in CHD pts, suggests the specific role of HDV induced necro-inflammation as a driver of disease progression with splenomegaly and platelet count reduction. Longer follow up in CHD treated patients are needed to define the curative impact of the current antivirals.

SAT-263

Enhancing hepatitis delta virus detection in Spain with the Delta Double Reflex (DDR) study

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Background and aims: Hepatitis delta virus (HDV) is responsible for the most severe form of chronic viral hepatitis due to its rapid progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma. The Delta Double Reflex (DDR) Spain study seeks to implement a double reflex diagnostic strategy for HDV, evaluate the seroprevalence and prevalence of chronic HDV infection, and characterize the virological, clinical, and demographic features of HDV in Spain.
Method: This multicenter, national study follows an ambispective and observational design, comprising a retrospective evaluation of DDR implementation during 2022–2023 and a prospective phase starting in 2024 to examine the virological, clinical, and demographic characteristics of diagnosed patients. The study examined the diagnostic cascade, from identifying HBsAg-positive individuals to confirming HDV-RNA positivity
Results: The cohort included 41,449 HBsAg-positive patients from 69 centers across 16 of 17 Autonomous Communities (ACs) of Spain. Reflex testing rates increased significantly from 55.1% in 2022 (participation range: 4.2%–98.7%) to 64.8% in 2023 (25%–100%; $p < 0.0001$). The anti-HDV seroprevalence declined from 5.6% (95%CI 5.2–6.1) in 2022 to 4.9% (95%CI 4.6–5.3) in 2023, with significant inter-regional variability. Testing for HDV-RNA among anti-HDV-positive individuals improved from 72.6% in 2022 to 90.8% in 2023 ($p < 0.0001$). The prevalence of chronic active HDV infection decreased from 40.2% (95%CI 35.5–45.1) in 2022 to 31.6% (95%CI 28.0–35.3) in 2023. Starting in the third quarter of 2024, the prospective phase had enrolled 87 anti-HDV-positive patients with a median age of 53 years (IQR 42–58), 59% being male and 54% of Spanish origin. Co-infection rates included 20% for HIV and 21% for HCV (2 with active hepatitis C). Elevated fibrosis markers were observed in 22% of patients with FIB-4 > 2.67, and 16.9% presented APRI > 1.5. Active HDV-RNA was detected in 37% (n = 32) of cases, with a median viral load of 4.17 log IU/mL (IQR 3.18–5.10).
Conclusion: This study, the largest of its kind in Spain, underscores significant disparities in HDV diagnostic practices across ACs. These findings highlight the urgent need for nationwide efforts to standardize diagnostic protocols, enhance professional education, and promote awareness to ensure equitable care and better outcomes for HDV patients.

SAT-264

New strategies to enhance molecular diagnosis of hepatitis Delta

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Background and aims: Hepatitis delta virus (HDV) aggravates chronic hepatitis B virus (HBV) infection, accelerating progression to liver failure, cirrhosis or hepatocarcinoma. While 5–10% of HBV patients are estimated to have HDV co-infection, the true prevalence is likely underestimated. Accurate detection and quantification of ribonucleic acid (RNA) of HDV are crucial for the effective management of chronic HDV hepatitis. However, variability of commercial assays or viral genotype may affect the accuracy of results. Unlike other RNA viruses, HDV RNA exhibits unique folding and supercoiling characteristics. The aim of our study was to assess the impact of pre-heating on RNA elution for the detection of HDV.
Method: We conducted a retrospective study for HDV RNA detection and quantification. Genetic material was extracted from 300 microlitres of serum using the TANBead Maelstrom 4800 system, with a final elution volume of 60 microlitres. A 10 microlitres aliquot of the eluate underwent thermal-shock, consisting of heating at 95°C for 10 minutes followed by freezing at −20°C for another 10 minutes, as per the manufacturer's instructions. Both heat-treated and untreated aliquots were analysed in parallel using the Hepatitis Delta Realtime PCR kit (Vircell SL, Granada) on a BioRad CFX96 thermal cycler.
Results: We analysed 118 serum samples, 49 were negative and 69 positive, with a 97.5 % qualitative agreement between results obtained with and without pre-treatment. Pre-heating enabled detection of viraemias above the detection limit (24 international units per mililitre [IU/ml], 43 UI/ml and 118 IU/ml) in three samples initially reported as negative. Among positive samples, pre-heating increased viraemia by at least one logarithm in 74 % (51/69) of cases. Changes by log level, compared to quantification without pre-heating, were as follows: a) Log 6: 2/5 increased by one log a) Log 5: 5/7 increases by one log; b) Log 4: 9/18 increased by one log, 4/18 by two logs; c) Log 3: 7/16 increased by one log, 4/16 by two logs; d) Log 2: 6/14 increased by one log, 5/14 by two logs; e) Log 1: 2/3 increased by one log. Notably, only five positive samples showed no log increase after pre-heating.
Conclusion: Our findings demonstrate that pre-heating enhances HDV-RNA detection and quantification. This strategy could improve the diagnosis and monitoring of patients co-infected with HDV and HBV.

SAT-269

Molecular epidemiology of hepatitis delta virus in Spain using whole-genome sequencing

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Background and aims: Currently, eight distinct genotypes of HDV have been identified, each encompassing multiple subgenotypes. Genotype 1 (G1) is the most widely distributed worldwide, with genotype 5 (G5) following in prevalence. Investigating the molecular epidemiology of HDV is crucial for understanding its pathogenic potential, implications for treatment strategies, and diagnostic challenges, as RNA detection methods may vary in their effectiveness across genotypes. This research focused on examining the molecular epidemiology of HDV in Spain through whole-genome sequencing (WGS).

Method: A retrospective observational study was carried out between August 2019 and November 2024, focusing on patients with confirmed HDV RNA positivity. Genotyping was performed using WGS, employing overlapping primers and Illumina's tagmentation-indexing protocol on a NextSeq 1000 platform. Sequence assembly was performed using the CLC Genomics Workbench, referencing the HDVdb database for genotype determination. Phylogenetic relationships were inferred using the Neighbor-Joining method in the MEGA software. Sequences with > 90% coverage were included in the analysis alongside reference sequences representing all eight recognized genotypes and their subgenotypes. Potential recombination events were assessed using the RDP5.63 software.

Results: A total of 122 patients were analyzed, of whom 66 (54.1%) were of Spanish origin. The median HDV RNA level was Log 4.91 (IQR: 3.74–6.17). Genotyping was successful in 112 cases (91.8%) with an average sequence coverage of 98% (range: 70%–100%). G1 was the most frequent (101 cases, 90.2%), followed by G5 (10 cases, 8.9%), exclusively identified in patients of West African origin. One case (0.9%) belonged to genotype 7. Genotyping failed in 10 samples due to either non-amplification (3 cases) or insufficient coverage (7 cases). Phylogenetic analysis was performed on 110 sequences with >90% coverage. Within G1, subgenotype 1d represented 87.1% of cases, while subgenotype 5b accounted for 60% of G5 cases. None of the 112 sequences displayed evidence of recombination.

Conclusion: HDV genotyping provides critical insights into its molecular epidemiology within Spain. Consistent with previous studies, G1 is the most prevalent among Spanish patients, while G5 is exclusively linked to individuals of West African descent. These findings offer valuable data on the distribution of HDV genotypes and their regional variability.

SAT-270

Burden of hepatitis D virus infection in Italy: results from the HDV describe study

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Background and aims: Migratory flows are reconstituting the hepatitis D virus (HDV) reservoir in Italy, displacing the infection in Italians. We aimed to compare the features of contemporary Chronic Hepatitis D (CHD) in native Italians and foreign-born patients.
Method: Consecutive hepatitis B surface antigen (HBsAg) carriers positive for antibodies to HDV (anti-HDV) referred to 32 Italian Centres, were prospectively enrolled from 08/2022 to 07/2024. Sera were centralized in Torino for virologic assessment.
Results: Overall, 432 of 515 (83.9%) patients were HDV-RNA-positive (4.39, IQR 1.30–5.82 Log IU/mL; 99.0% HDV genotype-1). HDV-RNA levels correlated with ALT (rs = 0.58, 0.51–0.63) and liver stiffness (rs = 0.28, 0.19–0.37). The 317 native Italians (61%) were older than the 198 foreign-born patients (39%) (median age 60, IQR 55–65 vs 46, IQR 39–54 years; $p < 0.001$), most likely males (68.1% vs 49.5%; $p < 0.001$), and exhibited a higher prevalence of liver cirrhosis (70.3% vs. 50.5%; $p < 0.001$) and hepatocellular carcinoma (14.8% vs. 0.5%; $p < 0.001$). Most (70.3%) of the ageing native Italians had liver cirrhosis acquired long ago. However, 29.7% (94/317) had no cirrhosis: their features denoted an active and viremic CHD in 44.7% (42/94) and an inactive/minimal disease with low viremia (<3 Log) in 55.3% (52/94), presumably acquired as a slow infection decades before. Despite the younger age, foreign-born patients already exhibited a 50.5% rate (100/198) of symptom-free compensated cirrhosis (median albumin: 4.1, IQR 3.8–4.4 g/dL); in the other 45.5% (98/198), 50 (51.0%) had an active CHD and 48 (49.0%) an inactive/mild infection with low viremia (<3 Log).
Conclusion: In Italy, the current scenario of chronic HDV infection is more heterogeneous than expected, changing the perspective of CHD as a most severe disease; about a quarter of native Italians and foreign-born patients had a lingering less virulent CHD, and half of foreign-born patients presented with recently acquired liver cirrhosis, which was compatible with a stable clinical condition. This research was supported by Gilead Sciences, Inc (study ID: IN-IT-980-6382).

SAT-271

Impact of drugs for hepatocellular carcinoma development in chronic hepatitis B patients who treated with entecavir and tenofovir disoproxil as initial therapy: population-based study

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Background and aims: Entecavir (ETV) and Tenofovir disoproxil fumarate (TDF) have been used as the first-line antiviral agents for patients with treatment-naive chronic hepatitis B (CHB), resulting in successful decline of hepatocellular carcinoma (HCC) development and mortality. However, there has been controversy about the equivalence of long-term efficacies between ETV and TDF. In addition to antiviral agents, other drugs including aspirin, statin, and H1-antihistamines had protective effects on HCC development in several studies. Thus, we aimed to compare these effects of diverse drugs in a unified population-based cohort.
Method: Using the Korean National Health Insurance Service database, we extracted a nationwide population cohort of patients with CHB who initiated ETV or TDF between January 2012 and December 2020. Then, a 15,569 pair propensity score-matched cohort was constructed. We compared cumulative incidence rates of HCC and mortality one year after starting treatment according to the drug prescription and dosage, using competing risk analyses.

Results: The incidence of HCC was 51.0 and 41.5 per 1000 person-years in the ETV and TDF groups of a total cohort. In the matched cohort, HCC development was significantly lower in the TDF group than ETV group (subdistribution hazard ratio [SHR], 0.91). In addition, the use of statin and H1-antihistamines was significantly associated with a low risk of HCC development (SHR, 0.57 and 0.69, respectively). Even after applying antiviral groups, the low risks of statin and H1-antihistamines independently remained (SHR, 0.58 and 0.69, respectively). Furthermore, H1-antihistamines use had a dose-response relationship with the risk of HCC. The SHR of the H1-antihistamines use of 28–90, 90–180, and > 180 cumulative defined daily doses were 0.48, 0.31, and 0.29, respectively, relative to no H1-antihistamines use.
Conclusion: In this study, TDF showed a more protective effect on HCC development compared to ETV. In addition, the use of statin and H1-antihistamines was independently associated with a lower risk of HCC development relative to no use of each drug. The effects of various drugs on the development of HCC were confirmed, and further research is needed on these mechanisms.

SAT-272

Comparing Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate in reducing hepatocellular carcinoma risk in chronic hepatitis B: a propensity score matching study

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Background and aims: Tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) are both recommended as first-line treatments for antiviral-naïve patients with chronic hepatitis B (CHB). However, it remains controversial which drug is more effective in preventing hepatocellular carcinoma (HCC). We aimed to compare the effects of TAF and TDF on HCC risk.
Method: We included 1,628 treatment-naïve CHB patients who underwent antiviral therapy with either a TAF-based regimen (TAF group: n = 335) or TDF only (TDF group: n = 1,293) between 2007 and 2021. The TAF group consisted of patients who received TAF as a first-line treatment and those who switched from TDF to TAF. Propensity score (PS) matching was used to reduce the effects of confounding factors.
Results: After PS matching, we analyzed data from 334 patients in the TAF group (mean age: 48.0 ± 11.7 years; 192 men [57.5%]) and 573 patients in the TDF group (mean age: 47.4 ± 11.6 years; 326 men [56.9%]). During a 60-month follow-up, 8 patients in the TAF group (2.4%) and 46 patients in the TDF group (8.0%) developed HCC. TAF treatment was associated with a significantly lower risk of HCC compared to TDF (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.16–0.72; P < 0.001). In multivariate analysis, factors independently associated with HCC development included age (adjusted HR [aHR], 1.07; P < 0.001), liver cirrhosis (aHR, 2.02; P = 0.045), diabetes (aHR, 4.78; P < 0.001), alcohol use (aHR, 3.07; P = 0.002), and TAF treatment (aHR, 0.22; P < 0.001).
Conclusion: TAF treatment was associated with a 66% lower risk of HCC compared to TDF treatment. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

SAT-273

Characteristics and predictors for elevated alanine transferase in 3,399 treatment-naïve HBV/HDV co-infected patients, with comparison to propensity score-matched mono-HBV infected patients

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Background and aims: Chronic HDV infection causes the most severe form of viral hepatitis. However, knowledge regarding the characteristics and predictors of elevated alanine aminotransferase (ALT) in treatment-naïve patients with HBV/HDV co-infection is limited, and data on young adults are lacking. This large cohort study aimed to (1) characterize ALT levels, virological, and fibrosis parameters in treatment-naïve patients with HBV/HDV co-infection (2) identify predictors of elevated ALT, and (3) compare these parameters in propensity score-matched pairs of HBV/HDV co-infected and mono-HBV infected patients, to elucidate the impact of HDV.
Method: We analyzed 51,113 individuals who underwent HBsAg testing at the Liver Center, Mongolia, between 2015–2023, using data from an electronical database. Persons with prior hepatocellular carcinoma, HCV or HIV co-infection, or previous anti-HDV/HBV therapy were excluded. HBsAg+ patients were categorized into two cohorts based on virological parameters: 1) HDV infection, if serum HDV RNA level ≥50 IU/mL (n = 3,399), and 2) mono-HBV infection, if negative anti-HDV or HDV RNA test, and no record of anti-HDV or HDV RNA positivity (n = 2,556). Pairwise comparisons were conducted using Spearman correlation coefficient (rho). Univariable and multivariable logistic regression analyses were conducted to identify predictors for elevated ALT. Propensity score matching for sex, age and HBsAg test date resulted in 2,231 matched pairs of HBV/HDV co-infected and mono-HBV infected patients, with odds ratio (OR, 95% CI) calculated for risk of ALT elevation.
Results: Among 3,399 patients with HDV infection, elevation of ALT levels was seen in 78.5% of patients, with the highest frequency in the 18–29 years age group (n = 340, 84%). This age group displayed 4.80-odds for elevated ALT, 2.76-odds of elevated GGT, and 5.08-odds of cirrhosis, compared to matched mono-HBV infected patients (all p < 0.05). The proportion of elevated ALT increased with higher fibrosis stages, with 93% displaying elevated ALT among those with liver stiffness measurements (LSM) ≥ 15.2 kPa. ALT levels correlated weakly with HDV RNA (rho = 0,23; p < 0.001) and LSM levels (rho = 0,37, p < 0.001), moderately with GGT levels (rho = 0.48, p < 0.001), while no correlation with HBV DNA or HBsAg levels in HBV/HDV co-patients. In multivariable analysis, significant predictors of elevated ALT were age <30 years, elevated GGT level and HDV RNA ≥100,000 IU/mL.
Conclusion: In this large cohort of patients with HDV infection, hepatic necro-inflammatory process, as indicated by elevated ALT and GGT levels, was significantly more frequent and severe already in patients under 30 years compared to matched mono-HBV infected patients. These findings underscore the urgent need for early antiviral intervention in HDV infection to prevent severe disease progression and reduce the risk of hepatocellular carcinoma.

SAT-274

Enhanced 2- and 3-Year recurrence-free survival rates with switching from Entecavir to Tenofovir post-radiofrequency ablation treatment in HBV-HCC patients

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Background and aims: Antiviral therapy for hepatitis B virus (HBV) is crucial for reducing the recurrence rate following curative treatment of HBV-related hepatocellular carcinoma (HCC). There remains controversy regarding whether nucleoside analogs (NAs) and nucleotide analogs (NtAs) differ in their efficacy in preventing HCC recurrence after radiofrequency ablation (RFA). This retrospective

study aimed to compare the 3-year recurrence-free survival (RFS) rates among HBV-related HCC patients who switched from entecavir (ETV) to tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) after RFA with those who continued long-term ETV therapy.
Method: This study consecutively enrolled patients with hepatitis B cirrhosis and newly diagnosed HCC at Tianjin Third Central Hospital between August 2018 and December 2020. All patients had received more than one year of ETV treatment before the diagnosis of HCC. We observed the 3-year HCC recurrence rate in patients who switched to NtAs (TDF or TAF) post-RFA and compared it with those who remained on long-term ETV therapy. Propensity score matching (PSM) was used to balance confounding variables, including age, sex, tumor stage, Child-Pugh classification, and alanine transaminase (ALT) levels, and 3-year survival curves were plotted.
Results: A total of 270 patients with initially diagnosed HBV-related HCC were included in this study. Among them, 203 patients who underwent RFA for HCC were divided into two groups based on the type of oral antiviral medication post-RFA: the ETV group (n = 152) and the switch therapy group (from ETV to TDF or TAF, n = 47). The 1-, 2-, and 3-year RFS rates were 71.05% vs 85.11% (P = 0.054), 44.08% vs 80.85% (P < 0.01), and 39.47% vs 72.34% (P < 0.01) for the ETV and switch therapy groups, respectively. After propensity score matching, the switch therapy group showed significantly lower HCC recurrence rates at 2 years (hazard ratio [HR] 0.298, 95% confidence interval [CI] 0.140–0.635, P = 0.003) and 3 years (HR 0.366, 95% CI 0.182–0.735, P = 0.006) compared to the ETV group, although no significant difference was observed at 1 year.
Conclusion: In HBV-HCC patients after RFA treatment, switching from ETV to NtAs (TDF or TAF) results in higher 2- and 3-year RFS rates compared to continuous NA therapy, indicating that NtAs may be superior to NAs in reducing the recurrence rate following curative treatment of HBV-related HCC.

SAT-275-YI
Likelihood level of a functional HBV-specific CD8 cell response upon discontinuation of eAg(-) chronic hepatitis B treatment correlates with long-term clinical outcome
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Background and aims: There are not clear predictors of HBV control after nucleos(t)ide analogue (NA) withdrawal in e-antigen negative chronic hepatitis B (CHBe(-)). A logistic regression model (LRM) predicting the likelihood of functional HBV-specific CD8 cell response upon NA stop (Peña-Asensio, Aliment Pharm Therap 2022) could help select cases able to control HBV off-treatment. The aim of this study was to test the validity of this LRM regarding to this issue.
Method: 27 Caucasian CHBe(-) patients (64% male, Age 47 ± 11 years) with liver fibrosis <F3 were chosen to stop NA at Guadalajara University Hospital (Spain). Patients were followed for 60 months or until retreatment or functional cure. Treatment was restarted if patient developed virologic flare (ALT > 5 upper limit of normal plus HBsAg level increase) or HBV DNA > 10000 IU/ml on 3 occasions or if HBV DNA was between 2000 and 10000 IU/ml plus age >50 years and/or transient elastography >9 kPa. Patients were followed monthly for first six months and every three months thereafter. ALT, HBV DNA and HBsAg levels were tested at each appointment. Patients were split into two groups according to LRM probability (P < 0.7 & P ≥ 0.7) based on the following predictors: treatment duration, age at treatment start, HBsAg level, patient age. Repeated measures ANOVA was used to compare HBsAg decline between both cohorts. Generalized linear regression with Poisson distribution was used to compare HBV DNA events >10000 IU/ml between both groups. Kaplan-Meier curves were used to compare retreatment-free survival between both cohorts. Speed of HBsAg change was calculated by the tangent of the slope angle of HBsAg curve. In 13 HLA-A2+ cases, at treatment stop, HBV-specific CD8 cell expansion was tested after 10day HBV-core/HBV-polymerase (pol) peptide in-vitro challenge. Functional cure rate was compared between groups.
Results: HBsAg level decline was 7-fold faster in P ≥ 0.7 group (p < 0.001). HBV DNA > 10000 IU/ml incidence rate ratio was 66% lower in P ≥ 0.07 group (p = 0.034). 1/13 patients in P ≥ 0.7 group and 7/14 in P < 0.7 cohort received retreatment with significantly different Kaplan-Meier survival curves, with a 50% increase in retreatment-free survival in P ≥ 0.7 group (p = 0.019). Functional cure was achieved in 4 cases in P ≥ 0.07 group and no case in P < 0.07 cohort (p = 0.027). No patient experienced liver failure, and all retreated patients achieved negative HBV DNA after NA restart. 100% of P ≥ 0.07 and 28% of P < 0.07 HLA-A2+ patients had expanding HBV-specific CD8 cells after HBVcore/HBVpol stimulation at treatment stop (p = 0.011).
Conclusion: In CHBe(-), a high probability of functional HBV-specific CD8 cell response at the time of NA withdrawal correlates with faster HBsAg decline, lower incidence of HBV DNA > 10.000 IU/ml, low risk of retreatment, presence of a reactive HBV-specific CD8 response and higher rate of functional cure after 60-month follow-up.

SAT-276
Investigation the persistent effects following HBsAg clearance in chronic hepatitis B patients treated with Interferon therapy
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Background and aims: The clinical cure regimen for chronic hepatitis B (CHB) based on interferon therapy is increasingly attracting the attention of clinicians; however, there are few studies on the sustained response of HBsAg after achieving HBsAg clearence. This study investigates the persistent effects following HBsAg clearance in CHB patients treated with Peg-IFNα-2b treatment, aim to explore the sustained viral response after HBsAg clearance.
Method: CHB patients who received Peg-IFNα-2b alone or in combination with nucleos(t)ide analogues (NAs) and achieved HBsAg clearance at Tianjin Third Central Hospital from January 2018 to May 2024 were collected. Regular follow-ups were conducted to observe the dynamic changes of HBsAg. The time of HBsAg recurrence (HBsAg > 0.05 IU/mL) was recorded, the pattern of HBsAg recurrence was analyzed, and the optimal timing for sustained HBsAg clearance was explored.
Results: A total of 173 patients with chronic hepatitis B or compensated cirrhosis were included. The average age was 41.5 ± 9.0 years, with 16.28% with compensatory cirrhosis. The median follow-up duration was 89.3 weeks, with HBsAg recurrence in 26 patients, yielding a recurrence rate of 15.03% (26/173). Of the 26 patients who recurred, 50% (13/26) occurred within 24 weeks, and 80.77% within 48 weeks, with a gradual decrease in recurrence after 48 weeks. The sustained viral response (SVR) rate at 48 weeks was 95.45%, and it stabilized at 100% at 120 weeks and beyond. For patients with regular re-examinations, no recurrence was observed after 72 weeks. At the time of HBsAg recurrence detection, ALT, AST, and TBiL were normal in all 26 patients, with a median HBsAg level of 0.70 IU/mL (0.05 IU/mL–8.13 IU/mL), and only one case was accompanied by low-level positivity for HBV-DNA (117 IU/ml). No adverse events such as liver failure, decompensated cirrhosis, or hepatocellular carcinoma occurred during the follow-up period

Conclusion: CHB patients have good durability after achieving HBsAg clearance with Peg-IFNα-2b treatment, but there is still a risk of HBsAg recurrence after treatment discontinuation. Most HBsAg recurrences occur within 48 weeks after treatment cessation. SVR48 is a necessary follow-up time period for CHB patients after HBsAg clearance, SVR72 may be an ideal follow-up time point, and SVR120 can be considered as an extended follow-up time point.

SAT-277

Accurate prediction of long-term hepatitis B surface antigen seroclearance with machine learning: prognostic and management implications

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Background and aims: Hepatitis B surface antigen (HBsAg) seroclearance is a favourable yet uncommon outcome in chronic hepatitis B (CHB). With the emergence of novel hepatitis B virus (HBV) antivirals, accurate prediction of HBsAg seroclearance may influence management decisions. We utilized machine learning approaches on routinely available clinical data for predicting HBsAg seroclearance.

Method: We included CHB patients with longitudinal quantitative HBsAg (qHBsAg) data up till 15 May 2024 from Queen Mary Hospital, Hong Kong. Patients were randomly divided in an 8:2 ratio into training and internal validation cohorts. Baseline clinical variables (Age, sex, alanine aminotransferase [ALT], antiviral treatment status, hepatitis B e antigen [HBeAg] status, HBV DNA) were utilized to develop a baseline random forest model. A gated recurrent unit (GRU) model was also developed using longitudinal qHBsAg data. We subsequently merged the baseline and longitudinal models to develop a combined model for predicting HBsAg seroclearance. Model performance was evaluated through area-under-curve (AUC), positive and negative predictive values (PPV/ NPV), specificity, and sensitivity.

Results: This analysis included 4,287 patients (62.5% male; mean baseline age 48.0 ± 12.8. years; median baseline ALT 28.0 [20.0–42.0] U/L; 24.9% baseline HBeAg positive; 45.2% on antivirals at baseline for an average of 5.5 [3.6–8.1] years; baseline median qHBsAg 630.8 [117.1–1875.5] IU/ml). After follow-up for 7.0 [6.1–15.6] years, 526 patients (12.3%) developed HBsAg seroclearance at a median time of 4.2 [3.0–9.3] years from baseline. In the validation cohort, the baseline random forest model achieved AUC 0.74 (PPV 0.62, NPV 0.89, specificity 0.97, sensitivity 0.28), whereas the longitudinal GRU model achieved AUC 0.88 (PPV 0.69, NPV 0.94, specificity 0.96, sensitivity 0.61) for predicting HBsAg seroclearance. The diagnostic performance improved with combination of both baseline and longitudinal models, and our combination model achieved AUC 0.91 (PPV 0.75, NPV 0.93, specificity 0.97, sensitivity 0.53). The performance of the model remained robust after stratification by age, sex, antiviral treatment status, and fibrosis level respectively.

Conclusion: Using routinely available data, we developed and validated a highly accurate machine learning model for predicting HBsAg seroclearance. With high specificity of 97%, the model can identify patients who are unlikely to achieve HBsAg seroclearance, and these patients may attain the greatest benefits from novel HBV antivirals.

SAT-278

A marker of cccDNA transcription - hepatitis B core-related antigen (HBcrAg) - mimics HBV RNA decline during antiviral therapy with bulevirtide in chronic hepatitis delta (HDV) patients

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Background and aims: HBsAg mediates viral entry via NTCP receptor attachment and is critical to propagation of hepatitis delta virus (HDV). HBsAg originates from both cccDNA and integrated DNA. Hepatitis B core-related antigen (HBcrAg) and pre-genomic HBV RNA (pgRNA) reflect cccDNA transcriptional activity. Bulevirtide (BLV) mimics a pre-S1 HBsAg protein and blocks viral entry to hepatocyte by inhibitory competition. While total HBsAg concentrations did not change during BLV therapy, there no data comparing changes in HBcrAg, pgRNA and pre-S1 during BLV therapy. We aimed to compare levels of HBV markers (HBV DNA, HBsAg, HBcrAg, pgRNA, pre-S1) in sequential samples one year before therapy vs during BLV therapy and assess changes in relation to therapy response (HDV RNA decline).

Method: Plasma samples from 14 patients with HBV/HDV co-infection (all HDV RNA+, median age 45 yrs, 8 males, 79% compensated cirrhosis) treated with BLV were collected sequentially one year before therapy start, at therapy start, week 24 & 48 and levels of following markers were measured: HBsAg by Abbott Architect® [IU/ml], HBcrAg by CLEIA Fujirebio [log_{10}U/ml], pgRNA by Abbott Diagnostics dual-target real-time-PCR assay, LLoQ = 0.49 log_{10}U/ml, pre-S1 by Abbkine ELISA [IU/ml] and HDV RNA by in-house real-time PCR (LLoQ 640 IU/ml) at same time-points. The levels of HBV DNA, HBsAg, HBcrAg, pgRNA, pre-S1, HDV RNA and ALT were compared between time-points (pre-therapy vs on-therapy) and according to HDV RNA decline from start vs week 24 & 48.

Results: Therapy start levels of HBsAg, HBcrAg, pgRNA, pre-S1, HDV RNA & ALT were not predictive of HDV RNA decline >2 log_{10} at week 24 and 48. Levels of all markers 1 year before start of therapy vs at therapy start were similar. *Week 24 vs therapy start*: From 12 patients who completed week 24: 5 (42%) patients had >2 log_{10} HDV RNA decline, 5 (42%) patients had HDV RNA drop 1–2 log_{10} and 2 (16%) patients decline <1 log_{10}. There were significant changes in levels of ALT (−46 IU/L), HDV RNA (−1.72 log_{10}IU/ml) and HBcrAg (−1.42 log_{10}U/ml), all $p < 0.01$ and increase in pre-S1 levels (66 IU/ml, $p = 0.05$), but HBsAg (9082 vs 9389 IU/ml, $p = 0.67$), HBV DNA (0 vs 0 IU/ml, $p = 1$) and pgRNA (1.5 vs 1.58 log_{10}U/ml, $p = 0.58$) levels were similar. *Week 48 vs therapy start*: From 10 patients who completed week 48: 5 (50%) patients had >2 log_{10} HDV RNA decline, 4 (40%) patients had HDV RNA drop 1–2 log_{10} & 1 (10%) patient had decline <1 log_{10}. There were significant changes in levels of ALT (−53 IU/L), HDV RNA (−2.13 log_{10}IU/ml) and HBcrAg (−1.78 log_{10} U/ml) and decline in pre-S1 levels (−77 IU/ml), all $p < 0.01$, but HBsAg (9082 vs 8829 IU/ml, $p = 0.33$), HBV DNA (0 vs 0 IU/ml, $p = 1$) and pgRNA (1.5 vs 1.45 log_{10}U/ml, $p = 0.28$) levels did not differ. These were similar irrespective of BLV therapy responses for weeks 24 & 48.

Conclusion: Of several novel HBV biomarkers only HBcrAg levels mirrored HDV RNA decline during antiviral therapy with BLV, in contrast to no changes in levels of HBsAg and pgRNA. Larger studies assessing the role of HBcrAg during HDV therapy would be beneficial.

SAT-279

Infants with chronic hepatitis B can achieve functional cure through a definite duration of antiviral treatment

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Background and aims: This study aims to investigate whether and how antiviral treatment can achieve a functional cure for infants with chronic hepatitis B (CHB).
Method: This real-world study enrolled 28 infants (13 boys and 15 girls) with HBeAg-positive CHB who were perinatally infected with HBV via mother-to-child transmission (MTCT). The median baseline age was 9 months. Five infants received lamivudine monotherapy. The other 23 cases started LAM monotherapy at first, and then interferon-α treatment was added when they were more than 12 months old. The virological responses, functional cure and treatment safety were analyzed for 36 months (treatment plus follow-up visit duration).
Results: All 28 infants with CHB (baseline median HBV DNA was 7.50 log10 IU/ml) had full viral suppression after antiviral treatment and the median time taken for undetectable HBV DNA was 6 months (range: 1–19 months). Correspondingly, the median time taken for HBeAg seroconversion was 7 months (range: 3–18 months) for 27 infants, and one case didn't obtain HBeAg seroconversion; 25 of the 28 infants achieved a functional cure through a median time of 9 months (range: 3–28 months) since baseline. Three infants didn't achieve functional cure at the 36-month endpoint, but they achieved undetectable HBV DNA, and two of them had HBeAg seroconversion. Flu-like symptoms associated with IFN-α treatment were the common side effects, however, no serious adverse events were observed. In discussion section, we analyzed the natural history and related characteristics of infants with HBV infection.
Conclusion: Our findings indicate that under one-year-old infants with CHB can achieve a significantly high probability of a functional cure when they receive a definite duration of antiviral treatment using available agents.

SAT-280

SE London emergency department (ED) testing for BBV demonstrates a high HBV prevalence: an effective public health intervention to address inequalities for people living with HBV

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Background and aims: From April 2022, in areas of high (>5/1000) HIV prevalence, NHS England launched 'opt out' testing for blood borne viruses BBV (HIV, HBV and HCV) in 34 Emergency Departments (EDs) with integrated linkage to clinical care. SE London is an area of high deprivation and high diversity with 38% of the population born outside the UK (ONS). We aim to report the results of the first 18 months of BBV testing in all EDs in SE London.
Method: We report on ED testing at three SE London trusts. Due to staggered initiation there was 18 months of data Nov 2022-May 2024 from two trusts and May 23–May 24 for the third trust. Screen positivity and demographics including deprivation index for people newly diagnosed with HBV were reported.
Results: Between November 2022 and May 2024 in SE London, 565,289 people attended ED. After exclusion of duplicate testing, 282,363 had blood tests and were eligible for BBV testing. Of these, 223044 (79%) underwent HBV testing. We found 1885 individuals screen positive for HBsAg, giving a SE London HBV prevalence rate of 1885/223044 = 0.85%. This compares to 2704 positive HIV tests out of 247,699 HIV tests performed giving an HIV prevalence of 1.09%. Out of the 1885 positive tests, 756/1885 (40%) were confirmed new diagnoses. Demographics of the 756 people newly diagnosed with HBV are as follows: 482 (64%) male, 272 (36%) female. Median age 49 yrs, IQR (39, 59). 344 (45%) Black ethnicity (271 (78%) of whom are black African), 25 (3.3%) White British, 75 (9.8%) White other Europe, 46 (6.1%) Chinese or SE Asian, 146 (19%) not known. Where 1 is the most deprived and 10 the least deprived; 392 (52%) live in IMD decile 1–3, 218 (29%) decile 4–6, 106 (14%) decile 7–10.
Conclusion: ED testing has been a success in SE London, with 79% of eligible persons being tested. SE London has the highest prevalence of HIV in the UK and these results show a similar high prevalence of Hepatitis B infection. 40% of the patients with positive HBV were confirmed new diagnoses. ED testing is reaching a group of patients with undiagnosed HBV, the majority of whom are of black African ethnicity and living in the most deprived areas. The fact that they have reached a median age of 49 yrs without knowing the diagnosis suggests that they have not had the opportunity to be tested previously and would not be tested in other settings. This represents a health inequality, as in a proportion of patients, the lack of access to testing will eventually result in decompensated cirrhosis or liver cancer. ED testing helps address this inequality and in an area of high HBV prevalence is an important public health tool to prevent future morbidity and HBV transmission.

SAT-285-YI

Performance of the PAGE-B score for the prediction of hepatocellular carcinoma in chronic hepatitis B patients with metabolic dysfunction

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Background and aim: The presence of metabolic comorbidities and metabolic dysfunction-associated steatotic liver disease (MASLD) are associated with an increased risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). The PAGE-B score, which includes age, sex, and platelet count, stratifies the risk of HCC in patients with HBV mono-infection, but whether this score can be applied in CHB patients co-affected by metabolic dysfunction is unclear.
Method: Our study cohort included patients with CHB mono-infection from 9 centers in Europe and Canada, who had at least one metabolic comorbidity (overweight, diabetes mellitus type 2 [DM2], hypertension or dyslipidemia). The PAGE-B score was calculated patients were stratified as at low, intermediate or high risk of HCC. Presence of steatosis was assessed by ultrasound or CT, controlled attenuation parameter or liver histology. HCC incidence was assessed in the overall cohort and in the CHB-MASLD cohort stratified by PAGE-B risk groups.
Results: We included 1968 CHB patients with metabolic dysfunction. The median age was 42 years (IQR 34–51), the majority was male (64.5%), 239 (12.1%) had cirrhosis and 1077 (54.7%) received antiviral therapy. 1770 patients (89.8%) had overweight, 450 (22.8%)

hypertension, 259 (13.1%) dyslipidemia, 234 (11.9%) DM2 and 758 (38.5%) MASLD. During a median follow-up of 7.9 years, 87 patients developed HCC. The 5-year cumulative incidence of HCC was 2.3% in the overall cohort. HCC risk was significantly higher in those with cirrhosis at baseline (14.9% vs 0.6% at 5 years, p < 0.001), but was similar for those with and without MASLD (2.8% vs 2.1%, p = 0.972). In the overall cohort, the 5-year risk of HCC was 0.1% in those with a low PAGE-B scores (n = 873, 45.4% of cohort), compared to 2.0% and 12.4% in patients with intermediate (n = 831, 43.2% of cohort) and high PAGE-B scores (n = 219, 11.4% of cohort, p < 0.001). PAGE-B effectively stratified HCC risk in those without cirrhosis (5-year HCC risk: 0% vs. 1.2% and 1.8%, p < 0.001). Amongst those with cirrhosis, 5-year HCC risk was 4.2% for patients with low PAGE-B score, compared to 6.9% and 27.3% for intermediate and high scores. In the subset of patients with MASLD the 5-year HCC risk was 0%, 2.8%, 11.1 for low, intermediate and high risk score patients (p < 0.001). Excluding patients not on antiviral therapy did not change the results.

Conclusion: CHB patients with metabolic dysfunction are at significant risk of HCC. In patients without cirrhosis, low PAGE-B scores, even in patients with MASLD, was associated with a negligible 5-year risk of HCC. Conversely, a significant residual risk of HCC was observed amongst CHB patients with metabolic dysfunction and cirrhosis despite low PAGE-B scores, highlighting the need for continued HCC surveillance in this subgroup of patients.

SAT-286

Risk of hepatocellular carcinoma and other liver-related events in chronic hepatitis B patients with or without hepatitis D virus co-infection

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Background and aims: Previous studies suggest that HDV co-infection (chronic hepatitis delta, CHD) is associated with an excess risk of HCC and other adverse liver-related outcomes compared to HBV mono-infection (CHB). Whether this excess risks persists in patients with established cirrhosis remains uncertain. We aimed to compare the clinical outcomes of patients with CHD to those with CHB, stratified by the presence or absence of cirrhosis.

Method: We analysed all consecutive patients with CHD (HDV RNA positive) managed at 10 sites in the Netherlands and the United Kingdom and compared clinical outcomes to all consecutive CHB patients managed at one academic site in the Netherlands. We studied the cumulative incidence of HCC and liver-related events (LRE; defined as the first of a composite of HCC, liver transplantation and liver-related mortality), in the overall study population, and stratified for presence of cirrhosis (defined by biopsy showing METAVIR F4, liver stiffness measurement ≥12 or signs or cirrhosis on imaging).

Results: We analysed 1468 patients, 144 CHD patients with a median age of 38 (IQR 33–47) and 1324 CHB patients with a median age of 40 years (IQR 32–50, p = 0.252). Patients with CHD were more likely to have cirrhosis (50.0% vs. 7.8%, p < 0.001), had lower HBV DNA levels (1.6 vs. 3.0 log UI/mL, p < 0.001) and higher ALT (84 vs. 33 U/L, p < 0.001). During a median follow-up of 8.0 years (IQR 4.6–12.4), 57 first events (30 HCC, 22 liver transplantations, 5 liver-related deaths) were recorded. The 5-year cumulative HCC incidence for CHD patients was 6.0%, compared to 0.8% for CHB patients (p < 0.001) and the 5-year cumulative incidence of LRE was 20.9% for CHD patients, compared to 0.8% for CHB patients (p < 0.001). Among patients with cirrhosis (n = 175), of which 158 (90.3%) were on NUC therapy, the 5-year cumulative HCC incidence for patients with CHD was 12.4%, compared to 4.1% for CHB patients (p = 0.002). Findings for LRE were consistent (41.9% vs. 4.1%, p < 0.001). In multivariable analysis adjusted for age, platelet count, HBV DNA log10 and cirrhosis at baseline, the presence of CHD was significantly associated with an increased risk of HCC (aHR 5.6, 95% CI 2.0–15.9, p = 0.003) and LRE (aHR 7.7, 95% CI 3.8–15.8, p < 0.001).

Conclusion: Patients with CHD are at increased risk for the development of HCC and other liver-related events compared to patients with CHB. The excess risk persisted amongst patients with cirrhosis, underscoring the need for diagnosis and treatment of HDV infection even in patients who already progressed to cirrhosis.

SAT-287

Metabolic comorbidities are risk factors for adverse liver-related events in individuals with HIV-HBV on tenofovir-based antiretroviral therapy

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Background and aims: Individuals with HIV have an increased risk to develop diabetes mellitus (DM), hypertension (HT) and dyslipidemia (DL). These metabolic comorbidities (MC) are risk factors for the hepatocellular carcinoma (HCC) and liver-related mortality in individuals with HBV mono-infection. We aimed to study the association between MC and liver-related events in individuals with HIV-HBV on tenofovir-based antiretroviral therapy (ART).

Method: We analysed data from the ongoing nationwide AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. We included all individuals with HIV-HBV who commenced tenofovir-based (ART) and studied the association between baseline metabolic comorbidities and liver-related events (composite endpoint of HCC, liver transplantation and liver-related mortality) using Cox proportional hazards regression in the overall cohort and in the subset of patients at highest risk (i.e. those with cirrhosis and/or intermediate-high PAGE-B score).

Results: We analyzed 1205 individuals, the majority of whom were male (85.5%) and born in Europe (49.6%). At baseline, median age was 45 years, 737 (61.1%) had intermediate-high PAGE-B scores and 71 (5.9%) had cirrhosis. Median nadir CD4+ was 280 cell/mm^3 (IQR 134–450) and 21.5% had previous exposure to thymidine analogues (d-drugs). In total, 417 (34.6%) individuals had one or more metabolic comorbidities (7.1% DM, 26.9% HT and 13.3% DL). During a median follow-up of 10.2 (IQR 5.2–14.7) years, a total of 28 liver-related events occurred (17 HCC, 1 liver transplantation and 10 liver-related deaths). In univariable analysis, DM (HR 4.7, p = 0.002) and HT (HR 3.6, p < 0.001) were associated with liver-related events, but DL (HR 1.3, p = 0.622) was not. The highest risk of liver-related events was observed in individuals with both DM and HT (1 MC: HR 3.0; 2 MC: HR 12.5, p < 0.001). Findings were consistent in multivariable analyses adjusting for age, platelet count, nadir CD4+ T-cell count and previous exposure to D-drugs (diabetes aHR 3.4, p = 0.024 and hypertension aHR 2.8, p = 0.016). Presence of DM and HT was also

associated with an increased risk of liver-related events amongst individuals with intermediate-high PAGE-B scores and in the subset of individuals with cirrhosis.
Conclusion: Metabolic comorbidities are prevalent in individuals with HIV-HBV on tenofovir-based ART. Presence of DM or HT was independently associated with an increased risk of liver-related events. These findings underscore the need for metabolic assessment for thorough risk stratification in patients with HIV-HBV.

SAT-288

Predictive performances of PAGED-B and reREACH-B models in non-cirrhotic, treatment-naive patients with chronic hepatitis B

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Background and aims: PAGED-B and reREACH-B models, consisting of fibrotic burden and moderate hepatitis B virus (HBV) DNA levels, were recently proposed to predict development of hepatocellular carcinoma (HCC) in non-cirrhotic patients with chronic hepatitis B (CHB). We validated their predictive performances in non-cirrhotic, treatment-naive patients with CHB.
Method: Between 2007 and 2023, this multicenter retrospective cohort study recruited 4,190 non-cirrhotic, treatment-naïve, adult patients with CHB from 3 medical centers in South Korea. The index date was defined as the date of the first test for serum HBV DNA levels and the primary outcome was HCC development. The discrimination performance of the PAGED-B and reREACH-B models was assessed using time-dependent area under the receiver operating characteristics (AUROC), and the calibration performance of the two models was also assessed. In addition, the models were compared to the two default strategies "Treat All" and "Treat None" using decision curve analysis (DCA).
Results: The mean age was 47.3 years, and hepatitis B e antigen was positive in 797 (19.0%) patients. During a median follow-up period of 6.8 years (interquartile range, 3.6–10.3 years), 32 (0.8%) patients developed HCC (0.11 per 100 person-years) and 672 (16.0%) patients started antiviral therapy (AVT). The HCC development was significantly higher in CHB patients who started AVT (n = 17, 2.5%) than in those who did not (n = 15, 0.4%; $p < 0.001$). The 5-year time-dependent AUROC of the PAGED-B model (0.850) was higher than that of the reREACH-B model (0.825). Calibration performance of the PAGED-B model was better than that of the reREACH-B model which overestimates the HCC risk (Integrated calibration index; PAGED-B: 0.001 vs. reREACH-B: 0.023). DCA also showed that the clinical utility of the PAGED-B model (0.002) was superior to that of the reREACH-B model (-0.001) at a threshold probability of 1% for 5-year HCC risk. When the predictive performances of the two models were compared at the time of starting AVT, the PAGED-B model (0.858) had significantly higher 5-year time-dependent AUROC than reREACH-B model (0.578), with better calibration performance and higher net benefit by DCA.
Conclusion: The predictive performances of the PAGED-B model was comprehensively better than those of the reREACH-B model in non-cirrhotic, treatment-naive patients with CHB. The PAGED-B model may also be more useful than the reREACH-B model even in CHB patients who start AVT in a natural course, which is a high-risk group for HCC development.

SAT-289-YI

Scaling up treatment of chronic hepatitis B in Africa: 1-year results from a simplified public-sector treatment program in Ethiopia

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Background and aims: In the global efforts to combat chronic hepatitis B (CHB), the African continent is falling behind with only 0.2% of an estimated 65 million CHB patients receiving antiviral therapy. The new WHO guidelines advocate for simplified treatment criteria to reach a larger proportion of CHB patients in low- and middle-income countries, but it is unclear how this simplified approach works in real-life. In this study, we present 1-year results from a large, simplified CHB treatment program in Ethiopia, where a modified version of the new WHO guidelines has been used for several years.
Method: In 2021/22, CHB treatment clinics were established at four regional hospitals in Ethiopia (Adama, Dubti, Jigjiga and Jimma). Adult HIV-negative CHB patients were enrolled and assessed with blood samples, including liver enzymes and viral markers. The treatment eligibility criteria were: i) clinically diagnosed cirrhosis, ii), AST to platelet ratio index (APRI) ≥0.7, iii) ALT > 40 U/L and HBV DNA > 2000 IU/ml, and iv) HCC in first-degree relative and HBV DNA > 2000 IU/ml. Patients who met the criteria were given Tenofovir disoproxil fumarate (TDF) free of charge, and appointed for follow-up after three, six and twelve months. Changes in ALT and APRI were analyzed with Wilcoxon signed-rank test, while logistic regression models were used to identify predictors for virological failure (HBV DNA > 10 IU/ml) after 12 months.
Results: A total of 4,356 patients were enrolled between December 2021 and June 2023, of whom 1,135 treatment-naïve patients fulfilled the treatment criteria and started TDF before July 01, 2023. Of the patients starting treatment, the median age was 30 years (interquartile range 25–39 years) and 827 (72.9%) were men. In total, 531 (46.8%) patients completed one year of treatment, while 508 (44.8%) were lost to follow-up, 56 (4.9%) died, 23 (2.0%) withdrew, 10 (0.9%) started due to pregnancy and stopped postpartum, and 7 (0.6%) were transferred out. Of the 56 patients who died within the first year, 51 (91.1%) died from complications related to advanced chronic liver disease. Of the patients who completed one year of treatment, the median ALT and APRI declined from 48 to 32 U/L ($p < 0.001$) and 0.72 to 0.48 ($p < 0.001$), respectively, and 78.3% had suppressed HBV DNA (<10 IU/ml). HBV DNA > 10^6 IU/ml (adjusted odds ratio (AOR) 5.24; 95% CI 3.18–8.73) and decompensated cirrhosis (AOR 2.29; 95% CI 1.03–4.98) were independent predictors of virological failure at 12 months.
Conclusion: About half of the patients who initiated antiviral therapy completed one year of treatment, with evidence of biochemical and virological treatment response. However, roughly 45% were lost to follow-up after one year, highlighting the need for improved understanding of sociocultural barriers to long-term CHB care in Africa.

SAT-290

Staging liver fibrosis using non-invasive tests in people with chronic hepatitis B (CHB) to inform WHO 2024 guidelines: a systematic review and meta-analysis

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Background and aims: Non-invasive tests (AST-to-platelet ratio index (APRI) and transient elastography (TE)) were recommended in the 2015 World Health Organization (WHO) guidelines to guide treatment decisions in people with chronic hepatitis B (CHB). Those guidelines were based on a systematic review that included 69 studies. We undertook an updated systematic review and meta-analysis to inform new cut-offs for NITs for diagnosis of significant fibrosis and cirrhosis for the 2024 WHO global guidelines for care and treatment of persons with CHB infection.

Method: We conducted an updated systematic review and meta-analysis of studies comparing the diagnostic accuracy of APRI, FIB4, and TE against liver biopsy in diagnosing ≥F2 and ≥F4 liver fibrosis. We searched PubMed, Embase and Science Citation Index Expanded for studies published between January 2014 until February 2023 and combined the data with those from the 2014 meta-analysis. We performed meta-analyses using the bivariate random-effects model. We report on the results of this review and how it was used to inform the 2024 WHO treatment recommendations.

Results: We included 264 studies, of which 211 with 61665 patients were used in the meta-analysis. For ≥F2 the summary sensitivity and specificity were: 73% and 65% for APRI low cut-off (>0.5); 30% and 92% for APRI high cut-off (>1.5), 75% and 79% for TE >7.0 kPa, respectively. For cirrhosis (F4) the summary sensitivity and specificity were: 59% and 74% for APRI low-cut-off (>1.0), 30% and 88% for APRI high cut-off (>1.5), 83% and 89% for TE >12.5 kPa. Using an APRI cut-off of >0.5 for unselected CHB patients with an assumed ≥F2 prevalence of 25%, 26% of treated patients would be false positives, while only 6.8% would be false negatives. This approach prioritises minimising false negatives over false positives, aligning with the goal of expanding access to antiviral treatment in resource-limited settings.

Conclusion: An APRI score >0.5 or a TE value of >7.0 kPa was shown to identify most adults with ≥F2 and an APRI score of >1.0 or a TE value of >12.5 kPa to identify most adults with cirrhosis. The findings informed decisions on new thresholds of APRI and TE for diagnosis of ≥F2 and ≥F4 in the 2024 WHO guidelines on CHB. These findings offer a robust evidence base for expanding treatment eligibility in resource-limited settings, enabling earlier intervention and improved outcomes for CHB patients globally.

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Characterizing serum HBcAg and phosphorylated HBcAg in the natural history of chronic hepatitis B infection

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Background and aims: Serum hepatitis B virus core antigen (HBcAg) and its phosphorylated form (P-HBcAg) are novel biomarkers in chronic hepatitis B infection (CHB). We aimed to describe the profile of HBcAg and P-HBcAg in the various disease phases of CHB infection.

Method: In this cross-sectional study, patients with CHB at different disease phases according to the EASL classification who were never on antiviral treatment with retrievable serum samples were included for analysis. HBcAg and P-HBcAg are detected with a fully automated high throughput assay, with S/CO ≥1 considered to be positive. Hepatitis B virus (HBV) pre-genomic RNA (pgRNA) was measured by Research Use Only RealTime HBV RNA v2.0 (0.2 mL) (Abbott Diagnostics) which has lower limit of detection (LLOD) of 0.8 log U/mL. HBcrAg was measured by the Lumipulse G HBcrAg chemiluminescence Enzyme Immunoassay (Fujirebio, Tokyo, Japan), with LLOD of 100 U/mL. Values were log transformed.

Results: A total of 156 patients (32 hepatitis B e antigen [HBeAg]-positive chronic infection, 59 HBeAg-positive chronic hepatitis, 21 HBeAg-negative chronic infection, 33 HBeAg-negative chronic hepatitis, 11 [hepatitis B surface antigen] HBsAg seroclearance) were recruited, with median age 41.9 years old, 54.5% male, and 53.2% genotype C infection (the rest were genotype B). The median serum HBV DNA, pgRNA, HBcAg, P-HBcAg, HBsAg and HBcrAg were 4.66 log IU/mL, 4.58 log U/mL, 0.39 log S/CO, 2.49 log S/CO, 6.63 log mIU/mL and 6.99 log U/mL, respectively. The profile of HBcAg and P-HBcAg mirrors the trend of HBV DNA, HBV pgRNA and HBcrAg across disease phases. Serum HBcAg demonstrates excellent correlation with P-HBcAg ($r = 0.936$), HBV DNA ($r = 0.840$), HBV pgRNA ($r = 0.823$) and HBcrAg ($r = 0.706$); all $p < 0.001$, whereas serum P-HBcAg demonstrates strong correlation with HBV pgRNA ($r = 0.886$), HBV DNA ($r = 0.796$) and HBcrAg ($r = 0.827$); all $p < 0.001$. Patients infected with genotype C HBV had lower HBcAg (0.00 vs 1.26 log S/CO, $p = 0.023$) and P-HBcAg (1.58 vs 4.23 log S/CO, $p = 0.019$) compared to patients infected with genotype B HBV. HBeAg negative patients were more likely to have undetectable HBcAg (81.7% vs 23.1%) and P-HBcAg (61.1% vs 1.1%) compared to HBeAg positive patients; both $p < 0.001$. Both markers were not detectable in patients with HBsAg seroclearance. In patients with undetectable HBcAg, HBV DNA and pgRNA were 14.7% and 29.3% undetectable, respectively. In patients with undetectable P-HBcAg, HBV DNA and pgRNA were 21.6% and 45.9% undetectable, respectively.

Conclusion: HBcAg and P-HBcAg showed excellent correlation with other HBV biomarkers in the natural history of CHB and change dynamically with disease phases, thus representing as promising markers for assessing transcriptional silencing of covalently closed circular DNA.

SAT-292-YI

In HDV sub-genotypes 1, the high degree of genetic variability can drive the selection of divergent genetic pathways modulating HDV replicative potential and cytolytic activity

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Background and aims: So far, paucity of information is available on the extent of HDV genetic diversification in HDAg domains and CTL epitopes across the different sub-genotypes 1 and their correlation with virological and biochemical parameters.
Method: 103 individuals with chronic HDV infection (CHD) were included. Full-length HDV genome sequences were obtained by Illumina (median [IQR] reads/seq: 62045[30460–91899]). Sub-genotypes 1 were defined by phylogenetic analysis. Amino acid (aa) residues were defined conserved if not mutated in 95% of sequences. HDAg domains and cytotoxic T lymphocytes (CTL) epitopes (N = 18) were defined according to Pascarella 2010 and Kohsar 2021.
Results: CHD were mostly males with a median age of 54 (44–60) years coming mainly from Eastern Europe (51%) and Italy (44.8%). Serum HDV-RNA and ALT were 5.6 (4.9–6.2) logIU/ml and 94 (65–152) U/L. Sub-genotypes 1c and 1e were the most prevalent (47.1% and 45.2%), followed by 1a (4.8%), 1b (1.9%) and 1d (1%). Sub-genotype 1c predominated in CHD from Eastern Europe (77.6% vs 22.4%, P < 0.001) while 1e in Italians (77.5% vs 22.5%, P < 0.001). Overall, the number of conserved aa in HDAg was only 33.2% (71/214) ranging from 38.5% in RNA binding domain (RDB)1 to 36.4% in RBD2, 27.3% in coiled coil sequence (CCS), 25% in virus assembly signal (VAS), 19.1% in nuclear localization sequence (NLS) and 18.2% in RBD3, indicative of high genetic diversification. Similarly, the degree of genetic conservation ranges from 0% in CTL epitope 81–90 to 33.3% in CTL epitopes 105–112 and 194–202. Notably, a lower degree of genetic conservation was noted in CTL epitope 170–179 from CHD with HDV-RNA > 5 logIU/ml (70% of conserved aa with vs 20% without HDV-RNA <5 logIU/ml, P = 0.025), suggesting that an enrichment of mutations in this CTL epitope can enhance viral replication. Finally, despite a comparable degree of genetic conservation between sub-genotypes 1e and 1c, they were characterized by divergent genetic pathways. In particular, sub-genotype 1c was significantly associated with the selection of 7 specific mutations (I16T/V, N22S, D47E, R112K, T180A, A202S, prevalence ranging from 26.5% to 44.9% vs 0% in 1e, P < 0.001). Conversely, sub-genotype 1e was significantly associated with the selection of 6 specific mutations (D29E, D46E, K113R, R131K, M171L, I188V prevalence ranging from 23.9% to 43.5% vs 0% in 1c, P < 0.009). Notably, in sub-genotype 1c, the co-presence of I16V/T+D47E+A202S correlated with ALT > 3ULN (100% vs 27.5%, P = 0.001).
Conclusion: Sub-genotypes 1 are characterized by a conspicuous degree of genetic diversification that has led to the selection of divergent genetic signatures. The enrichment of mutations in specific CTL epitopes could hamper HDV recognition by immune response and in turn enhancing viral replication. Overall, the role of the high degree of genetic variability in affecting the proper HDV detection by the currently available diagnostic assays deserves further investigation.

SAT-293
High FIB-4 index predicts liver decompensation in chronic hepatitis B patients who develop clinical relapse after antiviral therapy cessation

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Background and aims: Finite nucleos(t)ide analogues (NA) therapy may facilitate HBsAg seroclearance to achieve a functional cure. However, clinical relapse (CR, HBV DNA > 2000 IU/mL and ALT > 2-fold elevation) developed in more than 30% of patients who discontinued NA therapy, and liver decompensation may occur. Our aim was to identify risk predictors for liver decompensation after discontinuation of NA therapy.
Method: We conducted a prospective study to consecutively enroll 320 noncirrhotic patients with chronic hepatitis B (CHB) who discontinued NA therapy in a tertiary medical center since 2012. They were monitored at 1st and 3rd month off therapy, and every 3 months afterwards. Patients who developed a CR were included, and they were traced for liver decompensation, or censored at time of retreatment, or last follow-up. Clinical parameters and the fibrosis-4 (FIB-4) index were collected for statistical analysis. To validate our findings, we conducted a retrospective cohort study using electronic medical records (EMRs) from the Integrated Medical Database of the National Taiwan University Hospital (NTUH-iMD) and subsequently investigated their outcomes.
Results: Overall, 320 patients were included in the prospective study, of whom 144 (45%) developed CR. These patients received entecavir (56%) and tenofovir (31%) for a median of 37 months before NA cessation. Of 144 patients, 98 (68%) fulfilled the APASL stopping rule, and 124 (86%) received retreatment. Liver decompensation developed in 12 patients (3.8%) who had comparable pretreatment HBeAg status, HBV DNA, ALT, NA regimens, end-of-therapy (EOT) HBsAg level, and fulfillment of stopping rule compared to those without decompensation. Decompensated patients had a longer consolidation duration (31.5 vs. 16.5 months, p = 0.026) and higher EOT FIB-4 index (1.79 vs. 1.10, p < 0.001). Multivariable Cox regression analysis showed that EOT FIB-4 index > 1.5 (vs. ≤1.5) increased subsequent liver decompensation risk (adjusted HR: 31, 95%CI: 4–242, p = 0.001). Moreover, higher ALT level and FIB-4 index >4.4 (vs. ≤4.4) at CR significantly increased the risk of liver decompensation (adjusted HR: 10, 95%CI: 2–51, p = 0.005). In our validation study, we retrospectively assessed 1214 patients using identical inclusion and exclusion criteria as the original cohort. Of these, 317 patients who experienced CR were included in the final analysis, with 7 patients developing liver decompensation. Previous findings were corroborated in the retrospective cohort.
Conclusion: An EOT FIB-4 index of >1.5 can help identify patients at a high risk of developing liver decompensation following CR. These patients should be closely monitored after NA discontinuation. Moreover, patients with a FIB-4 index >4.4 at CR indicate an even greater risk and should receive prompt retreatment.

SAT-294
Should EASL expand its 2017 treatment criteria for chronic hepatitis B virus infection to ineligible people: analysis from a UK-based cohort

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Background and aims: Expansion of treatment criteria to CHB people who are ineligible to current criteria is increasingly debated as proposed in the revised WHO guidelines despite limited evidence. From a cohort study of patients with chronic hepatitis B virus infection (CHB) in London, we assessed i. the liver-related mortality and ii. the rate of liver disease progression and HBsAg loss, in patients with e-antigen negative CHB who are ineligible for antiretroviral therapy (AVT) according to the 2017 EASL criteria

Method: Between January 2016 and December 2018, we implemented a cohort study of patients with CHB who were ineligible for AVT according to the 2017 EASL treatment criteria, and had follow-up liver assessment. All patients were recruited at Imperial College NHS Healthcare Trust in London, UK across 2 hospital sites. We excluded patients coinfected with HIV, HCV or HDV and patients with HCC or cirrhosis at enrolment. Liver disease progression was defined as becoming newly eligible for treatment and/or increasing liver fibrosis stage using Fibroscan and/or developing hepatocellular carcinoma (HCC).
Results: Out of 493 patients with CHB, 381 treatment-naïve, ineligible, eAg-negative CHB patients were enrolled, 39 (10.2%) were lost to follow-up, leaving 342 patients for this analysis (52% female, baseline median age 42 years (IQR: 35–49 years), median HBV DNA 337 IU/mL (IQR 69–1,482 IU/mL), median ALT 28 IU/L (IQR 21–37 IU/L), median LSM 4.6 kPa (IQR 3.9–5.5 kPa), 60% were in the eAg-negative chronic HBV infection phase, median BMI 27 kg/m^2 (IQR 23–30 kg/m^2), 19.7% were obese, 7.9% had liver steatosis and 2.9% reported excessive alcohol intake. Median follow-up time between enrolment and last reassessment was 5.04 years (IQR 4.73–5.32). Out of 342 patients, 4 (1.2%) died from non-liver-related causes with no liver-related deaths reported. Over the study period, only 1 patient (0.3%) developed HCC, 2 (0.6%) had hepatic flares, 16 (4.7%) spontaneously lost HBsAg and 13 (3.8%) experienced liver disease progression; no patient progressed to cirrhosis. Univariate analysis identified only HBV viral load ≥2,000 IU/mL and elevated ALT (>ULN) as associated factors for liver disease progression. When applying the 2024 revised WHO guidelines, the proportion of patients newly eligible for AVT increased significantly with 53 patients (15.5%, 95%CI: 12.0–19.0%) becoming eligible at year 5. However, out of the 13 patients who had liver progression, only 4 of these patients would have been captured by the recently expanded WHO treatment criteria.
Conclusion: Due to the very low risk of liver-related events observed in this UK-based study, there is little evidence to support expansion of AVT to eAg-negative CHB people who are currently ineligible to treatment according to the 2017 EASL guidelines.

SAT-295

Functional cure of chronic HBV: natural history, determinants, and outcomes: a real-world experience from a tertiary liver center

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Background and aims: Functional cure, defined as sustained HBsAg loss after chronic HBV infection, is rare. Recent studies report it occurs in 3–5% of non-Asian patients after prolonged NA therapy. Toronto is a multi-ethnic city where >53% of residents are foreign born. Our clinic has been testing HBsAg annually in all patients with chronic HBV infection since 2010. This study evaluates the prevalence of functional cure and its associated long-term outcomes.
Method: Retrospective study analyzed 1,846 chronic HBV patients who were seen in clinic from June 2022 to November 2024. The SlicerDicer module of Epic EMR was used to identify cases of chronic HBV (ICD-10 B18.19, B18.1, B18.10) or functional cure (ICD-10 Z09.9). Chart review confirmed functional cure, treatment history and liver disease outcomes.
Results: Of the 1,846 patients, 148 (8.0%) achieved functional cure, 101 (68%) were male. Functional cure occurred in 27/180 (15%) of Caucasian patients, 12/117 (10.2%) Black patients and in 108/1021 (10.5%) Asian patients. The mean age at HBsAg loss was 59 years (95% CI: 57.46–60.48) with median follow-up duration of 4 years (range: 0.2–21) after achieving HBsAg loss. The majority were treatment naive N = 90 (61%). Treated patients (N = 58) received TDF (35%), LAM (28%), or Entecavir (19%), and the mean therapy duration was 5.2 years (95% CI: 4.48–5.9). Only 16 (28%) achieved HBsAg loss during therapy while 42 (72%) achieved HBsAg loss after stopping therapy (P > 0.05), with a median interval of 6 years (range: 1–23) from stopping therapy to HBsAg loss. In those who stopped therapy, the median HBsAg at end of treatment was 208 IU/ml (0.19–2043). N = 10 (24%) experienced ALT flares (ALT > 200 U/L) within 6 months, median ALT was 334 U/L (range: 205–1274), all resolved without retreatment and the median time from stopping therapy to HBsAg loss was 5.5 years (range: 1–19). 18 (43%) had ALT (≤40 U/L) and 14 (33%) had ALT levels >40–<200 U/L and the median time from stopping therapy to HBsAg loss was 5.7 years (range: 1.5–22), and 6.5 years (range: 2–23) respectively. Hepatocellular carcinoma (HCC) occurred in 11 (7.4%) of those with functional cure, mostly in males (81.8%) and those with cirrhosis (72.7%) or advanced fibrosis (36.4%). Half of the patients developed HCC after HBsAg loss, median time was 0.6 years (range: 0–5) from HBsAg loss to diagnosis. Occult HBV DNA was detected in 4.73% (n = 7), none developed HCC. No patients underwent liver transplantation, 3 deaths (2%) occurred, none related to liver disease.
Conclusion: Functional cure was observed in 8.0% of the cohort, a prevalence higher than that previously reported in the literature. This might be due to routine annual HBsAg testing for all patients. Most with functional cure were treatment-naïve. Most treated patients (72%) achieved HBsAg loss after stopping antiviral therapy. Despite favorable outcomes, HCC occurred in 7.4%, primarily in those with cirrhosis or advanced fibrosis, underscoring the need for ongoing HCC surveillance and tailored follow-up for high-risk patients.

SAT-296

High rates of advanced chronic liver disease in patients with chronic hepatitis D virus infection in Uzbekistan

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Background and aims: Chronic hepatitis B virus (HBV) infection is endemic in Uzbekistan. Previous data showed a high prevalence of anti-hepatitis D virus (HDV) antibodies in HBsAg-positive individuals. Limited data are available on disease severity, treatment availability and uptake, and hepatocellular carcinoma (HCC) prevalence in patients with chronic HDV infection in Uzbekistan.
Method: The Scientific Research Institute of Virology (SRIoV) is the leading medical and scientific reference center for viral hepatitis in Uzbekistan. Patients diagnosed with viral hepatitis are referred to the SRIoV by hepatology centers throughout the country for further diagnostics and treatment. In this cross-sectional, retrospective study, epidemiological, clinical, and laboratory data were collected and analyzed from all anti-HDV-positive patients presenting to the SRIoV between June 2023 and May 2024. Data from HBV-mono-infected patients presenting during the same period were collected for comparison.
Results: A total of 1030 HBsAg-positive, anti-HDV-positive individual patients presented to the SRIoV during the study period. The majority were male (52%, n = 532/1030) with a median age of 41.9 years (IQR 37.3–48.7). HDV RNA was detectable in 79% (812/1023; median HDV RNA 5.11 $\log_{10}$ IU/ml [IQR 3.99–5.85]) of patients. Liver cirrhosis was present in the majority of patients (78.4%, n = 808/1030), of whom 30.4%, 57.2%, and 11.4% were classified as Child-Pugh Score A, B, and C,

respectively. Signs of portal hypertension (spleen size >13.5 cm and platelets <150,000/µl, or ascites) were detected in 76.9% of patients with liver cirrhosis. There was no significant difference in nucleos(t)ide analogue (NA) treatment between patients with and without cirrhosis (72% vs. 65%, p = 0.063), while only a minority had ever received interferon treatment (0.4%, n = 4/1030). The proportion of patients with HBV monoinfection in the study period was lower (26.1%, [n = 363/1393] vs. 73.9% [n = 1030/1393]). They were significantly older (p < 0.001), had a lower prevalence of liver cirrhosis (43.9 % vs. 78.4 %, p < 0.001), and were more likely to be diagnosed in the same year as the presentation to the SRIoV (16.8 % vs. 12.3 %, p = 0.032) compared to HDV co-infected patients. The HCC detection rate was low in both patient groups (HBV: n = 11/363, HDV: n = 7/1030).
Conclusion: Chronic HDV infection exceeds chronic HBV infection in terms of number of cases and severity of disease. HDV-infected patients presenting to the SRIoV have advanced liver disease with high rates of decompensated liver disease and currently no access to HDV-directed treatment. These results emphasize the need to strengthen preventive and diagnostic measures, including screening programs for HDV detection and HCC surveillance, as well as access to HDV-directed antiviral treatment.

SAT-300

The effect of antiviral therapy on the outcomes of baseline grey-zone (GZ) patients with HBeAg-negative chronic hepatitis B virus infection (CHBVe-)

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Background and aims: The optimal management of GZ CHBVe- patients (pts) remains controversial, but a proportion of them starts nucleos(t)ide analogue (NA) therapy, although the effect of therapy has not been clarified. In this retrospective cohort study, we assessed the potential effect of NA initiation on HBsAg loss and hepatocellular carcinoma (HCC) development in GZ CHBVe- pts.
Method: All GZ CHBVe- pts with ≥1 visit between 2010–2019 were included. GZ was defined at baseline as ULN < ALT ≤2×ULN, or HBV DNA 2000–20,000, or HBV DNA ≥20,000 and ALT ≤ULN, or ALT > 2×ULN and HBV DNA < 2000 IU/ml. Patients with HCV/HDV/HIV coinfection, immunosuppression, decompensation, HCC or other liver injury were excluded. Epidemiological, clinical and laboratory parameters based on a predefined CRF were collected. Typical treatment indications (TTI) included a) HBV DNA > 20,000 and ALT > 2×ULN, b) HBV DNA > 2000 and advanced fibrosis [Ishak's stage 3–4 or liver stiffness (LS) 9.1–12/12.1–15 kPa in case of ALT ≤/> ULN] or c) detectable HBV DNA and cirrhosis (Ishak's stage 5–6 or LS > 12/>15 kPa in case of ALT ≤/>ULN). NA initiation was decided by the treating physicians. Cumulative incidence rates were derived from Kaplan-Meier curves, whereas Cox regression analyses including time varying covariates were used for assessment of the effects of TTI and therapy on outcomes.
Results: At baseline, 811 of 2012 chronic HBV pts (40%) (age:45 ± 14 yrs, 64% males, born in Greece 58%, BMI 26 ± 4 kg/m^2, follow-up 6.8 ± 5.4 yrs) fulfilled the criteria for GZ CHBVe- cases. TTI were present at baseline by LS ± histology in 165 (20%) pts and developed during follow-up in another 115 (14%) pts resulting in 3-, 5- and 10-yr cumulative rates of 33%, 35% and 38%. NA was initiated in 523 (65%) pts resulting in 1-, 5- and 10-yr cumulative rates of 49%, 68% and 77%. NA was initiated in 277/280 (99%) pts who developed TTI and 246/531 (46%) pts remaining in GZ (p < 0.001). Patients with vs without NA initiation were more frequently males (69% vs 56%, p < 0.001) and had older mean age (47 vs 41 yrs, p < 0.001) and lower baseline platelets (206 vs 223 × 10^3/mm^3, p < 0.001). HBsAg loss was observed in 19 (2.3%) pts with 1-, 5- and 10-yr cumulative rates of 0.1%, 1.0% and 4.2%. HBsAg loss was not associated with any baseline characteristic, development of TTI or NA initiation. HCC developed in 32 (4%) pts with 1-, 5- and 10-yr cumulative rates of 1%, 3% and 5%. HCC development was independently associated with older age [HR/yr:1.09 (1.05–1.14), p < 0.001], male gender [HR: 2.86 (1.15–7.12), p = 0.024] and lower baseline platelets [HR/10^3/mm^3: 0.98 (0.97–0.99), p < 0.001], but not with development of TTI or NA initiation or HBsAg loss, although it developed in no pt with HBsAg loss.
Conclusion: The probability of HBsAg loss and HCC development does not seem to be affected by NA therapy in treated GZ CHBVe-pts, who however are at higher baseline HCC risk compared to such pts remaining untreated.

SAT-301

Prevalence and burden of hepatitis delta virus infection in a large cohort of hepatitis B- infected individuals in the Brazilian Amazon

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Background and aims: HBV-HDV co-infections result in the most severe form of viral hepatitis. Despite the severity of HDV, there is scarce recent data on its prevalence and clinical burden in the Brazilian Amazon. This study evaluated the prevalence and clinical characteristics of HDV-infected individuals in a large HBV-infected cohort from the Brazilian Amazon.
Method: This was a prospective study performed on HBV-infected individuals (HBsAg +) followed at two Viral Hepatitis Referral Units in the state of Amazonas, Brazil from October 2022 until February 2024. Clinical and laboratory information was taken from medical records. Blood samples were evaluated for the presence of HBV, HDV, HIV and hepatitis C virus (HCV) serological markers. Commercial kits (Architect i1000TM, Abbott Diagnostics, Brazil and DiaSorin®, Italy) were used to detect HBsAg, anti-HBc, anti-HBs, HBeAg, anti-HCV, anti-HIV and anti-HDV. HBV DNA and HDV RNA were identified by commercial kits (Abbott RealTime HBV Viral Load Assay and Altona Diagnostic RealStar® HDV RT-PCR kit). For statistical analysis, the Student t-test, Mann–Whitney U-test or Fisher's exact test were applied when applicable to evaluate differences between variables. Bivariate logistic regression was used for each variable to estimate an odds ratio (OR) with 95% confidence intervals for anti-HDV reactivity. All tests were performed at a 5% significance level.
Results: Among 356 individuals included, 75.6% (n = 269) were mono-infected with HBV, while 24.4% (n = 87) were also co-infected with HDV. Among the anti-HDV positive patients mean age was 42.6 (±9.4) years, 57.5% were male,43 (49.4%) were HDV-RNA-positive, 85 (98%) presented with an HBV DNA viral load below 2,000 IU/mL, 3 (3.4%) were HBeAg positive, one individual (1.2%) was anti-HIV positive, and none were anti-HCV positive. Univariate logistic regression analysis revealed that younger age (p = 0.009), indigenous racial origin (p = 0.001), signs or symptoms of advanced liver disease (p = 0.002), low leukocyte count (p = 0.001), low or undetectable HBV DNA viral load (p = 0.001), low platelet count, and an AST or ALT level five times the upper limit of normal (p < 0.05) were associated with anti-VHD reactivity. A stepwise multivariate logistic regression analysis revealed that low platelet count (p = 0.002), an AST/ALT> five times the upper limit of normal (p = 0.024) and an HBV DNA viral

load under the limit of detection were independently associated with HDV infection.
Conclusion: Our data confirm a high prevalence of anti-HDV /RNA positive individuals among HBV-infected patients in the Brazilian Amazon and its association with laboratory markers suggestive of active liver disease. An undetectable or low HBV viral load, in conjunction with elevated liver enzymes, are predictive of HDV infection among HBV-infected individuals in this region.

SAT-302

Dynamics of HBsAg isoforms during up to 9 years in treated and untreated HBeAg-negative chronic hepatitis B patients

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Background and aims: Recent findings suggest that lower isoforms of hepatitis B virus (HBV) surface antigen large (LHBs) and medium (MHBs) to be associated with HBeAg-negative stages of HBV infections and HBsAg loss. A decrease of intrahepatic viral activity has been associated with silenced cccDNA activity in patients with HBeAg-negative HBV infection (ENI) or HBeAg-negative chronic hepatitis B (CHB). In our study we have investigated the dynamics of HBsAg isoforms during long-term courses of treatment with tenofovir disoproxil fumarate (TDF) or natural course of the disease.
Method: Two cohorts with either ENI (n = 38) or CHB (n = 96) patients were retrospectively enrolled. In the HBeAg negative CHB cohort, patients received first (n = 24) or second line (n = 72) treatment with TDF for up to 8 years. In the ENI cohort, untreated patients either with (n = 19) or without (n = 19) subsequent HBsAg loss were analysed over a duration of 9 years. HBsAg components and other viral markers were quantified at baseline (BL) and during up to 9 years of TDF treatment on a 1–3 yearly basis.
Results: In the CHB cohort, median HBsAg levels (log ng/mL) declined slightly over time from 3.5 at BL to 3.0 after 8 years in groups (p = n.s). The ratios of LHBs declined from 9.4 (3–18)% at BL to 4.2 (1–14)% (p = 0.005) after 3 years and remained unchanged during up to 6 years of consecutive TDF treatment. Mean MHBs (%) strongly declined over time from 12.9 (1–26)% at BL to 3.3 (0–10)% after 8 years of TDF treatment in both groups. In the ENI cohort, patients with and without subsequent HBsAg loss showed significantly lower levels of total HBsAg (2.9 vs. 3.5 log ng/mL, p < 0.001) and ratios of LHBs (3.6% vs. 9.4%, p < 0.001) and MHBs (1.3% vs. 12.9%, p < 0.001) at BL compared to the CHB-cohort. However, after 8 years of TDF treatment, the CHB cohort showed similar ratios of LHBs (4.1%, p = ns), but not MHBs (3.3%, p = 0.02) compared to ENI (at BL). In ENI patients with HBsAg loss, MHBs (%) decreased from 1.2 (0–7.2)% at BL to 0.5 (0–5.0)% after 4–6 years (p = 0.05). In contrast, in ENI patients without HBsAg loss, MHBs (%) increased from 1.3% at BL to 3.3% at 4–6 years.
Conclusion: During long-term TDF treatment in HBeAg-negative CHB patients, LHBs and MHBs initially decrease but later approximate the levels observed in ENI patients without HBsAg loss. However, ENI patients who experience HBsAg loss show a consistent decline in LHBs and MHBs. Our findings indicate that LHBs and MHBs may be subject to different transcriptional regulation depending on the clinical context. LHBs and HMBs could potentially serve as predictive markers for HBsAg loss.

SAT-303

Comprehensive analysis of the intrahepatic immune microenvironment and gene expression profiles in a large cohort of patients with untreated hepatitis B virus infection

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Background and aims: Chronic hepatitis B virus (HBV) infection progresses through distinct clinical phases, with some patients falling into a "gray zone" (GZ). This study aimed to characterize the intrahepatic immune microenvironment and the gene expression profiles across the gray zone and other well-defined clinical phases in a large cohort of untreated HBV patients.
Method: Three hundred forty-nine HBV patients who underwent liver biopsy between 2005 and 2020 at Henri Mondor University Hospital (Créteil, France) were evaluated and classified according to the EASL criteria into four phases [chronic infection (CI)/chronic hepatitis B (CHB), HBeAg±]. Those not fitting into these phases were categorized as GZ-1 (HBeAg+) and GZ-2 (HBeAg–). RNA sequencing was performed to assess gene expression profiles, and supervised clustering was applied. Immune liver infiltrates were estimated by the MCP counter. Statistical analyses were performed with R version 4.2.0.
Results: One-hundred twenty-four HBV patients [93 males, median age 39 years (32–50)] were included in the analysis: 28 HBeAg+ (4 CI, 11 CHB, 13 GZ-1), 96 HBeAg- (15 CI, 53 CHB, 28 GZ-2). In the HBeAg+ phases, gene-expression analysis revealed 277 differently expressed genes (DEGs) in CI *vs.* GZ-1, 91 in CHB *vs.* GZ-1, and 301 in CHB *vs.* CI. *Up*-regulated genes were related to inflammatory processes and immune response modulators in GZ-1 *vs.* CI, the formation/regulation of extracellular matrix in CHB vs. GZ-1, and both in CHB *vs.* CI. At enrichment analysis, GZ-1 *vs.* CI showed *over*-expression of adaptive immune-activation gene-set pathways, CHB *vs.* GZ-1 *over*-expression of gene pathways related to liver tissue regeneration, but CHB *vs.* CI *over*-expression of gene pathways related to immune activation/cytokine-signaling and liver cells (stellate/Kupffer cells). GZ-1 microenvironment (*vs.* CI) was richer in cytotoxic lymphocytes (p = 0.003) and B/T-cells (p = 0.01; p = 0.045); no significant differences were observed in GZ-1 *vs.* CHB. In the HBeAg- phases, 74 DEGs were found in GZ-2 *vs.* CI, 254 in CHB *vs.* GZ-2, and 231 in CHB *vs.* CI. *Up*-regulated genes were related to the immune response in GZ-2 *vs.* CI, the formation of extracellular matrix/inflammation in CHB *vs.* GZ-2, and cytokines/receptors involved in inflammatory processes and

tissue remodeling/extracellular matrix structure in CHB *vs*. CI. At enrichment analysis, GZ-2 *vs*. CI showed *over*-expressed immune response related-gene pathways, CHB *vs*. GZ-2 *under*-expressed metabolism/hepatocyte processes gene pathways, and CHB *vs*. CI *over*-expression of gene set pathways related to immune response/liver tissue regeneration. The liver microenvironment was enriched with fibroblast (p = 0.008) and B-cells (p = 0.034) in CHB *vs*. CI and fibroblast (p = 0.029) in CHB *vs*. GZ-2.
Conclusion: GZ profiles, like CHB, showed significant immune activation, warranting closer monitoring and potentially early antiviral therapy.

SAT-304
Insufficient implementation of pretherapeutic hepatitis B and C screening guidelines in academic and general belgian hospitals
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Background and aims: Hepatitis B virus reactivation (HBVr) still occurs in patients receiving immunosuppressive therapies (IT). This study aims to assess pretherapeutic HBV screening rates in haematological (H), oncological (O), inflammatory bowel disease (IBD), rheumatological (R), and dermatological patients (D) according to EASL guidelines and pretherapeutic HCV screening rates in haematological patients according to ECIL-5 guidelines. Real life data on this topic are scarce.
Method: Between 2023 and 2024, a retrospective patient file analysis was done in the above-mentioned departments in two academic and two general hospitals in Belgium (AH1, AH2, GH1, GH2). All patients that had at least two documented administrations of any systemic chemotherapy or immunomodulating/immunosuppressive therapy regimen were included. HBV (and HCV) screening was considered correct if both HBsAg and HBcAb (and HCVAb in haematology patients) were performed prior to the initiation of therapy. In addition, demographics were documented and class of IT regimen according to risk of HBV reactivation. B-cell depleting agents, anthracyclines, and TNF inhibitors were considered high risk (HR) molecules. In addition, screening rates were re-evaluated after an information session at an haemato-oncology department in one general hospital.
Results: In total, pretherapeutic HBV screening rates were assessed in 2437 patients (H 410; O 1180; IBD 482; R 259; D 106) in 4 hospitals (AH1 22.9%, AH2: 29.3%; GH1: 22.6%; GH2: 25.2%). Overall, correct pretherapeutic HBV screening rates are low (H 62.5%; O 20,4%; IBD: 61.2%; R: 29.7%; D: 34.0%), as well as pretherapeutic HCV screening rates in haematological patients (66.5%). Haematological and IBD patients were most often on HR IT (H 49.3%; O 20.6%; IBD 65.8%; R 32.0%; D 13.2%). Pretherapeutic HBV screening was significantly better performed in academic hospitals (AH 50.3% vs GH 24.8%, p < 0.001). Overall, HBV screening rates are higher when only HBsAg is considered (H 64.6%; O 31.1%; IBD: 74.5%; R: 38.2%; D: 45.3%), instead of HBsAg and HBcAb as recommended by 2009 EASL guidelines. Patients on HR IT are often not screened at all (H 28,3%; O 68,4%; IBD 28.1%; R 47.0%; D 57.1%). HBV and HCV screening rates in haemato-oncologists improved after the information session [H: 49.2% up to 58.1% p < 0.001; O: 25.7% up to 59.1%; p < 0.001].
Conclusion: In this large and multicentric study we demonstrate that HBV and HCV screening prior to administration of chemotherapy and immunosuppressive therapy regimens is performed suboptimal. Despite general beliefs, pretherapeutic screening rates are low in both an academic and general hospital setting, particularly in oncology, rheumatology and dermatology departments. Low HBV screening in patients on high-risk therapy regimens is worrisome. Encouragingly, one single awareness session already significantly improved screening adherence.

SAT-305
Qualitative interviews to explore multicultural appropriateness and content validity of the hepatitis B quality of life (HBQOL) among highly impacted populations (chinese and vietnamese) with chronic hepatitis B (CHB) in the US
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Background and aims: Chronic hepatitis B (CHB) has a negative impact on patients' health-related quality of life (HRQoL),[1–5] particularly among people from high HBV prevalence regions, such as China or Vietnam.[6] Patient-reported outcome (PRO) measures like the Hepatitis B Quality of Life (HBQOL) assess symptoms and impacts of CHB from patients' perspectives; however, there may be gaps in culturally important concepts for these highly impacted populations. Qualitative interviews were conducted in the US to explore CHB experiences among native Mandarin and Vietnamese speakers and English-speaking adults to assess content validity of the HBQOL.
Method: Virtual concept elicitation (CE) interviews were conducted in English, Mandarin, or Vietnamese with adults with CHB recruited from US clinical sites. Participants first described their CHB experiences spontaneously then were probed for other known CHB symptoms and impacts.
Results: Twenty-three interviews were completed, including eight in Vietnamese and four in Mandarin. The 11 English-speaking participants self-reported being Asian (n = 5), White (n = 3), Black (n = 1), and Other (n = 2). Fewer than 5% of symptoms and impacts were first reported in the final interviews, indicating that saturation of concept was reached. The three symptoms in the HBQOL (tiredness, memory problems, muscle aches) were among the most frequently reported symptoms in the total sample. Other frequently reported symptoms not currently in the HBQOL were itching (n = 16/23, 69.6%) and joint pain and decreased energy (n = 10/23 each, 42.5%). Notably, all Mandarin-speaking participants (n = 4/4, 100%) reported "decreased energy," in contrast to a smaller proportion of English (n = 2/11, 18.2%) and Vietnamese-speaking participants (n = 4/8, 50.0%). The impacts of CHB reported by over half of the participants included concerns about developing liver cancer in the future (n = 16/23, 69.6%), disrupted sleep (n = 14/23, 60.9%), and feelings of shame and sadness (n = 12/23 each, 52.2%). Among English-speaking participants, other impacts frequently reported were feelings of stigmatization (n = 7/11, 63.6%), difficulties with work or school and difficulties with sexual activities (n = 6/11 each, 54.5%). Most of the Mandarin-speaking participants (n = 3/4, 75.0%) reported social difficulties due to CHB. Participant's reported impacts largely matched those in the HBQOL, but additional impacts such as disrupted sleep (n = 14/23, 60.9%) and caution with alcohol consumption (n = 4/23, 17.4%) were also identified.
Conclusion: These interviews provided insights into the content validity and multicultural appropriateness of the HBQOL. The next step will be to modify the HBQOL based on these results and administer the modified version during cognitive debriefing interviews. This study may also be replicated in communities with persons born in other regions with high reported HBV prevalence.

SAT-306

Assessment of hepatocarcinogenesis risk using CAMP-B and PAGE-B in patients with chronic hepatitis B

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Background and aims: The suppressive effect of nucleos(t)ide analogs on hepatocarcinogenesis in patients with chronic hepatitis B (CHB) remains inconclusive. Risk-based stratification is essential for identifying high-risk patients, emphasizing the need for effective hepatocarcinogenesis risk evaluation methods. While PAGE-B has been widely used, the recently proposed CAMP-B scoring system offers another approach to risk stratification. This study aimed to evaluate the utility of CAMP-B in stratifying hepatocarcinogenesis risk and to characterize its performance compared to PAGE-B in CHB patients.
Method: Among 866 HBV-infected patients regularly attending our institution, 230 CHB patients without prior hepatocellular carcinoma (HCC) and with baseline clinical data at the initiation of antiviral therapy were included. Risk scores were calculated using PAGE-B (low risk: ≤9, intermediate risk: 10–17, high risk: ≥18) and CAMP-B (low risk: ≤3, intermediate risk: 4–6, high risk: ≥7; maximum score limited to 6 for non-cirrhotic cases).
Results: The cohort comprised 230 patients, with a median age of 47 years and 126 males (54.5%). Over a median follow-up of 7.8 years, the 10-year cumulative incidence of HCC was 4.7%. Based on CAMP-B, 150 patients were classified as low risk and 80 as intermediate risk, with cumulative incidences of 2.7% and 8.8%, respectively (HR 3.61, 95%CI: 1.01–13.0, $P < 0.05$). According to PAGE-B, 75, 126, and 29 patients were categorized into low (4.2%), intermediate (1.6%), and high-risk groups (19.4%), respectively, with a significantly elevated risk in the high-risk group (HR 9.14, 95%CI: 1.72–48.5, $P < 0.01$).
Conclusion: Patients classified as high-risk by PAGE-B require rigorous surveillance due to their substantially increased risk of HCC. Furthermore, the presence of HCC cases across all risk groups in both CAMP-B and PAGE-B highlights the importance of regular surveillance in all CHB patients.

SAT-307

Transient liver stiffening and mechanosignaling activation promote IFN-mediated anti-HBV response

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Background and aims: Elevated liver stiffness measurement (LSM) values have been reported to correlate with adverse outcomes in patients with liver disease. A transient increase in LSM value has been observed in some chronic hepatitis B patients undergoing interferon therapy, yet the correlation between this fluctuation and clinical outcomes remains unclear.
Method: This study included 291 HBeAg-negative patients with normal ALT levels and HBV DNA levels below 2000 IU/mL who received 48 weeks of PegIFNα therapy. The training set comprised 183 patients, while the validation set included 108 patients. HBsAg, ALT level, and LSM were assessed every 12 weeks. The correlations between HBsAg loss and LSM during therapy were analyzed. LSM was also measured in C57BL/6 mice receiving IFN treatment.
Results: In the training set, patients with HBsAg clearance exhibited significantly higher elevated LSM values compared to those without HBsAg clearance (4 vs 1 kPa, $P < 0.0001$). Notably, 88.9% of patients with an increased LSM value above 8 kPa achieved HBsAg clearance. In contrast, no patients without LSM elevation during treatment achieved HBsAg clearance. ALT elevation was not significantly correlated with HBsAg clearance, but with HBsAg decline at week 48. Both baseline HBsAg levels and elevated LSM values demonstrated significant diagnostic value for predicting HBsAg clearance, with AUROC of 0.823 ($P < 0.001$) and 0.776 ($P < 0.001$), respectively. The combination of baseline HBsAg level <2.35 log IU/mL and LSM elevation >2 kPa predicted HBsAg clearance with high specificity (88.9%). Additionally, patients with a ≥1 $\log_{10}$ IU/mL decline in HBsAg levels at week 48 had significantly higher elevated LSM values during treatment. In the validation set, similar results were observed. In C57BL/6 mice, LSM values were also significantly elevated following IFNα treatment.
Conclusion: A transient increase in LSM value during IFN therapy may indicate a high likelihood of HBsAg clearance or reduction in HBeAg-negative patients.

SAT-308

Anti-HDV prevalence in HBsAg positive patients and virological characterization of HBV/HDV co-infected individuals at the diagnostic laboratory of the university medical center Hamburg-Eppendorf between 2008 and 2024

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Background and aims: Hepatitis B and D virus (HBV/HDV) coinfection represents the most severe form of viral hepatitis. However, epidemiological studies and real-world data on prevalence are scarce. Therefore, we aimed to analyze i) the anti-HDV prevalence between 2008 and 2024 and ii) the virological characteristics of HBV/HDV co-infected patients in the diagnostic laboratory of the University Medical Center of Hamburg-Eppendorf.
Method: Patients who yielded a reactive test result for hepatitis B virus surface antigen (HBsAg) for the first time during the study-period (2008–2024) were retrospectively included in the study and analyzed for anti-HDV, HBV DNA and HDV RNA. HDV genotyping was performed either by Sanger sequencing of the R1 or R0 region or by next-generation sequencing (NGS) utilizing the iSeq100 system.
Results: Overall, 7,378 HBsAg positive individuals were newly diagnosed of which 62% (n = 4,249) were screened for anti-HDV. The screening rate varied from 30.4%–70.5% per year. In total, 5.5% were anti-HDV positive with positivity rates ranging from 3.9–8.2% per year. Although overall anti-HDV testing increased over the observation period, anti-HDV prevalence remained unchanged. The majority of the HBsAg and anti-HDV positive individuals (n = 234) were male (63%) and had a median age of 42 years (range 19–76). The median HBsAg level was 4,365 IU/ml (n = 176; range 0.05–1 × 10^5 IU/ml). HBV DNA was detectable in 70% with a median viral load of 570 IU/ml (range 2–9 × 10^8 IU/ml) and, consistent with low viral activity, only 9% of the patients were HBeAg positive. HDV RNA was tested in 66% (156/234) of which 43% had detectable HDV RNA with a median HDV RNA titer of 15,000 copies/ml (n = 52; range 20–2 × 10^8) or 165,070 IU/ml (n = 16; range 86–1 × 10^7). HDV genotyping was successfully performed in 64/68 HDV RNA positive patients and revealed 86% GT1 (n = 55), 11% GT5 (n = 7) and 3% GT8 (n = 2).
Conclusion: This mono-center study shows an anti-HDV prevalence of 5.5% in HBsAg positive patients in Germany, confirming previous studies. Interestingly, increased adherence to HDV screening guidelines among newly diagnosed HBsAg-positive patients did not result in a decrease of anti-HDV prevalence, but showed an overall lower rate of HDV RNA-positive patients. Finally, HDV genotyping revealed that an unexpected 10% of patients within the cohort were infected with non-GT1 HDV.

SAT-309

Hepatitis B surface antigen loss after nucleot(s)ide analogue cessation in patients living with chronic hepatitis B: a model-based meta-analysis of published studies

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Background and aims: Hepatitis B virus (HBV) infection is a major global health issue (estimated prevalence in 2022 of 256 million). Nucleot(s)ide analogues (NAs) are commonly used to treat chronic hepatitis B (CHB) infection. Indefinite treatment is often required to prevent virological and clinical relapse, but functional cure (sustained loss of hepatitis B surface antigen (HBsAg) with both undetectable hepatitis B e-antigen [HBeAg] and HBV DNA ≥24 weeks after treatment cessation) is rarely achieved. The need for lifelong NA therapy has been questioned. We conducted a systematic literature review in patients with CHB infection, the results of which were used to perform Model-Based Meta-Analysis (MBMA) to estimate the proportion of patients achieving HBsAg loss after NA cessation.
Method: We searched Medical Literature Analysis, MEDLINE and Embase over the period from inception to Aug 2023. Results were screened versus predefined criteria to identify observational studies and clinical trials of patients with CHB who discontinued NA therapy. Most studies were conducted in Asia-Pacific (~72%) in HBeAg-negative patients. The MBMA population included HBsAg-positive patients enrolled in NA treatment arms before cessation. Longitudinal data were utilised, with time of NA cessation considered as the index date. Multiple variables were explored as potentially influential covariates of HBsAg loss, including time, baseline demographic and disease characteristics (e.g. HBsAg levels, cirrhosis status), HBeAg status, and average NA treatment duration prior to cessation; impact of other variables will be analyzed.
Results: The final MBMA dataset consisted of summary-level HBsAg loss results from 41 studies, 11 of which were stratified by baseline HBsAg levels. Study sample size ranged from 8 to 1,368 patients, and study duration ranged from 24–521 weeks. Longitudinal data was reported in 24 studies, ranging from 2–16 timepoints. Model-estimated HBsAg loss in a population with mean baseline HBsAg of 3.04 log10 IU/mL ([1105 IU/mL] geometric mean of a uniform distribution between 1 and 3000 IU/mL) was 1.08% (95% confidence interval [CI]: 0.86, 1.37) after 6 months of NA cessation, and 1.67% (1.33, 2.14) after 1 year. The main factors driving between- and within-study variability (applied in the logit domain) were time (exponential rate constant [k] 0.0142 wk−1; 95% CI: 0.0105, 0.0195), and baseline HBsAg level, both as an additive effect per log10 IU/mL (−0.69 [95% CI: −1.1, −0.3]) and as a proportional effect on k (per unit log10 IU/mL; 0.36 [95% CI: 0.29, 0.44]).
Conclusion: HBsAg loss occurs infrequently after NA cessation in populations with a mean HBsAg level of ~3 log10 IU/mL, particularly in the first year after cessation. This indicates a need for alternative therapies for patients with CHB that have a finite treatment duration and potential to achieve functional cure.
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SAT-310

Immune profiling of peripheral and intrahepatic B cells in chronic hepatitis B

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Background and aims: The host immune response plays a fundamental role in the control of hepatitis B virus (HBV) infection. However, there is limited knowledge regarding the characteristics of B cells in peripheral blood and the intrahepatic compartment, primarily due to their low frequency. This study aimed to compare the frequency and gene expression profiles of global and HBV-specific B-cell populations in circulation and liver tissue in patients with chronic hepatitis B (CHB).
Method: Intrahepatic samples were obtained through fine-needle aspiration, while peripheral blood lymphocytes (PBMC) were isolated via density gradient centrifugation. Global B-cell subsets, HBV core antigen-specific memory B cells (HBcAg-MBC), and follicular helper T cells (Tfh) were analyzed using spectral flow cytometry (Aurora, Cytek) (n = 16). Single-cell RNA sequencing was employed in patients with paired peripheral and intrahepatic samples to assess gene expression (n = 11).
Results: Sixteen untreated HBV patients (88% male, median age 42 years) were included, of whom 75% had HBeAg-negative CHB. Median ALT was 65 U/L (IQR 50–177), qHBsAg 1879 IU/mL (598–5301), and HBV DNA 6.02 log IU/mL (3.43–7.56), with 88% testing positive for HBcrAg. The frequency of peripheral B cells was higher than that intrahepatic B cells (5.8% vs. 3.1%, $p < 0.01$). However, intrahepatic B cells predominantly exhibited activated (CD21+CD27+) and atypical memory (CD21-CD27-) phenotypes compared to circulating B cells (6.3 vs 5.0% and 7.2 vs 4.5%; respectively; $p < 0.05$). Pathway enrichment analysis showed differential gene expression between intrahepatic and circulating B cells. Especially, B cell activation pathways were upregulated in all B cell subtypes in the intrahepatic compartment compared to the periphery. Intrahepatic B cells also showed upregulation of innate immune signaling and metabolic pathways. Although at low frequencies, virus-specific HBcAg-MBC were detected in 94% of peripheral blood samples and 75% of liver samples (0.42 vs. 0.64% of total MBC, n.s). A positive correlation between HBcAg-MBC percentages in blood and liver was observed ($r = 0.85$, $p < 0.05$), independent of HBV viral replication. Tfh proportions were similar in both compartments, but circulating Tfh expressed higher levels of CD40L (4.5% vs. 1.9%, $p = 0.02$), a key marker for B-Tfh interactions.
Conclusion: In CHB, the frequency of intrahepatic B cells is lower than in circulation, however, these cells exhibit distinct gene expression profiles and signs of a more activated state likely reflecting increased antigen exposure within the liver. Elevated CD40L expression in circulating Tfh cells suggests enhanced interactions with B cells, potentially promoting their activation and migration to the liver.

SAT-311

Prevention of HBV mother to child transmission using HBV three dose and selective use of HBV BD and treatment of high viral load pregnant women in Uganda

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Background and aims: In Uganda ≥80% of all infants have received three doses (3D) of pentavalent vaccines since 2004 and ≥90% since 2013. Hepatitis B virus (HBV) universal birth dose (BD) vaccination of infants started in 2023. However, access to the BD vaccination

remains limited and sometimes intermittent outside of the large cities. Approximately 58% of annual 1.7 million births occur at home, posing a challenge to the complete rollout of universal BD vaccination. We aimed to evaluate the impact of combining universal 3D infant vaccination, targeted BD vaccination, and antiviral treatment of mothers on HBV prevalence among infants.

Method: This study was conducted over 18 months in 5 regional maternity hospitals. All pregnant HIV- women attending the hospitals were screened for HBsAg using rapid diagnostic tests. Among the 661 women who tested HBsAg+, HBV DNA viral load testing was performed to stratify them into three groups: high viral load (HVL, ≥20,000 IU/mL), low viral load (LVL, <20,000 IU/mL), and LVL currently on antiviral treatment. HVL women were prescribed 3 months of TDF/ 3TC during their third trimester.

Infants born to HBsAg+ mothers received a BD vaccine within 24 hours of birth, followed by the pentavalent 3D vaccination series. Infants born to HBsAg negative mothers (n = 662) adhered to the national pentavalent 3D vaccination schedule. All infants were tested for HBsAg at 9 months.

Results: Among the 661 HBsAg+ mothers, 83 women (12.6%, 95% Confidence interval: 10.0–15.1%) had HVL, 538 women (81.4% (78.4–84.4%)) had LVL, and 11 women (1.7% (0.7–2.6%)) with LVL were already on antiviral treatment. Of the HVL mothers, 95.2% (n = 76, 90.6–99.8%) initiated antiviral treatment during their last trimester. This group delivered 80 infants, of whom 88.8% (n = 71, 81.8–95.7%) received the BD vaccination, and 81.3% (n = 65, 72.2–89.8%) completed the 3D vaccination series. None of the infants in this group tested HBsAg+ at nine months. Low viral load mothers gave birth to 425 infants, 90.1% (n = 383, 87.3–93.0%) of whom received the BD vaccination. Among these, 82.1% (n = 349, 78.5–85.8%) completed the 3D vaccination. Three infants tested HBsAg+ at nine months and all three had completed 3D vaccination series. The 11 mothers with low viral loads who were on antiviral treatment delivered 11 infants. All these infants received the HBV BD, and 90.9% (n = 10, 73.9–100%) completed the 3D vaccination schedule. None of these infants tested HBsAg+ at nine months. Among the 662 HBsAg negative women, 99.5% (n = 659, 99.0–100%) of their infants completed the 3D vaccination series and none of the infants tested HBsAg+ at nine months.

Conclusion: Implementing these strategies in countries with a high number of home births can effectively minimize HBV MTCT. By applying these findings to a national program, Uganda can achieve its target of reducing HBV prevalence among infants to less than 0.1% before 2030

SAT-312-YI

Distinct circulatory and intrahepatic mono-mac and CD8 T cell clusters associated with fibrosis in patients with low levels of hepatitis B surface antigen

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Background and aims: Chronic hepatitis B virus (HBV) infection can lead to liver fibrosis, a precursor to cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) levels are commonly used to monitor disease progression. However, the relationship between HBsAg levels, immune cell profiles, and fibrosis severity remains unclear.

Method: Liver infiltrated immune cells and peripheral blood mononuclear cells (PBMCs) from six chronic HBV patients with low (<2000 IU/mL) and high HBsAg (>2000 IU/mL) were subjected to single-cell sequencing. Validation of soluble factors CXCL8, CXCL11, CXCL12 and histopathological analysis were performed in 36 naïve chronic HBV patients with low and high HBsAg levels.

Results: Chronic Hepatitis B patients with low HBsAg levels had significantly high fibrosis score than patients with high HBsAg levels. Single-cell sequencing of PBMCs and liver biopsies revealed that mono mac population was expanded and differentiated into unique and distinct clusters in HBsAg low patients. Out of 15 distinct monocyte clusters (M_c0–c14) in PBMCs, M_c1 and M_c6 clusters were only appeared in HBsAg low with high expression of CXCL8, CCL3 CXCL2, CCL4, CCL3L1, CCL20, IL1B, CROCC, TNFAIP6, TEX14, EREG, SELL, FOS, PRIM1, CREB1, AL592429.2, ZFP36 associated with chemotaxis, cell recruitment and inflammation. Similarly, intrahepatic mono-mac populations also showed high expression of CXCL8, CXCL2, CCL20, IL1B, TNFAIP, RHOB, S100A9, and TEX14 in HBsAg low patients. Levels of CXCL8, CXCL12, CXCL11 and IL1B were also increased in plasma of HBsAg low patients compared to HBsAg high. Additionally, a distinct peripheral $CD8^+$ T cell cluster expressing GNLY, GZMH, GZMB, GZMA, ITGB1, CX3CR1, ADGRG1, CCL4, and TGFBR3 were identified in patients with low HBsAg levels, contributing to cell adhesion, activation, cytotoxicity, and fibrosis.

Conclusion: Despite low HBsAg levels, naïve CHBV patients had increased fibrosis score. Single-cell sequencing data revealed appearance of distinct mono-mac and CD8 T cell clusters only in $HbsAg^{lo}$ patients with high expression of chemotactic, inflammation and apoptosis genes associated with fibrosis.

SAT-313

Hepatitis B virus screening, antiviral prophylaxis, and reactivation in Rituximab-treated patients: insights from a large retrospective cohort study

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Background and aims: Hepatitis B virus (HBV) reactivation is a well-documented complication of rituximab, an anti-CD20 monoclonal antibody used to treat autoimmune diseases and hematologic malignancies. Screening and prophylactic antiviral therapy are essential strategies to mitigate this risk, but adherence to guidelines has historically been suboptimal. This study aimed to evaluate trends in HBV screening, antiviral prophylaxis, and reactivation rates in a large cohort of rituximab-treated patients.

Method: A retrospective cross-sectional analysis was conducted using data from Clalit Health Services (CHS), Israel's largest health maintenance organization. Adult patients who received rituximab between 2000 and 2022 were included. Data were collected on HBV serologic tests (HBsAg, anti-HBc), HBV DNA, liver function tests, and prescriptions for antiviral therapy. Screening was categorized as full (both HBsAg and anti-HBc) or partial (one test only) and considered timely if performed within 90 days before rituximab initiation. Temporal trends were analyzed, and HBV reactivation was defined based on standardized virologic criteria.

Results: Among 1,857 rituximab-treated patients (mean age: 60.5 years; 50.4% male), hematologic malignancies were the predominant indication for therapy. HBV screening rates improved significantly over the study period, with timely full screening increasing from <40% in 2000–2005 to >80% after 2014 ($p < 0.0001$). Of the cohort, 10.9% had positive HBV serology (8.6% anti-HBc+; 2.3% HBsAg+), and 122 of 188 screened-positive patients received prophylactic antiviral therapy. Prophylaxis rates rose from <40% in the early years to >80% after 2017 ($p < 0.0001$). Six cases of HBV reactivation were identified, all in hemato-oncologic patients; no significant liver enzyme elevations or reactivations were documented in non-hemato-oncologic settings.

Conclusion: Advances in HBV screening and prophylactic antiviral therapy among rituximab-treated patients, particularly through multidisciplinary collaboration, have significantly reduced reactivation rates. The notably low reactivation in non-hemato-oncologic settings underscores the need to integrate this observation into risk-based treatment and follow-up strategies, ensuring optimized and patient-specific HBV management.

SAT-314

HBV RNA ultra-deep sequencing as a tool for HBV genotyping and resistance monitoring in virologically-suppressed individuals with chronic hepatitis B infection

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Background and aims: In routine practice, the assessment of the HBV genotype and drug resistance mutations uses sequencing of plasma HBV DNA. However, in the context of the development of novel treatment regimens to achieve functional cure in virologically suppressed individuals with chronic HBV infection, an alternative to investigate HBV genotype and drug resistance is needed. As HBV RNA is detected in the plasma of a fraction of virologically suppressed individuals, our aim was to develop an ultra-deep sequencing assay targeting the viral Pol/RT domain to determine HBV genotype and monitor pre-existing and treatment-induced resistance in clinical trials recruiting virologically suppressed participants.
Method: HBV RNA was extracted from plasma samples obtained from a cross-sectional cohort of 60 adults with chronic HBV infection whose origin was mainly from Europe, Asia, and Africa. The median (IQR) HBV DNA level was 3.3 (1.4–4.5) $\log_{10}$ IU/mL; overall, 25% (15/60) were virologically suppressed on antiviral therapy (HBV DNA < 10 IU/mL). The HBV RNA level was assessed using qPCR. For HBV RNA sequencing, reverse transcription of HBV RNA followed by nested PCR amplification of the Pol/RT domain were performed. Libraries of the PCR products were prepared and then sequenced to a depth of 5000x using Illumina short-read sequencing. The HBV genotype was determined by phylogenetic analysis with reference sequences. In addition, 22 samples had sufficient volume to perform HBV DNA sequencing of the whole HBV genome.
Results: Of the 60 plasma samples tested, 45 had detectable plasma HBV RNA with a median (IQR) level of 3.4 (1.2–6.0) $\log_{10}$ copies/mL. HBV RNA sequencing was successful in 43 samples to which an HBV genotype was assigned: A = 4, B = 11, C = 20, D = 5, and E = 3. The median (IQR) HBV RNA level of samples successfully sequenced was 4.9 (2.9–6.6) $\log_{10}$ copies/mL with 2 samples that succeeded sequencing despite having undetectable HBV RNA levels. HBV DNA sequencing succeeded in 14 of 22 samples. The concordance rate between the HBV genotype assigned by RNA and DNA sequencing was 100% (A = 1, B = 4, C = 8, and D = 1). All 14 successful sample pairs showed a nearly identical sequence match between the RNA and DNA sequencing (99.3–100%). Using sequencing of *in vitro* transcribed HBV RNA at 3 concentration levels, the total error rate of the assay was estimated at 3.4%. Therefore, the use of a conservative cutoff threshold at 5% for variant calling offers a reliable option to monitor HBV RNA minor variants. The evaluation of the use of HBV RNA sequencing for resistance monitoring is underway.
Conclusion: HBV RNA sequencing is a sensitive method to determine genotype in samples from virologically suppressed individuals. The assay also reliably detects HBV RNA minor variants above a threshold of 5%, offering insights into the evolution of viral RNA species and resistance mechanisms. This method holds promise for supporting the development of new therapies targeting HBsAg aimed at HBV functional cure.

SAT-315

Establishment and application of a new method for dual detection of HDV RNA and HBV DNA based on CRISPR technology

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Background and aims: Hepatitis D virus (HDV) is a defective virus that is dependent on hepatitis B virus (HBV) for infection and replication, and co-infection with HDV and HBV exacerbates the development of viral hepatitis. In this study, we used the clustered regularly interspaced short palindromic repeats-CRISPR-associated proteins (CRISPR-Cas) system to establish a method for the detection of HDV RNA and HBV DNA, as well as dual detection.
Method: We constructed HDV and HBV plasmids by comparing conserved sequence regions; and we designed and screened RT-RAA primer pairs to amplify the HDV plasmid and RAA primers to amplify the HBV plasmid, as well as corresponding crRNAs (CRISPR-derived RNAs), respectively; the conditions of the assay were optimized, leading to the establishment of a new CRISPR-Cas13a/Cas12a-based assay. Then the sensitivity and specificity of the new method was evaluated by fluorescence and lateral flow test strip method of the "line elimination method". The established new assay was validated by collecting HDV- and HBV-related clinical samples in comparison with RT-qPCR and RT-ddPCR methods.
Results: RT-RAA-CRISPR-Cas13a/RAA-CRISPR-Cas12a fluorescence and "line elimination" lateral flow test strip assays were established for HDV RNA detection and HBV DNA detection, respectively. The sensitivities of RT-RAA-CRISPR-Cas13a for detecting HDV plasmids and positive samples were both 10 copies/μL, and the sensitivities of RAA-CRISPR-Cas12a for detecting HBV plasmids and positive samples were both 1 copy/μL. Moreover, we established a RT-RAA-CRISPR-Cas13a/Cas12a dual fluorescence and "line elimination" lateral flow test strip assays for HDV RNA and HBV DNA. The sensitivity for detecting HDV and HBV plasmids and positive samples was 10 copies/μL, and there was no cross-reactivity between the detection of HDV and HBV and other related viruses; the RT-RAA-CRISPR-Cas13a/Cas12a dual fluorescence and lateral flow test strip assays showed a detection rate of 70% and 65.7% for HDV RNA and HBV DNA, respectively.
Conclusion: We developed a novel CRISPR-Cas13a/Cas12a-based assay for accurate, convenient, highly sensitive and specific detection of HDV RNA and HBV DNA, providing a more effective alternative for early detection and treatment of HDV and HBV infections, as well as for the guidance of medication administration and the evaluation of clinical therapeutic effects.

SAT-316

Sustained HBsAg loss in HIV/HBV-coinfected patients is not a rare event under HBV-active ART even if a residual risk of viral reactivation and liver disease progression still persists over time

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Background and aims: To date, HBsAg loss is considered the best surrogate marker for HBV functional cure. Here, we investigate the still controversial rates of HBsAg loss in the setting of HBV/HIV coinfection, its clinical determinants and long-term outcomes.
Method: This study included HBV-chronically infected people with HIV (PWH) from the Italian Icona cohort who started an antiretroviral regimen (ART) with ≥1 HBV active drug (TDF/TAF and/or FTC or 3TC). HBsAg loss was defined as HBsAg negativity in 2 consecutive time-points or 1 HBsAg negative and HBsAb turned positive. Kaplan-Meier curve was used to estimate the probability of HBsAg loss. Cox regression models adjusted for age, CD4 count and calendar year of baseline, when appropriate, were used to assess baseline clinical factors associated with HBsAg loss. The rate of HBV-reactivation and the clinical progression to liver disease (FIB4 > 3.25) was investigated by Kaplan-Meier curve in PWH experiencing HBsAg loss.
Results: 344 PWH included, mostly males (84.6%), Italian (74.4%), infected by heterosexual (39.5%) and MSM transmission (35.2%), with a median age of 40 (IQR: 34–48) years. At the time of starting HBV-active ART, median CD4+ cell count and HIV-RNA were 272 (136–450) cells/mm^3 and 4.7 (4.1–5.2) log copies/ml. In a median follow-up of 7.5 (4.2–12.1) years, HBsAg loss occurred in 34 PWH (10%). Probabilities of HBsAg loss at 5 and 10 years were 8.6% [95%CI 5.6–13.2%] and 15.1% [10.3–21.9%], respectively; notably, 59.7% also seroconverted to antiHBs. Older age (aHR for 10 years older: 1.44, 95%CI 1.01–2.06) and MSM (aHR: 2.66, 95%CI 1.15–6.13) were the only factors associated with HBsAg loss. No other clinical parameters were associated with HBsAg loss, including the other hepatitis co-infections and baseline HIV viro-immunological status.After achieving HBsAg loss, in a median follow-up of 5.0 [3.2–7.4] years, 2 PWH, both anti-HBs negative, experienced HBV reactivation with HBsAg positivity and HBV-DNA reuptake (2.9 and 4.8 log IU/ml) despite still on TDF/FTC treatment, with a probability of HBV reactivation of 5.5% [0.8–33.4%] at 2-year and 16.0% [3.9–53.2%] at 5-years. Among PWH with FIB-4 <3.25 at HBsAg loss (N = 24), 2 (8.3%) PWH had liver disease progression (FIB4 > 3.25), after 3 and 6 years, while HBsAg negative (1 was HCV-RNA positive).
Conclusion: A substantial proportion of PWH with chronic HBV infection achieves HBsAg loss during HBV-active ART with a probability of 15% by 10-years. HBsAg loss was maintained even if reactivation occurred with a 5.5% probability at 5-years. This highlights the need to better understand viro-immunological features underlying HBsAg loss and the risk to develop HBV reactivation and liver disease progression. This can have relevant implications for the success of incoming antiviral strategies aimed at achieving HBV functional cure in the setting of HIV coinfection.

SAT-317
HCC risk in intermediate PAGE-B patients: implications for surveillance strategies

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Background and aims: Hepatitis B virus (HBV) is a leading global cause of hepatocellular carcinoma (HCC). PAGE-B score is widely used to predict HCC risk. Currently, International Guidelines recommend surveillance for patients with advanced fibrosis or those with high risk according to PAGE-B score (score > 17). However, the clinical utility of HCC surveillance in intermediate risk patients (PAGE-B 10–17) remains unclear. This study aimed to (1) assess the risk of HCC in patients with PAGE-B 10–17 and (2) identify additional baseline factors associated with HCC development.
Method: We included all chronic HBV patients with at least one PAGE-B score between 10 and 17 during their follow-up at the Liver Unit of Hospital Clinic, Barcelona. Patients with follow-up duration <12 months, HCC within 6 months of enrolment, or HDV, HCV, or HIV coinfections were excluded. Patients were stratified into low-risk (LR, ≤9), intermediate-risk (IR, 10–17), and high-risk (HR, ≥18) based on PAGE-B score and by baseline cirrhosis status. Demographic, clinical, and biochemical variables were collected at baseline and updated every 6–12 months.
Results: Among 654 patients (20.5% female, median age 50 years [41–59]), 56.7% were Caucasian, and 56% were diagnosed as HBeAg-negative chronic infection. Nearly half (48.3%) were under nucleos(t)ide analogues (NUCs), and 13.8% had baseline cirrhosis. Patients were categorized by PAGE-B scores as follows: LR (18.1%), IR (63.7%), and HR (18.1%). HR and IR groups showed significantly higher APRI, FIB-4, liver stiffness values, and cirrhosis rates compared to LR group. Additionally, the use of NUCs was more frequent in HR and IR than LR patients (61% vs. 46% vs. 39%, p = 0.008). Over a median follow-up of 6.5 years (2–11), 13 patients (2%) developed HCC. The cumulative incidence of HCC at 3, 5, and 10 years across the entire cohort was 1.1%, 1.4%, and 2.8%, respectively. At 10 years, HCC incidence was 1.6% for LR, 2% for IR and 6.7% for HR patients. Non-cirrhotic patients had a 10-year HCC incidence of 0.7% compared to 15% for cirrhotic patient. Interestingly, although Chinese patients comprised only 11.3% of the cohort, they accounted for 31% of HCC cases, underscoring ethnic disparities in the HCC risk.
Patients who developed HCC were more likely to have baseline cirrhosis and elevated ALT and GGT levels. Notably, PAGE-B categories did not significantly differ between patients who did or did not develop HCC (p = 0.370).
Conclusion: In this large cohort with extended follow-up, the incidence of HCC was low and mainly driven by baseline cirrhosis. Patients with intermediate-risk PAGE-B score demonstrated a very low risk of HCC, irrespective of antiviral therapy, raising the question if HCC surveillance in this subpopulation is required. More nuanced risk stratification tools are urgently needed, ensuring cost-effectiveness and competing risks for death while addressing the heterogeneity of HBV-related HCC risk.

SAT-318-YI
Treatment coverage of the WHO 2024 hepatitis B guidelines in patients with chronic hepatitis B

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Background and aims: Antiviral treatment can improve prognosis for patients with chronic hepatitis (CHB). The WHO 2024 hepatitis B guidelines expanded treatment criteria to increase treatment eligibility. This study assessed treatment coverage under the updated WHO guidelines and compared treatment coverage with 2015 WHO guidelines in a large cohort of CHB patients.
Method: A total of 6,925 treatment-naïve CHB patients were included from three medical centers. Treatment eligibility was determined by four treatment options of the WHO 2024 hepatitis B guidelines: option 1, APRI > 0.5 or transient elastography value > 7 kPa or

evidence of cirrhosis; option 2, HBV DNA > 2000 IU/mL and ALT > 1 × ULN; option 3, presence of co-infections, a family history of liver cancer or cirrhosis, immune suppression, co-morbidities, or extra-hepatic manifestations; the option 4 of persistently abnormal ALT is a conditional recommendation for settings where HBV DNA testing is unavailable and other treatment criteria have not been met.
Results: Among 6,925 patients (60.2% male, median age 38 years), 63.8% met treatment criteria according to options 1–3. The proportions of patients who met option 1, option 2, and option 3 were 37.7%, 39.2%, and 23.4%, respectively. Treatment eligibility was higher in patients aged >30 years (64.5% vs. 61.9%, P = 0.047), males (67.6% vs. 58.0%, P < 0.001), and HBeAg-positive patients (91.5% vs. 53.3%, P < 0.001). When considering 4 options, the overall treatment eligibility rate achieved 61.6% which was significantly higher than the rate of 36.2% by the criteria of WHO 2015 hepatitis B guidelines (P < 0.001).
Conclusion: The WHO 2024 guidelines significantly increase treatment eligibility in CHB patients using expanded and simplified criteria. Even in resource-limited settings without HBV DNA testing, treatment coverage remains as high as 61.6%. These updated WHO 2024 guidelines may contribute to accelerating the achievement of WHO's goal for eliminating HBV by 2030.

SAT-319

High GALAD scores predict hepatocellular carcinoma in hepatitis B-related cirrhosis patients who received antiviral therapy

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Background and aims: In hepatitis B-related cirrhosis patients on long-term antiviral therapy, hepatocellular carcinoma (HCC) risk persists, motivating the need for risk prediction. The GALAD score, encompassing gender, age, alpha-fetoprotein L3, alpha-fetoprotein, and des-gamma carboxyprothrombin (DCP) measurements, is designed for HCC detection. This study investigates the role of the GALAD score in HCC prediction in CHB-related cirrhosis patients on antiviral therapy.
Method: We conducted a retrospective cohort study to include HBV-related cirrhotic patients undergoing long-term antiviral therapy with regular HCC surveillance. The serum samples were retrieved for alpha-fetoprotein-L3, alpha-fetoprotein, and DCP measurements to calculate the GALAD score. Cox proportional hazard regression analysis identified risk predictors for HCC.
Results: A total of 252 patients were included, with a median follow-up of 6.1 years. HCC developed in 64 patients with an annual incidence of 4%. The GALAD scores were measured before therapy in 213 patients and after a median of 2.6 years of antiviral therapy in 39 patients, with a median GALAD score of −2.84 and −3.76, respectively (p = 0.012). Overall, the pre-treatment GALAD score classifies the risks of 1-year HCC significantly better than alpha-fetoprotein-L3, alpha-fetoprotein, and DCP, with an AUROC of 0.857. Higher GALAD scores significantly increased the risk of HCC before antiviral therapy (per 1 GALAD score increase, adjusted hazard ratio [aHR] 1.20, 95% confidence interval [CI]: 1.06–1.35), and during antiviral therapy (aHR: 1.72, 95% CI: 1.10–2.70). The pretreatment GALAD score ≥−1.35 (vs. <−1.35) or on-treatment GALAD score ≥−3.38 (vs. <−3.38) increased 1.83-folds and 3.85-folds risks of HCC, respectively.
Conclusion: High pre-treatment or on-treatment GALAD scores significantly stratified a greater risk of HCC. The GALAD score may be measured during routine HCC surveillance.

SAT-320

Combination therapy of entecavir, peginterferon alpha and granulocyte-macrophage colony stimulating factor enhanced HBsAg loss and HBsAb response

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Background and aims: Functional cure is considered the advanced treatment goal for patients with chronic hepatitis B (CHB). We aimed to evaluate hepatitis B surface antigen (HBsAg) loss rates after combination treatment of entecavir (ETV), peginterferon alfa-2b (Peg-IFN) with or without granulocyte-macrophage colony stimulating factor (GM-CSF).
Method: In this multicenter randomized controlled trial, 257 virally-suppressed patients undergoing nucleos(t)ide analogues treatment who had HBsAg <3000 IU/mL were randomized (1:1:1) to receive either ETV for 96 weeks (E group), or 48 weeks of Peg-IFN+ETV, followed by 48-week Peg-IFN alone (EP group), or 48 weeks of Peg-IFN+ETV+GM-CSF, followed by 48-week Peg-IFN alone (EPG group). The primary outcome is HBsAg loss at week 96.
Results: Among 249 patients (81 in E group, 83 in EP group and 85 in EPG group) receiving at least one dose of the study drug, EP group (30.12%, 35.53%) and EPG group (22.35%, 34.67%) achieved significantly higher HBsAg loss and hepatitis B surface antibody (HBsAb) positivity rates than E group (0.00%, 0.00%; p < 0.0001, p < 0.0001) at week 96. Multivariate analysis showed that age, HBsAg level at baseline and HBsAg decline at week 24 correlated with HBsAg loss or HBsAb positivity at the end of Peg-IFN-based treatment. HBV RNA decline at week 24 correlated with HBsAg loss. The HBsAg longitudinal trajectory could predict HBsAg loss with an AUROC of 0.944. More patients in EP group and EPG group experienced adverse events than E group. Peg-IFN-based therapy was generally well tolerated.
Conclusion: In virally-suppressed patients with CHB, combination of ETV and Peg-IFN with or without GM-CSF improved the rates of HBsAg loss and HBsAb positivity. HBsAg trajectory may accurately predict HBsAg loss under Peg-IFN-based therapy.

SAT-321

Immunological correlates of rapid HBsAg decline in chronic HBV hepatitis patients undergoing Tenofovir Amibufenamide treatment

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Background and aims: While most chronic viral hepatitis B (CHB) patients undergoing Tenofovir amibufenamide (TMF) antiviral therapy experience a rapid decline in HBV DNA levels, the same is not observed for HBsAg decline in all patients, highlighting unclear immunological mechanisms. This study aims to prospectively and dynamically observe immunological changes during the initial stage of TMF antiviral treatment.
Method: A total of 37 CHB patients who will initiate antiviral treatment with TMF were enrolled, comprising 18 HBeAg positive and 19 HBeAg negative individuals. Clinical assessment was performed over 48 weeks post-TMF treatment. The phenotypes of B cells, dendritic cells (DCs), monocytes, T cells, and HBV-specific T cell functions were longitudinally assessed using freshly isolated peripheral blood mononuclear cells (PBMCs).
Results: The study revealed a rapid decrease in HBV DNA and RNA levels following TMF antiviral treatment among all CHB patients. Notably, the HBeAg positive group exhibited a significant decline in HBsAg levels, characterized by abnormal ALT levels at baseline. Immunological marker monitoring revealed elevated frequencies of B cells and CD8 T cells in HBeAg positive group, while a significant decrease in T cells was observed in the HBeAg negative group, primarily due to a reduction in CD4 T cells. In general, both groups exhibited a transient upregulation in the expression of CD80, CD86, and CD72 on B cells following 8 weeks of TMF treatment. The HBeAg negative group showed a significant increase in the expression of CD80 and PD-L1 on B cells and PD-L1 on monocytes, while demonstrating a decrease in CD72 on B cells expression compared to baseline levels. Furthermore, they also manifested a more robust HBcAg-specific T cell response. Moreover, among those who exhibited a reduction in HBsAg above 0.5log within 12 weeks of treatment in HBeAg positive group, elevated levels of CD80 and CD72 expression were observed on B cells, along with increased expressions of CD86, CD80, and PDL-1 on monocytes. The expressions of both CD25 on CD4 T cells and HLA-DR on CD8 T cells remained consistently elevated throughout the entire follow-up period but showed a declining trend. However, these patients still did not exhibit a robust HBV-specific T cell response.
Conclusion: TMF antiviral treatment leads to a more pronounced HBsAg reduction in HBeAg positive naïve patients accompanied by consistent activation of B cells and monocytes, as well as a gradual decline in T cell activation. Only the HBeAg negative group exhibits a stronger HBV-specific T cell response. Our findings suggest potential differential immunological mechanisms underlying TMF's antiviral effect between HBeAg negative and positive patients, along with significant reduction of HBsAg during the early stage of TMF treatment.

SAT-322

Nucleos(t)ide analogue cessation outcomes in non-cirrhotic patients with HBeAg-negative chronic hepatitis B

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Background and aims: Since a functional cure is rare during nucleos (t)ide analog (NAs) therapy, this treatment is typically lifelong for patients with chronic hepatitis B (CHB). We aimed to determine the outcomes of discontinuing NA treatment after the cessation of NA therapy in a large cohort of patients with HBeAg-negative CHB at a single center.
Method: This HBeAg-negative CHB court study included 140 non-cirrhotic patients who had virally suppressed and stopped NA therapy. Seventy patients (male/female ratio: 39/31, median age: 53.0 years) discontinued their NA treatment, while 70 age- and gender-matched patients who continued long-term NA treatment for at least 60 months were randomized in a 1:1 ratio. NA treatment was discontinued in selected non-cirrhotic patients who received long-term (>5 years) antiviral treatment and had achieved at least 3 years of virological suppression under NA treatment. HBV reactivation (virological and biochemical relapse) was defined as a single elevation of HBV DNA >2000 IU/mL and a single elevation of serum ALT >2× upper limit of normal (ULN) level during the off-treatment follow-up period. The primary outcome was sustained HBsAg loss for up to week 96, and the secondary outcome was HBV relapse after NA cessation.
Results: The median off-treatment follow-up duration was 45.5 months. Four patients in the antiviral treatment discontinuation group experienced HBsAg loss, while none in the NA treatment group experienced HBsAg loss ($p = 0.042$). Sustained remission was achieved by 43 patients (61.4%, 43/70), while overall, HBV relapse occurred in 27 patients during the off-treatment follow-up period. HBV reactivation was most commonly observed within three months after the cessation of NA treatment (n = 21, 77.8%). Re-treatment with NAs was initiated in these 27 patients. A decrease in serum HBV DNA to undetectable levels and normalization of serum ALT was achieved in all patients undergoing NA treatment. No serious adverse events related to antiviral treatment cessation occurred.
Conclusion: The cessation of NA treatment in non-cirrhotic CHB patients was associated with a significant loss of HBsAg and was effective in achieving treatment endpoints.

Viral Hepatitis B and D – Current therapies

TOP-252

HBsAg decline and clearance with peg-IFN add-on therapy – an individual participant data meta-analysis of prospective trials (PROSPER)

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Background and aims: Peg-interferon (peg-IFN) plays an increasingly important role in HBV cure strategies, either in combination with novel antivirals or as a lead-in treatment to reduce viral antigen burden before novel antivirals are introduced. Robust estimates of HBsAg decline and clearance that can be achieved with peg-IFN addition to nucleo(s)tide analogue (NA) therapy are therefore urgently needed.
Method: We performed a post-hoc meta-analyses of individual participant data from 7 international prospective clinical trials involving CHB patients on NA therapy who received peg-IFN add-on treatment for 24 to 48 weeks. The primary endpoint of our analyses was HBsAg loss at end of follow-up (EOF, 6 to 12 months after end of peg-IFN therapy). Secondary analyses focused on on-treatment HBsAg decline to <1,000 IU/mL.
Results: We included 531 patients, 431 (81%) were male, 370 (70%) were Asian, mean age was 44 (±11) years. At start of peg-IFN therapy (SOT), 205 (39%) were HBeAg positive, mean HBsAg level was 3.02 (±0.96) log10 IU/mL (HBsAg <100 IU/mL: 66 (13%); 100–1,000 IU/mL: 152 (29%); >1,000 IU/mL: 306 (58%)), median HBV DNA was TND [IQR: TND-TND] and median ALT was 0.77 [IQR: 0.59–1.07]×ULN. Peg-IFN add-on was planned for 48 weeks in 446 patients (84%). At EOF, 49 (9.2%) patients achieved HBsAg loss. HBsAg loss rates varied with SOT HBsAg levels; HBsAg loss was achieved in 40.9/11.2/1.6% of patients with SOT HBsAg <100/100–1,000/>1,000 IU/mL ($p < 0.001$). Findings were also consistent across ethnicities (Caucasian: 30.0/8.7/3.6%, $p = 0.007$; Asian: 41.5/10.8/1.0%, $p < 0.001$). HBsAg loss was achieved in 20.2% amongst patients with SOT HBsAg <1,000 IU/mL, and in 13.2% amongst patients with SOT HBsAg <3,000 IU/mL. HBeAg status was not associated with HBsAg loss when adjusted for baseline HBsAg levels ($p = 0.39$). Mean HBsAg decline after 24 and 48 weeks of peg-IFN add-on was −0.61 (±0.96) and −0.96 (±1.19) log10 IU/mL. Amongst patients with HBsAg >1,000 at SOT, HBsAg <1,000 IU/mL was achieved in 28% at week 24 and in 45% at week 48. In pairwise analysis, 48 weeks of treatment was superior to 24 weeks in achieving levels <1000 IU/mL for patients with SOT HBsAg 1,000–2,000 IU/mL (79.4% vs. 68.3%, $p = 0.016$), 2,000–3,000 IU/mL (44.2% vs. 25.0%, $p = 0.013$), and >3,000 IU/mL (26.7% vs. 14.3%, $p = 0.004$).
Conclusion: Addition of peg-IFN to NA-therapy results in HBsAg loss in 20% of patients with SOT HBsAg <1,000 IU/mL, and in 41% of those with SOT HBsAg <100 IU/mL. Amongst patients with higher HBsAg levels, peg-IFN can be used to reduce HBsAg to below thresholds associated with response to novel antivirals, although 48 weeks of therapy seems required to optimize response rates. These findings can be used as a reference for the design of trials aiming for HBV cure.

TOP-265

Virological outcomes in patients with HDV-related compensated cirrhosis treated with Bulevirtide monotherapy for 144 weeks: a subanalysis of the retrospective multicenter european study (Save-D)

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Background and aims: Bulevirtide (BLV) monotherapy up to 144 weeks was safe and effective in patients with chronic hepatitis D virus (HDV) infection in the MYR-301 trial, however real-life data in large cohorts of patients with cirrhosis are lacking.
Method: Consecutive HDV patients with cirrhosis reaching week 144 of BLV 2 mg/day sc monotherapy in the retrospective multicenter real-life European study (SAVE-D) were included. Virological (HDV-RNA undetectable or ≥2-log decline *vs.* baseline), biochemical (ALT <40 U/L), combined response (biochemical + virological), adverse events and liver-related events (LREs) were assessed. HDV RNA was tested locally.
Results: 48 patients treated with BLV monotherapy for 144 weeks were enrolled: age 51 (IQR 41–58) years, 65% men, ALT 106 (66–144) U/L, liver stiffness measurement (LSM) 20.8 (14.6–27.5) kPa, platelets 76 (54–113) × 10^3/mm^3, 98% CPT score A, 52% with varices, 2% HIV-positive, 8% with a history of previous decompensation, 4% with active HCC, 100% on NUC. Baseline HBsAg levels and HDV-RNA were 3.8 (3.6–4.1) log IU/mL and 5.4 (4.4–6.3) log IU/mL, respectively, median HBcrAg (positive in 90% of available samples) 3.8 (3.5–4.4) $\log_{10}$ U/mL. Following 144 weeks of BLV monotherapy, 75% of patients achieved a virological response, 67% a biochemical response, 56% a combined response, 35% HDV RNA undetectability. 5 (10%) patients had <1 Log HDV RNA decline *vs.* baseline (non-virological response), whereas 7 (15%) had achieved at >1 but <2 Log HDV RNA decline (partial virological response). 42 (51%) of patients with a suboptimal response (non- or partial virological response) had at least a 50% ALT decrease compared to baseline. During long-term BLV monotherapy, AST, GGT, IgG and AFP levels significantly declined while albumin levels increased ($p < 0.001$ compared to baseline). Mean HBsAg levels declined (Bas → W144: 3.7 → 3.5 Log_{10}IU/mL, $p = 0.02$), as well as mean HBcrAg values (4.1 → 3.7 $\log_{10}$ U/mL, $p = 0.01$), LSM values (24.2 → 17.4 kPa, $p = 0.001$) and serological non-invasive tests of fibrosis (FIB-4, APRI score). At variance, no significant reduction in spleen

stiffness values was observed. No baseline predictors of HDV RNA undetectability at week 144 (baseline ALT, HBsAg levels HDV RNA levels, bile acids) were identified. Bile acids levels increased, 25% of patients reported mild and transient pruritus, independently of bile acid levels. During 144 weeks of BLV treatment, de-novo ascites occurred in 3 patients, no patients died or underwent liver transplantation.
Conclusion: BLV monotherapy 2 mg/day for 144 weeks confirmed safety and effectiveness in patients with HDV-related cirrhosis also in real-life setting. Liver-related events were rare.

WEDNESDAY 07 MAY

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Real-world evidence shows comparable Bulevirtide effectiveness in hepatitis D patients with and without cirrhosis: results from the prospective nationwide D-Shield multicenter study

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Background and aims: Bulevirtide (BLV) has been available in Italy since May 2023 for patients with chronic hepatitis Delta (CHD), but no studies have addressed features of patients treated with BLV and their responses to treatment yet.
Method: CHD patients starting BLV 2 mg/day as monotherapy were included in a multicenter prospective real-life Italian study (D-SHIELD). Patients' characteristics and treatment responses were assessed at baseline and trimonthly afterwards in patients with or without cirrhosis. The primary endpoint was the achievement of a virological response, defined as a reduction in HDV RNA >2 Log IU/mL compared to baseline or HDV RNA undetectable.
Results: 404 patients from 38 centers were enrolled in this ongoing study: 303 (75%) cirrhotics and, 101 non-cirrhotics (25%). At baseline, median HDV RNA was 5.1 (1.5–8.2) *vs.* 5.7 (2.3–7.4) Log IU/ml (p = 0.005), ALT 75 (12–1,074) *vs.* 75 (19–513) U/L (p = 0.20). Median age 55 (24–82) *vs.* 55 (26–76), 55% *vs.* 55% men, 97% *vs.* 93% on NA therapy; 94% *vs.* 94% European origin. Among cirrhotics, 40% had varices, 10% previous history of HCC, 10% previous history of ascites, 3% of varices hemorrhage, 6% were decompensated. As of the end of November 2024, 340 patients (257 cirrhotics and 83 non-cirrhotics) completed 24 weeks and 203 (160 cirrhotics, 43 non-cirrhotics) patients have completed 48 weeks of treatment. ALT declined in both groups at week 24 (median ALT levels 35 *vs.* 35 U/L, p = 0.60) and at week 48 (31 *vs.* 31 U/L, p = 0.90). HDV RNA decline was more pronounced in non-cirrhotics at week 24 (3.5 *vs.* 3.8 Log IU/mL, p = 0.04), but not at week 48 (2.9 *vs.* 3.2 Log IU/mL, p = 0.06). Virological, biochemical and combined responses were achieved by 47% *vs.* 42% (p = 0.60), 64% *vs.* 69% (p = 0.51), and 34% *vs.* 32% (p = 0.89) of patients at week 24; 68% *vs.* 50% (p = 0.04), 69% *vs.* 68% (p = 0.87), and 49% *vs.* 34% (p = 0.06) of patients at week 32, and by 66% *vs.* 65% (p = 1), 73% *vs.* 55% (p = 0.06), and 54% *vs.* 33% (p = 0.05), of patients at week 48 in cirrhotics *vs.* non-cirrhotics, respectively. At the same time points HDV RNA undetectability (defined as target not detected or <lower limit of detection or quantification) was achieved by 13% *vs.* 10% (p = 0.69), 22% *vs.* 14% (p = 0.53) and 24% *vs.* 20% (p = 0.68) of cirrhotics *vs.* non-cirrhotics, respectively. Among non-virological responders at week 24, a partial virological response (HDV RNA decline >1 Log IU/mL but <2 log IU/mL compared to baseline), was achieved by 24% *vs.* 23% (p = 1), and 20% *vs.* 14% (p = 0.76) of cirrhotics *vs.* non cirrhotics

patients at week 32 and 48, respectively and a virological response by 44% *vs.* 26% (p = 0.09) and 53% *vs.* 48% (p = 0.81), respectively.
Conclusion: D-SHIELD is the largest single country study on BLV treatment for CHD in Europe. Virological, biochemical and combined responses through week 48 were overall similar between patients with and without cirrhosis.

WED-286
Comparative renal safety of besifovir dipivoxil maleate and tenofovir disoproxil fumarate in chronic hepatitis B patients: insights from a nationwide cohort study
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Background and aims: Besifovir dipivoxil maleate (BSV) is a novel antiviral agent approved in Korea for chronic hepatitis B (CHB) treatment. While previous comparative studies between BSV and tenofovir disoproxil fumarate (TDF) suggested lower renal toxicity with BSV, these findings were limited by small sample sizes. This study aimed to comprehensively assess the incidence of chronic kidney disease (CKD) in CHB patients treated with BSV versus TDF using a nationwide cohort.
Method: In this retrospective cohort study, we analyzed treatment-naïve CHB patients who initiated BSV or TDF therapy between January 2018 and December 2022. Using South Korean national health database, we created balanced cohorts of 25,849 patients each through inverse probability of treatment weighting (IPTW). The primary outcome measure was CKD incidence.
Results: The incidence rate (IR) of CKD was significantly lower in the BSV group compared to the TDF group (3.11 vs. 4.75 per 1,000 person-years; incidence rate ratio [IRR] 1.53, 95% CI 1.28–1.82, p < 0.001). Using BSV as the reference, the adjusted hazard ratio (HR) for CKD in the TDF group was 1.26 (95% CI 1.05–1.52, p = 0.014). In patients aged 60 years and older, TDF showed a markedly higher incidence and risk of CKD (IR 3.93 vs. 10.18 per 1,000 person-years; IRR 2.59, 95% CI 1.87–3.59, p < 0.001; HR 2.45, 95% CI 1.74–3.47, p < 0.001).
Conclusion: BSV is linked to a lower incidence of CKD compared to TDF, particularly in patients aged 60 and older, suggesting it may be a safer treatment option for CHB, especially in elderly patients at higher risk of renal impairment.

WED-287
High levels of hepatitis B virus deoxyribonucleic acid integration by high-throughput viral integration detection method predict non-responsiveness of antiviral treatment
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Background and aims: Hepatitis B virus (HBV) integration influences antiviral response. We aimed to analyse the features of HBV integration in chronic hepatitis B(CHB) patients and identify integration parameters predicting antiviral response.
Method: A total of 257 nucleos(t)ide analogues (NUCs) experienced CHB patients were recruited in Anchor study, then were randomized (1:1:1) into ETV monotherapy group (Group I), pegylated interferon alpha-2b (Peg-IFN) & ETV combination therapy group (Group II), and Peg-IFN & ETV & Granulocyte-macrophage Colony Stimulating Factor (GM-CSF) combination therapy group (Group III), and 249 participants completed the entire 96-week antiviral treatment regimen. The patients who obtained HBsAg loss at week 96 were named as responders, otherwise named as non-responders. Respectively, 13 and 17 cases were randomly selected from responders and non-responders in the Peg-IFN & ETV group (Group II), as well as additional 15 cases from the ETV monotherapy group (Group I) for high-throughput Viral Integration Detection (HIVID) with pairs of liver samples (at baseline and week 48).
Results: At baseline, the levels of integration were much higher in patients with a family history of CHB compared to those without and were positively correlated with the duration of CHB, and the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), but not with the levels of HBsAg, HBcrAg, HBV RNA and HBV cccDNA quantification. After 48 weeks of antiviral treatment in either Group I or Group II, the levels of HBV integration were essentially comparable with those at baseline. Totally, the non-responders of antiviral therapy demonstrated greater elevated numbers of break-point types of integration at both baseline and week 48 when compared to responders. Especially, the non-responders in Group II displayed much higher numbers of recurrent integrations and clonal integrations than responders at week 48. A baseline number of breakpoint types exceeding 28 might serve as an indicator for predicting non-response at week 96 of antiviral therapy totally.
Conclusion: Duration of CHB, ALT and AST levels were associated with the integration levels of virally-suppressed CHB patients. The higher numbers of recurrent integrations and clonal integrations contributed to the non-responsiveness of Peg-IFN treatment and the number of breakpoint types might predict non-responsiveness of antiviral therapy totally.

WED-288
HBV reactivation in HBV/HDV coinfected patients during bulevirtide monotreatment
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Background and aims: In 2020 bulevirtide (BLV) was conditionally approved in the EU for the treatment of chronic hepatitis D (CHD) as combination treatment with nucleos(t)ide analogues (NA) or as monotreatment. BLV leads to normalization of transaminases and decrease of HDV viral load in most patients by blocking viral entry of HBV/HDV. We report three cases of HBV reactivation in patients with BLV monotreatment who had undetectable HBV DNA at start of treatment.
Method: Real life data collected in clinical routine. Serum CXCL-10 was measured by Quantikine[c] ELISA Human CXCL10/IP-10 Immunoassay. All patients provided written informed consent.
Results: Of 20 patients treated with BLV in our outpatient clinic, three had no detectable HBV-DNA and were therefore initially treated with BLV monotherapy. In patient A HBV-DNA was detectable in month (mo) 4 after BLV start and reached a peak of 25,800 IU/ml in mo. eight, while ALT rose from 91 U/l at start of flare to a maximum of 204 U/l. After starting treatment with tenofovir disoproxil fumarate (TDF) ALT normalized and HBV-DNA was undetectable again. For patient B HBV first became detectable after 30 months of BLV monotreatment, HBV-DNA rose to 2,000 IU/ml in mo. 36, and ALT increased from 29 U/l to 63 U/l. NA led to ALT-normalization and HBV suppression. Six months after the HBV reactivation HDV RNA became undetectable. In patient C, HBV was first detected six months after BLV start. Although HBV-DNA was only 10 IU/ml and ALT remained normal, we started NA-treatment, because the patient had a compensated liver cirrhosis. Reactivation led to an increase of the ISG (interferon-stimulated

gene) CXCL-10 in the sera of patients A (29 → 32 pg/ml) and B (22→34 pg/ml), which decreased after initiating NA treatment (median 32.4 →22.2 pg/ml, six months after NA start). In comparison the CXCL-10 levels of three HBV/HDV patients initially treated with a combination of NA+BLV and therefore without HBV reactivation showed a steady decline of CXCL-10 after starting with BLV before BLV: (median 40.2 pg/ml→ 23.7 pg/ml, 9 months after BLV).
Conclusion: All 3 CHD patients with undetectable HBV-DNA became HBV-DNA positive after initiation of BLV monotreatment. These patients need to be monitored by regular measurement of HBV-DNA, or receive combination treatment. The mechanism of HBV reactivation and profile of inflammatory markers in those cases needs to be further analyzed, because it could unveil interactions between HBV and HDV infection.

WED-289
Patient centered-outcomes in HDV-treated patients with Bulevirtide

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Background and aims: Chronic Hepatitis Delta (CHD) is recognized as the most severe type of viral hepatitis. Bulevirtide, recently approved for treatment, has demonstrated potential in lowering viral loads and improving liver function. However, there is limited real-world evidence regarding its effectiveness, treatment adherence, and patient-reported outcomes (PROs). This study aimed to assess the virological and biochemical responses to bulevirtide, alongside evaluating the impact of a pharmacist-led educational initiative (EXPLAIN) on therapy adherence, quality of life (QoL), and reported adverse effects.
Method: A total of 31 CHD patients undergoing bulevirtide treatment were prospectively monitored at Padua University Hospital. The pharmacist-led educational program aimed to improve patient understanding of the therapy. Primary outcomes measured included virologic response, QoL (assessed using the EQ-5D-5L questionnaire), and adherence (measured via the Proportion of Days Covered, PDC).
Results: At both 24 and 48 weeks, bulevirtide therapy resulted in significant reductions in HDV RNA levels and improved liver function tests. At 24 weeks, 90.3% of patients achieved optimal adherence (PDC ≥90%). QoL scores showed marked improvements during follow-up, particularly in pain and anxiety domains. The safety profile was consistent with prior clinical trials, with commonly reported adverse events including injection-site reactions and fatigue.
Conclusion: The EXPLAIN program facilitated excellent adherence rates and notable QoL improvements, underscoring the critical role of clinical pharmacists in managing CHD antiviral therapy. These findings highlight the value of pharmacist-led education programs in enhancing patient outcomes in real-world clinical settings.

WED-290
Effectiveness and renal safety following switching to tenofovir alafenamide in patients with chronic hepatitis B: Results from a five-year, multicenter cohort study

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Background and aims: Chronic hepatitis B (CHB) treatment requires long-term nucleos(t)ide analogue (NUC) therapy, making renal safety evaluation crucial. Tenofovir alafenamide (TAF) has shown favorable viral suppression and renal safety profiles in international clinical trials; however, long-term outcomes, particularly for patients switching to TAF and for those with chronic kidney disease (CKD) remain insufficiently characterized. This study examines the five-year virological efficacy and renal function of CHB patients undergoing sequential TAF therapy.
Method: This real-world, multicenter retrospective study included 414 CHB patients aged 18 and older switched from an NUC to TAF who were followed-up for at least five years. The primary endpoints included five-year virological efficacy (HBV DNA <10 IU/mL and HBsAg reduction), biochemical response (ALT normalization), and renal function (eGFR). Sensitivity analysis assessed patients with CKD (eGFR <60) at the time of TAF switch.
Results: The mean age in the TAF switch group was 57.5 ± 12.6 years, 254 were men (61.4%), 301 (72.7%) had normal ALT levels, and 54 (13.0%) had cirrhosis. Prior treatments included entecavir (ETV) for 177 patients, tenofovir disoproxil fumarate (TDF) for 122, and combination therapy for 115: 52 patients (12.6%) remained HBV DNA positive. After five years of TAF therapy, HBV DNA suppression was achieved by 99.3% of the patients ($P < 0.001$), and the percentage with undetectable HBV DNA (target not detected: TND) significantly improved from 70.5% to 91.7% ($P < 0.001$). No cases of HBV DNA breakthrough due to NUC resistance were observed, including among those previously on combination therapy. The ALT normalization rate increased from 72.7% to 85.8% over the five years ($P < 0.001$). HBsAg

reduction over five years averaged 0.39 ± 0.63 logIU/mL (annual rate: 0.077 logIU/mL), while eGFR decreased by −3.60 ± 7.47 mL/min/1.73 m^2. In the prior ETV group, the eGFR change was −4.51 ± 7.85, compared to −3.27 ± 7.21 in the TDF and combination groups (P < 0.01). Among the 100 patients (23.8%) with CKD at TAF initiation, the five-year HBV DNA suppression rate was 100%, the TND rate was 93.0%, and the ALT normalization rate was 91.0%, indicating robust therapeutic efficacy. The reduction of HBsAg at five years for these CKD patients was 0.36 ± 0.72 logIU/mL, similar to that of patients with normal renal function. Additionally, the eGFR change after five years of TAF therapy remained within the physiological range, at −2.50 ± 6.53.

Conclusion: This five-year follow-up of CHB patients who had been switched to TAF found sustained high virological and biochemical efficacy. Treatment efficacy and renal safety for patients with CKD were comparable to that of non-CKD patients.

WED-291

Long risk of decompensation and HCC in patients with HDV-related compensated cirrhosis treated with Bulevirtide monotherapy for up to 144 weeks: the retrospective multicenter european study (Save-D)

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Background and aims: Bulevirtide (BLV) has been approved by EMA for treatment of compensated chronic hepatitis D virus (HDV) infection, however data about liver-related outcomes in HDV cirrhotics treated with BLV are limited.

Method: Patients with HDV-related cirrhosis treated with BLV 2 mg/day sc were included in a retrospective multicenter real-life European

study involving 49 centers (SAVE-D). Virological (HDV-RNA undetectable or ≥2-log decline *vs.* baseline), biochemical (ALT<40 U/L), combined response (biochemical+virological) and liver-related events (LREs) were assessed. Clinically significant portal hypertension (CSPH) was defined according to Baveno VII criteria.
Results: 344 patients treated with BLV monotherapy up to 144 weeks were included: age 50 (IQR 40–58) years, 62% men, ALT 81 (54–130) U/L, liver stiffness measurement (LSM) 16.5 (12.6–25.5) kPa, platelets 100 (68–149) × 10^3/mm^3, 95% CPT score A, 47% with varices, 8% HIV-positive, 13% with previous decompensation, 5% with HCC, 90% on NUC. Baseline HDV-RNA and HBsAg levels were 5.4 (4.1–6.4) log IU/mL and 3.7 (3.2–4.1) log IU/mL, respectively. During treatment, 74%, 41% and 59% of patients achieved a virological, biochemical and combined response, respectively, while 41% HDV RNA undetectability. 21 patients developed a de-novo LRE: 13 HCC and 8 decompensations (ascites in 4, bleeding in 4). Overall, the 3-year cumulative incidence of de-novo LREs was 10.4% (95% CI 7–15%): 6.2% for HCC (95% CI 3–9%) and 3.3% for decompensation (95% CI 1–6%). Median time to HCC was 13 (10–23) months; 11 (85%) patients had early HCC (BCLC 0-A), 11 (75%) had CPT A and 10 (77%) CSPH at baseline. At HCC, 8 (62%) had achieved a virological response to BLV. Median time to decompensation was 14 (6–18) months: 6 (75%) patients had achieved a virological response to BLV, 75% had baseline CPT score A6, with a triggering event identified in 4 cases. In patients with or without baseline CSPH, the 3-year cumulative incidence of HCC was 8.1% (95% CI 3–12%) *vs.* 4.3% (95%CI 1–7%) ($p = 0.18$) and of decompensation 7.6% (95%CI 3–12%) *vs.* 0%, respectively ($p < 0.001$). At Cox regression univariate analysis, higher baseline BMI, spleen size, lower albumin values and CSPH at baseline were associated with LREs. At multivariate analysis, only lower albumin values independently predicted LREs (HR 0.28; 95% CI 0.11–0.71, $p = 0.01$). The 3-year liver transplantation (LT)/ death-free survival was 89.4% (95% CI 85–93%): 18 patients underwent LT (15 HCC, 3 decompensation) and 9 patients died, 4 of liver-related events.
Conclusion: In patients with HDV-related cirrhosis treated with BLV 2 mg/day monotherapy up to 144 weeks, the 3-year incidence of LREs remained low and was associated with lower baseline albumin values. Liver decompensation occurred only in compensated cirrhotics with baseline CSPH.

WED-292

A cross-sectional, intrahepatic analysis of HBV and HDV markers in liver trasplants of untreated and Bulevirtide-treated patients with chronic hepatitis Delta

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Background and aims: Bulevirtide (BLV) was approved by EMA for CHD treatment, however no data exists about intrahepatic features of BLV-treated patients who underwent liver transplantation (LT). Aim of the study was to compare intrahepatic and clinical features of untreated and BLV-treated CHD patients who received LT.
Method: BLV-treated (SAVE-D study) and untreated CHD patients who underwent LT were compared. Clinical and virological features were collected at LT; HDV RNA was quantified with Robogene® 2.0. Intrahepatic (i) HDAg, HBsAg, and HBcAg staining were performed by immune-histochemistry (Ventana Benchmark Ultra System).
Results: 45 LT were studied, 35 untreated patients and 10 patients treated with BLV monotherapy for 14 (5–18) months before LT. BLV-treated and untreated patients were similar in terms of age at LT (56 *vs.* 49 years), male gender (60% *vs.* 49%), indication for LT (HCC 70% *vs.* 49%), HBsAg levels (3.6 *vs.* 3.6 LogIU/mL), NUC therapy (100%) and undetectable HBV DNA (90% *vs.* 80%). By contrast, BLV-treated patients had lower MELD (11 *vs.* 17, $p = 0.01$), lower ALT (41 *vs.* 56, $p < 0.01$) and lower HDV RNA levels (3.0 vs 4.9 LogIU/mL, $p = 0.11$). At histology, iHBcAg stained negative in all patients, while iHBsAg stained negative in 3 (7%) patients, <10% positive in 12 (27%), 10–30% in 13 (29%), >30% in 17 (38%), without significant differences between groups. iHBsAg levels correlated with serum HBsAg ($p = 0.01$), but not with serum HDV RNA. iHDAg stained negative in 13 patients (29%), 1–5% positive in 16 (36%), 10–50% in 12 (27%) and >50% in 4 (9%), without significant differences between groups. Diffuse (42%) and focal (27%) were the most prevalent iHDAg patterns. iHDAg correlated with serum HDV RNA ($p = 0.04$), but not with serum HBsAg or iHBsAg.
Conclusion: In CHD patients undergoing LT, iHBsAg was positive in most patients and correlated with serum HBsAg; on the other hand, iHDAg staining correlated with serum HDV RNA levels but resulted negative or low positive in most patients, independently of BLV-treatment.

WED-293

Comparative performance of hightly sensitive HBcrAg and HBsAg assays in predicting clinical flares and HBsAg loss after nucleos(t)ide analgoues withdrawal in patients with chronic hepatitis B

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Background and aims: Finite nucleos(t)ide analogue (NA) therapy has recently been proposed as a potential strategy to facilitate seroclearance of hepatitis B surface antigen (HBsAg). However, NA withdrawal can lead to hepatitis flares with risks of liver failure and death. Monitoring serum levels of HBsAg and hepatitis B core-related antigen (HBcrAg) was reported to aid in predicting off-NA outcomes, but prior studies were limited by the insensitivity of older assays. Furthermore, the comparative performance of these two biomarkers remains incompletely understood.
This study aimed to compare the predictive performance of highly sensitive (iTACT) HBsAg and HBcrAg assays for clinical flares and HBsAg loss after NA cessation.
Method: We conducted a retrospective cohort study involving adults with chronic hepatitis B (CHB) who did not have cirrhosis or hepatocellular carcinoma and who discontinued entecavir or tenofovir after at least 3 years of therapy. Eligible participants had negative hepatitis B e-antigen (HBeAg) and undetectable HBV DNA for at least 12 months prior to treatment cessation. Clinical flare was defined as serum ALT >5 times the upper limit of normal (ULN) following the recurrence of viremia. Serum HBsAg and HBcrAg levels were

quantified using iTACT assays at the end of treatment and every 6 months thereafter for up to 3 years or until antiviral therapy was resumed, whichever occurred first. Time-dependent models were used to evaluate the associations between HBsAg and HBcrAg dynamics and the occurrence of subsequent hepatitis flares or HBsAg loss.

Results: The study enrolled 206 patients (median age, 50.0 years; 78.6% male) who discontinued NA after a median of 37.6 months of treatment (47.6% entecavir, 52.4% tenofovir). During post-NA discontinuation follow-up (median 36.1 months for hepatitis flares and 70.3 months for HBsAg loss), 67 patients experienced hepatitis flares, and 30 achieved HBsAg loss, yielding 8-year cumulative incidence of 38.9% (95% CI, 31.3–47.6%) for hepatitis flares and 16.0% (95% CI, 10.3–22.7%) for HBsAg loss. HBcrAg significantly outperformed HBsAg in predicting hepatitis flares with greater areas under the time-dependent receiver operating characteristic curves (0.71–0.73 vs. 0.58–0.64). Multivariable time-varying analyses confirmed that higher HBcrAg level (vs. HBsAg) was a stronger risk factor for hepatitis flares (adjusted HR, 1.61 per log U/mL; 95% CI, 1.37–1.89), while higher HBsAg level (vs. HBcrAg) was a stronger predictor for lack of HBsAg loss (adjusted SHR, 0.33 per log IU/mL; 95% CI, 0.23–0.47).

Conclusion: Using highly sensitive HBsAg and HBcrAg assays, we found that dynamic HBcrAg levels significantly outperformed HBsAg in predicting post-NA withdrawal hepatitis flares, while HBsAg dynamics were more effective predictors of HBsAg loss. These findings highlight the complementary roles of these two biomarkers in guiding the management of CHB patients discontinuing NA therapy.

WED-294

Virological response and safety of combination treatment with bulevirtide and pegylated interferon in chronic hepatitis D patients with advanced fibrosis/cirrhosis: 48 weeks interim results from SEE-D trial

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Background and aims: The Phase 2b MYR204 trial demonstrated that combination therapy with bulevirtide (BLV) and pegylated interferon alfa-2a (48 weeks) achieved higher virological response rates than mono-BLV therapy in patients with chronic hepatitis D (CHD). Clinical trial data on the efficacy and safety of extended combination treatment are lacking. We aimed therefore to evaluate the efficacy and safety of BLV 2 mg and peg-IFN (administered for 96 weeks:180 µg for first 48 weeks, then 135 µg for 48 weeks) therapy in SEE-D study. We present here interim results up to week 48 (w48).

Method: In total, 31 patients with advanced fibrosis/compensated cirrhosis and CHD were treated with BLV, peg-IFN and nucleos(t)ide analogues and assessed in SEE-D, an observational clinical trial conducted at Karolinska University Hospital, Sweden (EU nr 2023-504414-29-00). HDV RNA levels were measured using RoboGene HDV RNA Quantification Kit 2.0, with a lower limit of quantification (LLOQ) and a detection limit (LLOD) of 50 IU/ml and 6 IU/ml, respectively. Adverse events of special interest, serious adverse events (SAE) and SUSAR (suspected unexpected serious adverse reaction) were collected.

Results: At baseline (BL), mean age (±SD) was 44.6 (8.6) years, 58.1% were men, 87.1% Asian, 64.5% IFN-experienced, and median (IQR) liver stiffness measurement was 12.1 (4.2) kPa. Median (IQR) log 10 HDV RNA and HBsAg levels were 5.1 (1.4) and 3.9 (0.5) IU/ml, respectively at BL. At w24 and w48, all patients achieved >2 log HDV RNA reduction, among those who have reached these time points (n = 29 and n = 19, respectively). HDV RNA levels <LLOQ were seen in 75.9% at w24 and 89.5% at w48, while <LLOD was achieved in 34.5% and 78.9%, respectively. While no HBsAg loss occurred, HBsAg reduction of either >2 log decrease or to <200 IU/ml was achieved in 16% of patients (minimum level: 5.3 IU/ml). No significant predictors for HbsAg <200 IU/ml were identified. The proportion of patients with elevated ALT levels decreased from 80.6% at BL to 54.8% at w24 and 63.2% at w48. Bile acids increased from median (IQR) 9.0 (13.0) at BL, to 42.0 (51.8) at w24 and 36.0 (34.0) µmol/L at w48. Cytopenia (≥grade 3) occurred in 61.3%, and 9.7% developed grade 2 thyroid disorders. Peg-IFN dose reduction occurred in 48%. None discontinued BLV, while one discontinued peg-IFN due to exacerbation of inactive psoriasis, with resolved symptoms during follow-up. Three SAEs (9.7%), appendicitis, pyelonephritis, and suspected hepatocellular carcinoma, were reported, and none were classified as SUSAR. Updated data will be reported at the conference.

Conclusion: In this trial study, combination therapy with BLV and peg-IFN resulted in high rates of undetectable HDV RNA by w48, exceeding those reported in previous trials. Significant HBsAg reductions were observed in a subset of patients, with potential for HBsAg loss with extended peg-IFN therapy. These findings highlight the potential of this combination therapy, with need of further studies to define optimal finite therapy strategies.

WED-295

Comparative efficacy and safety of tenofovir amibufenamide vs tenofovir alafenamide and entecavir in the hepatitis B virus related acute-on-chronic liver failure patients: a single-centre retrospective study

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Background and aims: There is a scarcity of clinical studies on the use of tenofovir amibufenamide (TMF) for Hepatitis B Virus-Associated Acute-on-Chronic Liver Failure (HBV-ACLF) patients. The aim of this research is to investigate the efficacy and safety between entecavir (ETV), tenofovir alafenamide fumarate (TAF), and TMF in the treatment of HBV-ACLF.

Method: We selected patients diagnosed with HBV-ACLF, in accordance with the APASL 2019 guidelines. Admitted between May 2022 and January 2024 to the department of infectious diseases ward were the aforementioned patients, from whom we collected multiple clinical indicators and outcomes at the time of their admission and after two weeks and 60 days of their treatment. We then analyzed the differences in clinical indicators between and within ETV, TAF, and TMF. Concurrently, we conducted a survival analysis to assess the efficacy and safety profiles of these three medications. The research was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Results: A total of 235 patients were included in the study: 41 in the TMF group, 60 in the TAF group, and 117 in the ETV group. The 60-day overall survival rates for three groups were 71.11%, 73.77%, and 73.65%, respectively ($p > 0.05$). After two weeks of treatment, all the three groups of patients showed significant improvements in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ($p < 0.05$), and there were no significant differences between the three groups in above indicators. None of the groups experienced worsening deteriation of renal function after treatment, and the estimated glomerular filtration rate (eGFR) levels at two weeks post-treatment were significantly improved in the TAF and TMF groups

compared to the ETV group ($p < 0.05$). There were no significant changes in total cholesterol levels in any of the groups compared to baseline.

Conclusion: TMF, TAF, and ETV exhibited no differences in the 60 -day overall survival rate among patients with HBV-ACLF. However, TMF and TAF showed a greater improvement in renal function compared to ETV.

WED-296

Impact of long-term tenofovir-based treatment on hepatocellular carcinoma risk in patients with chronic hepatitis B using the reREACH-B score

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Background and aims: Chronic hepatitis B (CHB) is a leading cause of hepatocellular carcinoma (HCC), and oral antivirals can reduce HCC risk. Nomograms, such as the Risk Estimation for HCC in CHB (REACH-B) score, have been useful in assessing patient risk for HCC. Reports indicate that the relationship between hepatitis B virus (HBV) DNA level and HCC risk follows a nonlinear, parabolic pattern; thus, the REACH-B score was updated to incorporate age, gender, platelet count, and HBV DNA, alanine aminotransferase (ALT), and hepatitis B e antigen (HBeAg) status. We used the updated reREACH-B score to assess the impact of therapy on HCC risk among patients enrolled in tenofovir-based clinical trials.

Method: In 2 Phase 3 studies evaluating tenofovir alafenamide (TAF), HBeAg-positive (n = 1039) and -negative (n = 593) patients were randomised (2:1) to receive either once-daily TAF 25 mg or tenofovir disoproxil fumarate (TDF) 300 mg for up to 3 years (Y), followed by open-label TAF through Y8. ReREACH-B scores at baseline (BL) and over 8Y (384 weeks [W]) were generated. Patients with evidence of HCC at screening were excluded, and HCC was assessed every 6 months using hepatic ultrasonography, which was introduced after W96 and used throughout. Patients were stratified into low (<0.01) and high (≥0.01) HCC risk categories based on reREACH-B scores, reflecting an annual incidence rate of 0.2%, the cost-effectiveness threshold for HCC surveillance.

Results: Through 8Y of follow-up, HCC occurred in 26 of 1632 (1.6%) patients (TAF, 14/1093 [1.3%]; TDF, 12/539 [2.2%]). Of 26 cases of HCC, 9 patients (35%) had cirrhosis at BL. Patients who developed HCC were older (median age 52Y vs 39Y; $p < 0.0001$), more likely to be male (89% vs 65%; $p = 0.0119$), and more likely to have cirrhosis at BL (FibroTest score ≥0.75; 35% vs 9%; $p < 0.0001$). At BL, among 1632 patients, 547 were categorised as low risk and 1084 as high risk. Compared with patients at low risk, those at high risk were more likely to be older (median age 43Y vs 32Y) and male (74% vs 47%), and less likely to be HBeAg positive (57% vs 77%); had lower platelet counts (median 174 vs 233×10^3/μL); had lower HBV DNA (median 6.7 vs 8.2 $\log_{10}$ IU/mL) and higher BL ALT levels (median 89 vs 70 U/L). Among individuals characterised as high or low risk at BL, 24 of 1084 (2.2%) and 2 of 547 (0.4%) developed HCC over 8Y. At Y8, mean (range) change from BL in reREACH-B score was −0.1 (−1.0 to 0.1). Notably, 58% and 52% of patients deemed high risk at BL with available data at Y5 and Y8 transitioned to low risk; only 5% and 8% of patients shifted from low to high risk at Y5 and Y8.

Conclusion: Using data from studies of patients receiving tenofovir-based therapy, we highlight the importance of treatment to reduce HCC risk. Application of reREACH-B risk scores supports that few patients at low risk for HCC at treatment initiation developed HCC, while many high-risk patients improved to a lower risk after long-term treatment.

WED-300

Impact of long-term oral antiviral treatment on hepatocellular carcinoma risk in patients with chronic hepatitis B who are hepatitis B e antigen positive using the PAGED-B score

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Background and aims: Chronic hepatitis B (CHB) is a leading cause of hepatocellular carcinoma (HCC) worldwide, and while oral antivirals lower the risk of HCC, they do not eliminate it. Recent studies indicate that moderate hepatitis B virus (HBV) DNA levels may be strongly linked to HCC risk in hepatitis B e antigen (HBeAg)-positive people with CHB. The recently validated PAGED-B (platelets, age, gender, diabetes, and HBV DNA) score, which incorporates HBV DNA, can be used to stratify HCC risk in this population. We used the PAGED-B score to assess HCC risk in HBeAg-positive patients with CHB enrolled in a trial of tenofovir-based therapy.

Method: In a Phase 3 multicentre study (GS-US-320-0110), patients who were HBeAg positive with HBV DNA ≥20,000 IU/mL and alanine aminotransferase >60 U/L (males) or >38 U/L (females) were randomised to receive tenofovir alafenamide (TAF) 25 mg or tenofovir disoproxil fumarate (TDF) 300 mg once daily for up to 3 years. Thereafter, patients received open-label TAF through year 8 (week 384). PAGED-B scores at baseline (BL) and over 384 weeks were generated. Shifts in risk categories (low risk [0 to <7] and high risk [≥7]) were evaluated.

Results: Among 1052 (TAF, n = 703; TDF, n = 349) HBeAg-positive patients (66% male, 85% Asian [n = 893]/Pacific Islander [n = 4], 98% HBeAg positive [2% transitioned to HBeAg-negative status between screening and BL visits]), mean (range) BL PAGED-B score was 4.3 (0–

11); 885 (84%) and 167 (16%) were low and high risk, respectively. At weeks 240 and 384, mean (range) changes from BL in PAGED-B scores were −0.8 (−4 to 4) and −0.7 (−4 to 2), respectively. Among those in the low-risk category at BL with available data at week 384, the majority remained unchanged; only 6 (1%) shifted to high risk, primarily driven by age and platelet changes. In the high-risk group, most patients improved to low risk (69%), and only 31% remained at high risk. Overall, 12 HCC cases developed over 8 years (0.3%, BL low-risk group; 5.4%, BL high-risk group).
Conclusion: The application of the PAGED-B risk score demonstrates that among HBeAg-positive patients, most (69%) high-risk patients experienced a decrease in risk with long-term treatment, whereas shifts from low risk of HCC at the start of treatment to a higher risk category were rare (1%).

WED-301
Predictive value of baseline HBsAg, HBV RNA, and HBcrAg levels for HBsAg clearance in NAs-suppressed HBeAg-Negative chronic hepatitis B patients treated with pegylated interferon-alpha
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Background and aims: Predicting HBsAg clearance is essential for optimizing the management of chronic hepatitis B (CHB) patients receiving pegylated interferon-alpha therapy. Serum HBV RNA and HBV core-related antigen (HBcrAg) have emerged as promising markers of hepatitis B virus (HBV) infection. However, in HBeAg-negative patients, it remains uncertain whether HBV RNA and HBcrAg outperform other HBV markers in predicting HBsAg clearance. This study aimed to assess the predictive value of HBsAg, HBV RNA, and HBcrAg for HBsAg clearance in NAs-suppressed HBeAg-negative CHB patients undergoing pegylated interferon-alpha therapy.
Method: This retrospective study included 153 HBeAg-negative CHB patients who achieved HBV DNA suppression (HBV DNA <100 IU/mL) and HBsAg level ≤1500 IU/mL following more than 1 year of nucleos (t)ide analog (NAs) treatment. Patients were categorized into two groups based on their treatment outcomes at 48 weeks of pegylated interferon-alpha therapy: the Response group, comprising those who achieved HBsAg clearance (HBsAg <0.05 IU/mL), and the Non-Response group, consisting of those who did not. A comprehensive analysis was conducted on the baseline levels of various indicators, including blood cell counts,biochemical markers (ALT and AST), and serum virological markers (HBsAg, HBV RNA, and HBcrAg). Logistic regression analysis was conducted to identify independent predictors of HBsAg clearance at. The area under the curve (AUROC) was used to evaluate the predictive accuracy of these independent predictors for HBsAg clearance. p values of <0.05 were considered significant.
Results: Among 153 patients, 33.3% (51/153) achieved HBsAg clearance after 48 weeks of pegylated interferon-alpha therapy. The baseline HBsAg level [1.8 (0.7–2.2) vs. 2.5 (2.1–2.8) $\log_{10}$ IU/mL, $p < 0.001$], HBV RNA [2.0 (2.0–2.3) vs. 2.3 (2.0–2.7) $\log_{10}$ copies/mL, $p < 0.001$] and HBcrAg [3.1 (3.0–3.4) vs. 3.6 (3.0–4.3) $\log_{10}$ U/mL, $p < 0.001$] were significantly lower in the Response group compared to the Non-Response group. Logistic regression analysis indentified baseline HBsAg (OR = 4.29 [2.71–8.61], $p < 0.001$), HBV RNA (OR = 5.05 [1.80–14.19], $p = 0.002$) and HBcrAg (OR = 3.91 [1.96–7.81], $p < 0.001$) as independent predictors of HBsAg clearance at week 48. Among the biomarkers, baseline HBsAg showed the highest AUROC and was significantly superior to HBV RNA and HBcrAg ($p < 0.05$ for all comparisons). Combination analysis revealed that integrating HBsAg, HBV RNA and HBcrAg yielded superior predictive accuracy for HBsAg clearance compared to HBsAg alone [AUROC: 0.850 (0.787–0.912), $p < 0.05$].
Conclusion: A combined predictive strategy using baseline HBsAg, HBV RNA, and HBcrAg enhances the prediction of HBsAg clearance in HBeAg-negative CHB patients undergoing pegylated interferon-alpha therapy. This work was supported by National Natural Science Foundation of China (No. 82172254), and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYGD23030).

WED-302
Therapeutic options for persistent low-level viremia in patients with chronic hepatitis B: adding on peginterferon α-2b might be a better choice
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Background and aims: Low-level viremia (LLV) is usually defined as a detectable but lower than 2000 IU/mL hepatitis B virus (HBV) DNA level after 12 months or longer duration of first-line antiviral therapy in chronic hepatitis B (CHB) patients. We aimed to investigate the optimal therapeutic strategies related to LLV.
Method: From October 2021 to October 2024, this multicenter, prospective, observational study enrolled CHB patients who had been treated with first-line nucleoside analogues (NAs) for ≥12 months at 44 sites. CHB patients were grouped into 2 categories, LLV group and CVR group (complete virological response, hepatitis B virus DNA <10 IU/mL). For CVR and LLV patients, two therapeutic options are available, continuing NA(s) therapy or adding on peginterferon α-2b therapy for 96 weeks.
Results: A total of 1614 patients were included in the study (LLV group, n = 1264; CVR group, n = 350), and there was no difference in

gender or age between LLV group and CVR group. Compared with NAs therapy, adding on peginterferon α-2b showed a higher rate of HBV DNA undetectable in patients with LLV after 24 weeks [47.3% (107/226) *Vs.* 37.3% (157/421), *P* = 0.023], 48 weeks [63.5% (113/178) *Vs.* 40.8% (130/319), *P* = 0.000], 72 weeks [69.0% (80/116) *Vs.* 51.9% (95/183), *P* = 0.004] and 96 weeks [76.3% (45/59)*Vs.*59.4% (60/101), *P* = 0.03] weeks of treatment. According to the HBV DNA level at baseline, LLV group was divided into three subgroups (10–100 IU/mL, 100–500 IU/mL and 500–2000 IU/mL). In patients with baseline HBV DNA levels of 100–500 IU/mL, adding on peginterferon α-2b had higher rates of HBV DNA undetectable at 24, 48, 72 and 96 weeks. 81.33% (1028/1264) of LLV patients were HBeAg-positive and they got lower rates of HBV DNA undetectable at 12 [36.1% (60/166) *Vs.* 56.4% (22/39), *P* = 0.020], 24 [34.7% (118/340) *Vs.* 58.3% (35/60), *P* = 0.001] and 48 [37.3% (98/263) *Vs.* 62% (31/50), *P* = 0.001] weeks compared to HBeAg-negative patients. Interestingly, HBeAg-positive LLV patients still achieved higher rates of HBV DNA undetectable by adding on peginterferon α-2b compared with NAs treatment after 24 [61.4% (89/145) *Vs.* 37.3% (98/263), *P* = 0.000] and 72 [65.3% (66/101) *Vs.* 50.7% (76/150), *P* = 0.021] weeks of treatment. Furthermore, the HBsAg clearance rates were much lower in LLV patients comparing with CVR patients at 24 [1.5% (4/266) *Vs.* 9% (13/144), *P* = 0.000], 48 [3.1% (7/225) *Vs.* 11.9% (14/118), *P* = 0.001], 72 [0.7% (1/140) *Vs.* 18% (9/50), *P* = 0.000], and 96 [2.7% (2/73) *Vs.* 25% (6/24), *P* = 0.003] weeks.

Conclusion: Adding on peginterferon α-2b might be a better option for HBV DNA clearance in LLV patients. Compared with CVR patients, LLV status seriously affected the clearance of HBsAg.

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Assessment of response and impact of safety treatment with bulevirtide in patients with chronic delta virus infection: an observational trial for evaluating long-term efficacy. The ARISTOTELE study

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Background and aims: Hepatitis D virus (HDV) infection remains a significant global health challenge due to its severity and high risk of progression to cirrhosis and hepatocellular carcinoma (HCC). This study evaluated the efficacy and safety of bulevirtide in reducing HDV RNA levels and improving liver function in a real-life cohort of Italian patients with HDV infection.

Method: This multicenter prospective trial enrolled 85 consecutive patients with chronic HDV infection, from June 2023 to June 2024, who received 2 mg/day of bulevirtide as monotherapy or in combination with a nucleoside/nucleotide analogue for hepatitis B virus (HBV) infection. Patients with any stage of liver fibrosis or compensated cirrhosis were included.

Results: The virological response was achieved in 55.7% of patients (n = 47), with 32 demonstrating undetectable HDV RNA levels. Among responders, ALT levels decreased significantly from 66.0 U/mL (IQR 46.5–120.0) to 31.5 U/mL (IQR 25.0–37.0, $p < 0.001$), and AST levels from 71.0 U/mL (IQR 48.5–94.5) to 31.0 U/mL (IQR 27.0–38.5, $p = 0.021$). Median HDV RNA dropped from 16,410 IU/mL (IQR 2,530–339,400) to 0 IU/mL (IQR 0–84,000, $p < 0.001$). No significant predictors of response emerged. Mild adverse events, including pruritus (7.1%) and injection-site reactions (2.4%), were reported, with no treatment discontinuation.

Conclusion: Bulevirtide effectively reduces HDV RNA levels and improves liver function with a favorable safety profile, offering a promising therapeutic option for chronic hepatitis D.

WED-304

HERACLIS_BLV_D: Increasing response rates during 2-year bulevirtide real-life therapy in chronic hepatitis D

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Background and aims: Bulevirtide (BLV) was approved by the European Medicine Agency for the treatment of compensated chronic hepatitis D (CHD) and started to be used in European countries including Greece a few years ago, but there are limited real-life data to date. The aim of this study is to assess the efficacy and safety of up to 2-year BLV therapy in CHD patients treated at Greek liver centers.

Method: All adult (>16 years old) patients with CHD followed at any of the participating centers who started BLV before the approvals (05–11/2023) of the HERACLIS_BLV_D study (NCT05928000) were included. All patients were treated with daily BLV subcutaneous injections of 2 mg, with or without concomitant use of a nucleos(t)ide analogue (NA). Patients' monitoring was based on standard clinical practice according to the current recommendations for treatment of CHD. A predefined case report form was used for data collection. Serum HDV RNA during the study was determined by a polymerase chain reaction assay at a central lab (sensitivity: ≤100 IU/

ml). Virological response (VR) was defined as HDV RNA undetectable (complete VR) or decline >2 log_{10} compared to baseline levels. Biochemical response (BR) was defined as normal ALT (≤40 IU/L).
Results: In total, 76 patients were included; mean age: 50 ± 12 years, males: 37 (49%), born in Greece: 21 (28%), mean BMI: 25.4 ± 3.9 kg/m^2, mean liver stiffness (LS): 15.9 ± 9.5 kPa, cirrhosis: 45 (59%) (decompensated cirrhosis: 6/45), (peg-)interferon (IFN) in the past: 32 (42%) cases. No patient received combination of BLV with pegIFN; BLV alone was given in 9 (12%) and BLV plus a NA in 67 (88%) patients (ETV: 29, TDF: 35, TAF: 3). In 72, 70, 54 and 46 patients assessed at 6, 12, 18 and 24 months, rates of VR were 67%, 73%, 87% and 93%, of complete VR 38%, 57%, 70.4% and 80.4%, of BR 66%, 71%, 74% and 74% and of combined response (VR+BR) 49%, 51%, 62% and 74%, respectively. VR response at 24 months was not associated with any baseline characteristic, while 24-month complete VR was independently associated with lower baseline HDV RNA (OR per log IU/ml: 0.44, 95%CI: 0.22–0.88, p = 0.019) and platelets (OR per 10^3/mm^3: 0.986, 95%CI: 0.97–1.00, p = 0.045). Both 24-month BR and combined responses were independently associated with lower baseline GGT (OR per 10 IU/L: 0.85, 95%CI: 0.76–0.95, p = 0.004) and hemoglobin levels (OR per g/dl: 0.16, 95%CI: 0.05–0.59, p = 0.006). There was no drug-related serious adverse event (AE) and no patient discontinued BLV due to AE.
Conclusion: BLV therapy, with or without NA, is safe and effective for the treatment of CHD patients followed at Greek tertiary liver centers offering increasing rates of VR, complete VR and BR or combined response exceeding 90%, 80% and 70%, respectively, at 2 years of therapy.

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Quantification of plasma HDV RNA by three commercially available assays in untreated and Bulevirtide-treated real-life patients with CHD: Robogene 2.0 vs. Altostar vs. Eurobioplex EBX071

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Background and aims: Accurate quantification of HDV-RNA is essential for diagnosing and managing chronic hepatitis Delta (CHD), but there is considerable variability between different assays. In this study, we compared three methods for HDV-RNA quantification in both untreated and Bulevirtide (BLV)-treated CHD patients.
Method: Frozen plasma samples from untreated and BLV–treated CHD patients were tested in a single-center retrospective study by 3 different assays: Robogene HDV-RNA Quantification Kit 2.0 [Roboscreen GmbH; Lower Limit of Detection (LOD) <6 IU/mL, Lower Limit of Quantification (LOQ) 60 IU/mL on 7500 Fast Real-Time PCR System (Applied Byosystem)], AltoStar HDV RT-PCR RUO Kit 1.5 (Altona Diagnostics, estimated LOD <10 IU/mL estimated LOQ 20 UI/mL on AltoStar®AM16) and EurobioPlex HDV PCR quantitative EBX071 [Eurobio Scientific, LOD <20 UI/mL, LOQ 50 UI/mL on CFX96™ real-time PCR detection system (Bio-Rad)].
Results: 112 plasma samples collected from 79 CHD (10 untreated and 69 BLV-treated) patients were studied by 3 different assays (total 336 tests): median age 55 (32–76), 54% men, 76% cirrhotics, 100% GT 1 (available in 70 patients), 90% HBeAg negative. Median ALT were 34 (8–273) U/L, median HBsAg 3.5 (0.3–4.9) Log IU/mL. Overall, HDV RNA levels were 3.05 (−0.04–6.69) Log IU/mL with Robogene 2.0, 3.22 (−0.31–7.03) IU/mL with AltoStar, and 3.78 (−0.83–7.78) IU/mL with EurobioPlex EBX071 (Robogene *vs.* AltoStar p < 0.0001; Robogene *vs.* EurobioPlex p = 0.005; EurobioPlex *vs.* AltoStar p = 0.50; overall p < 0.0001). Compared to Robogene 2.0, AltoStar reported different (±>0.5 Log IU/mL difference) HDV RNA levels in 18% of positive samples. By contrast, EurobioPlex EBX071 reported different (±>0.5 Log IU/mL difference) HDV RNA levels in 45% samples. Overall, HDV RNA during therapy was TND in 13%, 9% and 21% of the samples tested with the 3 assays, respectively (p < 0.001). Rates of HDV RNA undetectability (TND or <LLOQ or <LOD) during BLV therapy differed at week 24 (33% *vs.* 15% *vs.* 33%; overall p = 0.02; Robogene *vs.* AltoStar p = 0.01; Robogene *vs.* EurobioPlex p = ns; AltoStar *vs.* EurobioPlex p = 0.01) and at week 48 (19% *vs.* 8% *vs.* 31%; overall p = 0.01; Robogene *vs.* AltoStar p = ns; Robogene *vs.* EurobioPlex p = 0.08; AltoStar *vs.* EurobioPlex p = 0.01) but not at week 96 (36% *vs.* 25% *vs.* 36%,; overall p = 0.10; Robogene *vs.* AltoStar p = 0.08; Robogene *vs.* EurobioPlex p = ns; AltoStar *vs.* EurobioPlex p = 0.08).
Conclusion: Quantification of HDV-RNA levels in untreated and BLV-treated patients significantly differed according to the commercial assay used. The proportion of patients achieving HDV RNA TND at different time points during BLV monotherapy differed as well.

WED-306
The kinetic of HBsAg isoforms predicts response to BLV and pegylated interferon alfa2a in patients with chronic hepatitis delta

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Background and aims: Chronic hepatitis D (CHD) can be treated with the entry inhibitor bulevirtide (BLV) or the immune modulator PEG-IFNα-2a. However, prediction of treatment response is not established. The composition of HBsAg (large [L], middle [M], and small [S] HBs) has been shown to be associated with HBsAg loss in HBV mono-infection. Our study aims at evaluating the association of HBsAg composition with response to different treatments in CHD.
Method: A real-world cohort of 106 CHD patients, treated with either 180 mg/week PEG-IFNα-2a (n = 56) or 2 mg/day BLV (n = 50), was followed for a median duration of 26 (6–156) months. HDV RNA (Robogene 2.0) and HBsAg isoforms were measured at baseline (BL) and in available samples at 6, 12, 18, 24, and 36 months. LHBs, MHBs

and SHBs were quantified by ELISA and ratios confirmed by western blot. Patients were categorized as non-responders (NR, n = 53), those with HDV RNA decrease >2 log IU/mL (n = 17), undetectable HDV RNA (n = 26), or HBsAg loss (n = 7) based on response after 12 months of treatment.

Results: Baseline HBsAg isoform levels significantly correlated with HDV RNA levels (LHBs: r = 0.340, p = 0.004; MHBs: r = 0.402, p = 0.001; SHBs: r = –0.380, p = 0.005). Interestingly, baseline ratios of LHBs and MHBs were lower in patients who subsequently achieved >2 log IU/mL HDV RNA decrease (7.9 and 6.0%), undetectable HDV RNA (6.5 and 5.0%), or HBsAg loss (8.5 and 3.4%) compared to NR (7.6 and 6.5%), regardless of treatment. Moreover, patients with a percentage of LHBs <4.8% at BL had a significantly higher likelihood of subsequently achieving response (HDV RNA decrease >2 log IU/mL and undetectable HDV RNA) to either PEG-IFNα-2a or BLV compared to patients with >4.8% LHBs at BL (83% vs. 16%, p < 0.001). In available samples taken during treatment from 86/106 patients we found that after 12 months of treatment HBsAg levels, MHBs%, and LHBs% did not change in NR receiving either PEG-IFNα-2a or BLV (p = ns). However, patients achieving undetectable HDV RNA exhibited a decrease in MHBs ratios from BL to month 12. This association was found in the PEG-IFNα-2a group (n = 5) who showed a decrease from 9.5% (2.9–19.3%) to 2.1% (0–3.1%) as well as in the BLV group (n = 14) with a decrease from 6.4% (2.3–13.3%) to 3.9% (0.9–9.9%) (p = 0.016). In addition, after 18 months of BLV treatment, patients with undetectable HDV RNA had significantly lower LHBs ratios compared to NR (2.0 vs. 2.8 log ng/mL, p = 0.05) and lower MHBs (2.1 vs. 2.9 log ng/mL; p = 0.05) levels, as well as lower ratios of LHBs (6.0 vs. 9.2%) and MHBs (6.0 vs. 7.4%; p = ns).

Conclusion: HBsAg isoforms have a high potential to become an efficacy marker during PEG-IFNα-2a or BLV treatments in HBV/HDV-coinfection.

WED-307

Good flare or bad flare? ALT variability predicts outcome after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B

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Background and aims: Flares are common after discontinuing nucleos(t)ide analogue (NA) treatment in patients with HBeAg-negative chronic hepatitis B (CHB). Whether these flares represent a beneficial immune response leading to HBsAg decline ("good flare") or are detrimental leading to hepatic necroinflammation and fibrosis progression ("bad flare"), is difficult to discern. We hypothesized that it is the variability in ALT levels after NA cessation that determines outcomes following a flare, rather than the magnitude of the ALT flare. Therefore, we aimed to investigate whether differences in ALT variability following a flare can predict outcomes in patients enrolled in an NA stop trial.

Method: This study was nested in the prospective Nuc-Stop Study, in which 127 HBeAg-negative CHB patients discontinued NA treatment and were followed for 36 months. Of these, all 38 patients who experienced a flare and did not restart treatment were included in the present analysis. Flares were defined as an ALT >2× the upper limit of normal (ULN) or >2× the baseline value. Good flares were defined as flares occurring in patients who achieved HBsAg loss, HBsAg decline >1 log10 IU/mL within 36 months, or sustained off-therapy virological control (HBV DNA <2000 IU/mL) at all study visits during year three of follow-up. Bad flares were defined as flares in patients with no HBsAg decline (<0.5 log10 IU/mL) and absence of off-therapy virological control, as defined above. Study visits were conducted at baseline, weeks four, eight, and 12, and every third month thereafter until the end of the study. The first flare was defined as the first occurrence of ALT > 2× ULN or >2× the baseline value. ALT values recorded at or before the first flare, as well as ALT values after HBsAg loss, were excluded from the analyses. Levene's test was used to assess variability, and Mann-Whitney U test to compare medians.

Results: Of the 38 patients who experienced a flare and did not restart NA treatment, 19 experienced a bad flare, 13 experienced a good flare, and six did not fit into either category and were excluded from further analysis. Following the initial flare, patients with a bad flare displayed more fluctuations in ALT levels compared to patients with a good flare. The mean standard deviation (SD) of ALT was 22.7 U/L in patients with bad flares compared to 9.7 U/L in patients with good flares (p = 0.002). Among patients with good flares, three achieved HBsAg loss, three had an HBsAg decline >1 log10, and seven had sustained off-therapy virological control. The median peak ALT was similar in patients with good and bad flares (89 (interquartile range (IQR) 52–179) vs. 103 (IQR 74–154) U/L; p = 0.66).

Conclusion: After discontinuing NA therapy in HBeAg-negative chronic hepatitis B patients, ALT variability following the initial flare might serve as a prognostic factor and distinguish good flares from bad flares.

WED-308

Improvement in 3 noninvasive tests through 144 weeks of bulevirtide monotherapy in patients with chronic hepatitis delta with and without virologic response

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Background and aims: Bulevirtide (BLV) is an entry inhibitor approved in Europe and Australia as a therapy for patients with chronic hepatitis delta (CHD); noninvasive tests (NITs) have

demonstrated improvements in hepatic function and burden of liver disease with BLV treatment. Here we describe changes in NITs through up to 3 years of treatment.

Method: A longitudinal analysis was conducted using the Phase 3 MYR301 (NCT03852719) study data to determine the effect of BLV on results of alanine aminotransferase (ALT) level measurements and 3 NITs: fibrosis index based on 4 factors (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), and liver stiffness measurement (LSM). In total, 150 patients with CHD were randomised to either no treatment for 48 weeks (W) followed by BLV 10 mg/d for 96W, or to BLV 2 or 10 mg/d for 144W. Change from baseline (BL) in NITs was assessed through 96W and 144W of treatment. This analysis was repeated for the pooled immediate treatment groups stratified by hepatitis delta virus (HDV) RNA response at W144: virologic responders (VR; undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL), partial responders (PR; ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL decline in HDV RNA from BL), and nonresponders (NR; <1 $\log_{10}$ IU/mL decline in HDV RNA from BL). Patients with HDV RNA values missing at W144 were excluded. Results are reported as median (quartile [Q]1, Q3) unless otherwise stated.

Results: Overall, 149 patients with CHD were treated with BLV monotherapy (BLV 2 mg [n = 49]; BLV 10 mg [n = 100]); 99 were randomised to immediate BLV treatment for 144W, and 50 in the BLV 10 mg group received treatment for 96W. NITs showed improvements in all cohorts after 48W of therapy, which were maintained through 144W of therapy. Changes from BL at W144 were: BLV 2 mg group, FIB-4, −0.52 (−1.19, −0.03); LSM, −4.00 (−6.00,−1.00) kPa; immediate BLV 10 mg treatment group, FIB-4, −0.43 (−0.94, −0.14); LSM, −3.80 (−6.70, −1.20) kPa; and BLV delayed treatment group at W144 after 96W of treatment, FIB-4, −0.27 (−0.62, 0.02); LSM, −3.15 (−7.00, −0.40) kPa. Improvements at W144 in NITs were also seen across all viral response groups in the pooled immediate treatment cohort, including VR (n = 74), PR (n = 7), and NR (n = 8) at W144. Among VR, changes from BL were FIB-4, −0.43 (−1.05, −0.11); and LSM, −3.85 (−6.50, −1.20) kPa. Among PR, changes from BL were FIB-4, −0.39 (−0.48, −0.09); and LSM, −1.30 (−3.80, 0.20) kPa. Among NR, changes from BL were FIB-4, −1.02 (−1.60, −0.78); and LSM, −4.00 (−15.70, −1.10) kPa. Changes from BL in ALT levels and APRI scores were consistent with the trends observed in FIB-4 across all treatment cohorts.

Conclusion: Treatment with BLV 2 or 10 mg monotherapy for up to 3 years resulted in longitudinal improvements in NITs in patients with CHD and were numerically greater with longer treatment duration. These improvements were seen even among the few patients without viral response.

WED-309-YI

Response-guided interferon add-on to bulevirtide treatment: updated real-world insights from the austrian hepatitis D cohort study

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Background and aims: Chronic Hepatitis D (CHD) causes rapid progression towards advanced chronic liver disease (ACLD) and hepatocellular carcinoma (HCC). Bulevirtide (BLV) is the only approved treatment for CHD, yet the management of suboptimal response and the option of finite treatment remain unclear.

Method: Patients were characterized at BLV initiation (baseline, BL) and virologic (HDV-RNA ≥2log-drop or PCR negativity) and biochemical (ALT normalization) response rates were recorded in six-months (M6-M24) intervals. Biomarkers, liver stiffness measurements (LSM), and clinical outcomes were assessed. Pegylated interferon alpha-2a (IFN) was added in some patients with inadequate response.

Results: Fifty-seven CHD patients (median age: 46.0 years, 62.4% male, median LSM: 13.2 kPa, ACLD: 73.7%) receiving BLV treatment (median treatment duration: 24 [IQR 17–36] months) were included. Virologic (M6: 33.3%, M12: 60.4%, M24: 66.7%), biochemical (M6: 57.4%, M12: 71.7%, M24: 69.2%), and combined response (M6: 22.2%, M12: 41.5%, M24:46.2%) rates increased over time. At M6, significant declines in median HDV RNA (1.90E+05 [IQR 1.10E+04–5.20E+05] co/mL vs. 1.56E+03 [IQR 3.33E+02–7,48E+03], p < 0.001), ALT (73 [IQR 45–123] U/L vs. 40 [29–60], p < 0.001), and LSM (13.2 [IQR 9.1–18.6] kPa vs. 10.7 [IQR 7.4–15.0], p < 0.01) and markers of systemic inflammation like C-reactive protein (0.29 [IQR 0.12–0.50] mg/dL vs. 0.25 [IQR 0.10–0.29], p < 0.01) and procalcitonin (0.11 [IQR 0.08–0.14] ng/mL vs. 0.05 [IQR 0.03–0.09], p < 0.01) were observed. Eighteen (31.6%) patients received IFN addon after a median 10 [IQR 7–16] months on BLV monotherapy, which resulted in a further median HDV RNA log10 decline of 1.49 (IQR 0.56–2.11) after 6 months (p = 0.004) and a significant a reduction in HBs antigen (median log10 3.85 [IQR 3.34–4.04] IU/mL vs. 3.57 [IQR 3.23–3.98], p = 0.008). Median IFN treatment duration was 12 months. Seventeen (29.8%) patients stopped BLV treatment, seven (41.2% of 17) after addon IFN, resulting in following outcomes: (1) n = 11 patients remained HDV RNA negative (n = 2 after liver transplantation resulting in CHD cure), (2) n = 3 patients relapsed, (3) n = 3 patients received an unapproved treatment as compassionate use. While on BLV treatment, one (1.8%) patient was diagnosed with HCC and two (3.5%) patients died. Mostly asymptomatic bile acids elevations were recorded (median BL 6.6 [IQR 4.33–14.4] µmol/L vs. M6 levels 21.9 [IQR 11.18–49.40], p < 0.001). No serious adverse events related to BLV or IFN occurred.

Conclusion: High BLV response rates were reproduced in our Austrian real-life CHD patient cohort comprising predominately of ACLD patients. Decreases in liver stiffness, hepatic and systemic inflammation, and the low liver-related event rate suggest an improved clinical course of CHD under BLV treatment. Add-on IFN to suboptimal BLV responders may rescue virologic response.

WED-310

A mathematical viral load model characterises the exposure-response relationship between bulevirtide and hepatitis delta virus and identifies the minimum duration of on-treatment viral load monitoring required for accurate prediction of long-term virologic response

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Background and aims: Bulevirtide (BLV) is a first-in-class entry inhibitor of hepatitis delta virus (HDV) and is approved in the European Union (EU) and other non-EU countries at 2 mg once daily

(QD) for treatment of chronic hepatitis delta. Ongoing investigations are also evaluating the efficacy and safety of BLV 10 mg QD and combined treatment with pegylated interferon alpha (PegIFN). We aimed to develop a mathematical model of the relationship between BLV exposure and the HDV viral load in blood samples from patients who received BLV with or without PegIFN during clinical trials. We used the model to determine the minimum duration of on-treatment viral load monitoring needed to accurately predict patient virologic response with longer BLV treatment.

Method: Data from 414 patients from 4 clinical studies (MYR202, MYR203, MYR204 [interim], and MYR301 [interim]) were included. Patients received subcutaneous injections of BLV 2, 5, and 10 mg QD, or 5 mg twice daily; 35% of the patients received PegIFN cotreatment. HDV viral load from blood samples was assessed at baseline, week (W)2, W4, and every 4–12 weeks thereafter up to W96. A mathematical model of hepatitis C infection was adapted to characterise the HDV viral load data. A saturable inhibitory effect of BLV exposure on the infectivity rate and a stimulatory categorical effect for PegIFN on the elimination rate constant of infected cells were implemented. Exploratory covariate testing was performed to identify correlations between patient- or treatment-related characteristics and model parameter variability. The final model was refitted to datasets with viral load data from W96 and earlier iteratively removed to evaluate the accuracy of predicted patient virologic responses at W96 with reduced viral load data.

Results: The developed model characterised the observed HDV viral load well; the estimated effective concentration causing 50% of the maximal response (EC50) of BLV was similar to the sub-nanomolar range of the in vitro EC50. BLV 10 mg QD dosing, but not 2 mg QD, exceeded the EC 95% (EC95) for most of the dosing interval. The estimated elimination rate constant of infected cells for PegIFN cotreatment was 21% greater than for BLV alone. No covariate effects on the drug parameters were identified. By iterative modelling, viral load sampling until W48 was necessary to achieve >90% accuracy in identifying virologic responder status (complete, partial, or no response) at W96; sampling beyond W48 minimally improved accuracy.

Conclusion: We identified a significant exposure-response relationship and a significant influence of PegIFN treatment on the elimination of HDV-infected cells, supporting further investigation of BLV 10 mg QD therapy with and without PegIFN to potentially enhance virologic response. Notably, viral load monitoring for at least 48 weeks of treatment was needed for reliable predictions of patient virologic response.

WED-311

Paediatric pharmacokinetic-pharmacodynamic extrapolation to identify suitable bulevirtide doses for children and adolescents with chronic hepatitis delta

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Background and aims: Bulevirtide (BLV) 2 mg once daily (QD) is approved in the European Union (EU) and other non-EU countries for treatment of chronic hepatitis delta (CHD) in adults; ongoing investigations are evaluating the potential of BLV 10 mg QD. No treatment options are currently approved for children with CHD. Given the unfeasibility of conducting a clinical trial in paediatric patients, we applied paediatric pharmacokinetic (PK)-pharmacodynamic extrapolation and exposure matching to identify BLV doses that would achieve similar exposure levels in children and adolescents as those seen in adults treated with BLV 2 or 10 mg QD.

Method: In the paediatric population PK model of BLV, the dosing regimens investigated were age-based dosing (3–6 years of age [y]: 1 mg QD; 6–12 y: 1.5 mg QD; 12–18 y: 2 mg QD), body weight–based dosing (10–25 kg: 1 mg QD; 25–35 kg: 1.5 mg QD; ≥35 kg: 2 mg QD), and flat subcutaneous (SC) dosing (1 mg QD, 1.5 mg QD, and 2 mg QD). Simulated PK profiles and steady-state exposures were compared with exposures in adults who received SC BLV 2 or 10 mg QD in Phase 2 and 3 studies (MYR202, MYR203, MYR204, and MYR301). A BLV effective concentration causing 50% of the maximal response (EC50) in adults with CHD treated with BLV was previously estimated via a longitudinal hepatitis delta viral load model and compared to the simulated paediatric exposures.

Results: The simulated age- and body weight–based dosing approaches produced similar BLV exposures across all paediatric age ranges. With flat dosing, younger children generally had higher exposures than older children and adolescents. For the 12–18 y range, flat 1 mg dosing yielded interquartile ranges (IQRs) of BLV exposure that extended below the 5th percentile of that in adults who received BLV 2 mg QD. For the 3–6 y and 6–12 y ranges, flat 1.5 mg and 2 mg doses generally yielded IQRs of BLV exposures exceeding the 95th percentile of exposure in adults who received BLV 2 mg QD, but the IQRs of exposures were generally contained within the 5th–95th percentiles for adults who received BLV 10 mg QD. For all paediatric age- or weight-based BLV doses, BLV exposure IQRs were generally within the 5th–95th percentiles for adults who received BLV 2 mg QD. With all dosing strategies, median simulated paediatric exposures in each age group exceeded the adult BLV EC50 over ≥80% of the dosing interval. Only the age-based, weight-based, and 2 mg flat dosing strategies produced simulated BLV exposures that exceeded the adult BLV EC 95% (EC95) for ≥25% of the dosing interval in all age groups.

Conclusion: Simulated age-based and body weight–based BLV dosing in children and adolescents predicted similar exposures compared to those in adults with CHD who received the BLV 2 mg QD dose, which is established as safe and efficacious. BLV exposures comparable to those observed with up to BLV 10 mg QD in adults with CHD may be achievable in children and adolescents with a 2 mg QD flat dose.

WED-312

Pharmacokinetics, pharmacodynamics, and safety of bulevirtide 10 mg once daily for 6 days in participants with moderate hepatic impairment and in matched control participants with normal hepatic function

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Background and aims: Bulevirtide (BLV) is a 47–amino acid lipopeptide, hepatitis delta virus (HDV) entry inhibitor that binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor. BLV is approved in the European Union (EU) and other non-EU countries for the treatment of chronic HDV with compensated liver disease at a subcutaneous dose of 2 mg once daily (QD). Evaluations exploring the potential benefit of an increased dose of 10 mg QD are in progress. By inhibiting NTCP, BLV treatment results in asymptomatic and transient elevations in bile acids (BAs). This study evaluated the influence of moderate hepatic impairment (HI) on the pharmacokinetics (PK), pharmacodynamics (PD), and safety of BLV.

Method: This was an open-label, multicentre, parallel-group, multiple-dose, Phase 1 study in participants without HBV/HDV infection with moderate HI (Mod HI; Child-Turcotte-Pugh Class B, n = 10) and matched controls (MCs) with normal hepatic function (n = 10, matched for age [±10 years], sex, and body mass index [±20%]). Participants received BLV 10 mg subcutaneously QD for 6 days (D), with intensive serial sampling for BLV PK and PD (total BAs). Geometric least-squares mean ratios (GLSMRs) and 90% confidence intervals (CI) of maximum plasma concentration (Cmax; ng/mL) and area under the time-vs-concentration curve (AUC; ng/mL·h) over 24

hours (AUC0–24) were evaluated for PK, and GLSMRs (90% CI) for Cmax and baseline-adjusted AUC (NetAUC; μM·h) values were evaluated for total BAs. Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs).
Results: BLV PK on D1 and D6 were lower in participants with Mod HI than in MCs: GLSMR (90% CI): D1, Cmax: 0.54 (0.26, 1.12), AUC0–24: 0.67 (0.40, 1.12); D6, Cmax: 0.58 (0.41, 0.83), AUC0–24: 0.73 (0.54, 0.99). Median elimination half-life was similar between groups (~3–4 hours). On D1 and D6, mean apparent clearance and apparent volume of distribution were higher in the Mod HI group than in MCs. Similar trends in transient BA elevations were observed between the Mod HI and MC groups on D1 and D6. Plasma BA elevations returned to predose levels within 24 hours of dosing. There were no Grade ≥3 treatment-emergent (TE) AEs, serious AEs, or AEs leading to BLV discontinuation. The frequency of TEAEs was similar between the two groups, and TEAEs were generally mild with no increased severity in participants with Mod HI vs MCs.
Conclusion: PK exposures following BLV 10 mg QD in the Mod HI group were reduced (~30%–40%) compared to those in MCs; however, exposures were still >5-fold higher than those observed with the currently approved 2 mg dose. There were no incremental elevations in total BAs observed with BLV 10 mg in participants with Mod HI versus MCs with normal hepatic function. BLV was generally safe in participants with Mod HI.

WED-313
Pharmacokinetics, pharmacodynamics, and safety of bulevirtide 10 mg once daily for 6 days in participants with severe renal impairment and in matched control participants with normal renal function

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Background and aims: Bulevirtide (BLV) is a 47–amino acid lipopeptide that binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor and blocks entry of hepatitis delta virus (HDV) into hepatocytes. BLV 2 mg once daily (QD) is approved in the European Union (EU) and other non-EU countries for treatment of HDV infection in adults. Evaluations exploring the potential benefit of an increased dose of 10 mg QD are in progress. By inhibiting NTCP, BLV causes asymptomatic and transient elevations in bile acids (BAs), which could possibly increase in renal impairment (RI). We assessed the pharmacokinetics (PK), pharmacodynamics (PD), and safety of multiple doses of BLV 10 mg in participants with severe RI vs matched controls (MCs) with normal renal function.
Method: This was an open-label, multicentre, multiple-dose, Phase 1 study in participants without HBV/HDV infection with severe RI (estimated glomerular filtration rate [eGFR] ≥15 to ≤29 mL/min/1.73 m^2, n = 10) and MCs (matched for age [±10 years], sex, and body mass index [±20%], n = 10) with normal renal function administered BLV 10 mg subcutaneously (SC) QD for 6 days (D). Intensive plasma BLV PK and PD (total BAs) samples were assessed on D1 and D6. Maximum BLV plasma concentration (Cmax; ng/mL) and area under the time-vs-concentration curve (AUC; ng/mL·h) over 24 hours (AUC0–24) were evaluated for BLV PK; Cmax and baseline-adjusted AUC (NetAUC; μM·h) were evaluated for total BAs. PK geometric least-squares mean ratios (GLSMRs) with 90% confidence intervals (CI) were calculated. Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs).
Results: On D1 and D6, BLV PK was similar between participants with severe RI and MCs: GLSMR (90% CI): D1, Cmax: 0.78 (0.43, 1.24), AUC0–24: 1.00 (0.56, 1.79); D6, Cmax: 1.08 (0.78, 1.51), AUC0–24: 1.04 (0.81, 1.33). Overall, both severe RI and MC groups had an estimated median BLV elimination half-life of ~ 2.8 hours. Total BAs showed similar trends of transient elevations after dosing with returns to near predose concentrations within 24 hours of dosing. Total BA parameters for participants with severe RI vs MCs were as follows: D1, Cmax: 0.87 (0.53, 1.41), NetAUC: 0.86 (0.54, 1.36); D6, Cmax: 0.73 (0.50, 1.05), NetAUC: 0.70 (0.49, 0.99). There were no BLV-related Grade ≥3 treatment-emergent (TE) AEs, serious AEs, or AEs leading to BLV discontinuation. The frequency of TEAEs was similar in both groups, with most AEs being Grade 1 or 2.
Conclusion: Following 6 D of BLV 10 mg SC QD dosing, there were no differences in BLV PK exposures and total BA changes from baseline between participants with severe RI and MCs. BLV was generally safe in participants with severe RI. These results suggest no dose adjustments are needed for BLV treatment with 10 mg QD dosing in the RI population.

WED-314
Hepatocellular carcinoma risk in patients with chronic hepatitis B: Tenofovir Disoproxil Fumarate vs Tenofovir Alafenamide from a korean nationwide study

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Background and aims: In phase 3 trials, tenofovir alafenamide (TAF) showed antiviral efficacy comparable to that of tenofovir disoproxil fumarate (TDF) for chronic hepatitis B (CHB), with an improved safety profile. This study aimed to compare the clinical efficacy of TAF and TDF in terms of the risk of hepatocellular carcinoma (HCC).
Method: We conducted a nationwide historical population cohort study on treatment-naïve adult patients with CHB receiving TAF (n = 29,309) or TDF (n = 58,046) as first-line therapy from 2017 to 2022 using data from the Korean National Health Insurance Service database. Cumulative HCC incidence and associated risk factors were estimated using competing risk factors. Propensity score (PS)-matched analysis was used to minimize the confounding effects.
Results: A total of 20,994 patients were included in the TAF group, and 33,191 in the TDF group. The annual incidence of HCC was significantly lower in the TAF group (7.5/1,000 patient-years [PYs]) than in the TDF group (10.3/1,000 PYs; SHR, 0.74; $p < 0.001$). After PS matching, TAF continued to exhibit a protective effect against HCC (7.5/1,000 PYs vs. 9.9/1,000 PYs; $p < 0.001$). Multivariable analysis Fine–Gray proportional subdistribution hazards model identified TAF as significantly associated with a reduced HCC incidence (SHR: 0.76; $p < 0.001$). Subgroup analysis confirmed the protective effect of TAF against HCC even in patients with cirrhosis (SHR: 0.78; $p = 0.003$).
Conclusion: This study showed that TAF had a protective effect against HCC in patients with CHB, providing valuable guidance for clinicians in selecting the appropriate initial treatment for these patients.

WED-315
Atherosclerotic cardiovascular risk in patients with chronic hepatitis B: Tenofovir Disoproxil fumarate vs Tenofovir Alafenamide from a korean nationwide study

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Background and aims: Concerns have been raised about the safety of tenofovir alafenamide (TAF) regarding potential changes in lipid profiles in chronic hepatitis B (CHB) patients, which could contribute to development of atherosclerotic cardiovascular disease (ASCVD). This study aimed to evaluate long-term risk of ASCVD in CHB patients treated with either TAF or tenofovir disoproxil fumarate (TDF).
Method: We retrospectively analyzed patients diagnosed with CHB and received either TAF or TDF as an initial antiviral treatment between 2017 and 2022. All claim data were obtained from the Korean National Health Insurance Service. Cumulative incidence of ASCVD was estimated by Kaplan-Meier method and compared

between two groups using the log-rank test. Propensity score (PS)-matched analysis was also performed, and risk factors associated with ASCVD were analyzed by Cox regression analysis.
Results: Among 44,714 patients with CHB, 16,120 (36.1%) and 28,594 (63.9%) were treated with TAF and TDF, respectively. During median follow-up period of 3.01 years, ASCVD developed in 817 patients, with an annual incidence of 6.18/1,000 patient-years (PYs). The cumulative incidence rates of ASCVD were 1.06% at 1 year, 1.60% at 2 years, 2.06% at 3 years, and 3.08% at 5 years in the TDF group, compared to 0.48%, 0.91%, 1.36%, and 2.75% in the TAF group. After PS-matching, TAF showed a significantly lower risk of ASCVD compared to TDF (4.67/1,000 PYs vs. 6.67/1,000 PYs; hazard ratio: 0.70, $P < 0.001$). In a multivariable analysis, TAF had a 27% lower risk of ASCVD, while increasing age, concurrent hypertension, current history of smoking, and elevated AST were identified as risk factors for ASCVD.
Conclusion: TAF showed a significantly lower risk of ASCVD compared to TDF in patients with CHB, providing valuable guidance for clinicians in selecting the appropriate initial treatment for these patients.

WED-316-YI

Treatment response to bulevirtide leads to improvement of portal hypertension in patients with chronic hepatitis D virus infection: results from the prospective IMPHROVE-D study

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Background and aims: Portal hypertension (PH) drives hepatic decompensation in patients with advanced chronic liver disease. The extent to which antiviral treatment with bulevirtide (BLV) improves PH and thereby reduces morbidity and mortality in patients with chronic hepatitis D (CHD) is unknown.
Method: CHD patients with PH treated with BLV were prospectively enrolled in this observational, multicenter study. Hepatic venous pressure gradient (HVPG) measurements were performed before (BL) and after a treatment minimum of 12 months (M12). HVPG-response (≥10% decline) rates were compared between patients achieving virological response (VR; HDV-RNA decline by ≥2 $\log_{10}$ IU or HDV-RNA undetectable), biochemical response (BR; ALT normalization), or combined response (CR, both VR and BR) at M12 and patients who did not achieve the respective endpoints. Biomarkers of bacterial translocation (CD163, lipopolysaccharide-binding protein), (dys) angiogenesis/endothelial dysfunction (Angiopoietin-1 and –2 [Ang2]) and fibrogenesis (transforming growth factor beta, platelet-derived growth factor), and systemic inflammation (measured by a 48-cytokine multiplex panel) were compared between BL and M12.
Results: Twenty patients with BLV treatment and paired HVPG measurements were included. At BL, 17 (85%) patients had CSPH (≥10 mmHg HVPG). After a median treatment duration of 13 months (IQR 12–17), HVPG significantly decreased in treatment responders, but not in non-responders (CR achieved by n = 12: 15.5 mmHg [IQR 10.5–21.8 mmHg] at BL to 12 mmHg [IQR 7.3–15.8 mmHg] at M12, Wilcoxon signed-rank test: $p < 0.001$; VR achieved by n = 14: 14.5 mmHg [IQR 10–21.3 mmHg] to 12 mmHg [IQR 7.8–16.5 mmHg], $p = 0.003$; BR achieved by n = 16: 12.5 mmHg [IQR 10–20.5 mmHg] to 10.5 [IQR 8–15 mmHg], $p = 0.002$; non-responders: all not significant). Among the patients with CSPH at BL, HVPG-response was achieved by all patients who showed CR (n = 10/10), and most of virological (83%, n = 10/12) and biochemical responders (85%, n = 11/13). Meanwhile, none of the CSPH patients without any treatment response (CR/VR/BR) achieved HVPG-response at M12. In two of the three patients with subclinical PH at BL, HVPG declined at M12, with PH fully resolving in one patient. Markers of bacterial translocation (CD163; $p = 0.001$), (dys)angiogenesis/endothelial dysfunction (Ang2; $p = 0.001$) and systemic inflammation (IFN-gamma, IL-1RA, sCD25/IL-2R alpha, CCL3/MIP-1alpha, HGF, all $p < 0.05$) decreased in responders but not in non-responders from BL to M12.
Conclusion: Along with biomarkers reflecting liver disease severity and systemic inflammation, HVPG decreased in CHD patients responding to BLV treatment as defined by endpoints used in clinical trials, indicating that their achievement confers a clinically meaningful benefit.

WED-317

Exploring predictive factors for treatment response to Bulevirtide in Delta-positive patients

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Background and aims: Bulevirtide (BLV) therapy can give rise to resistance phenomena; in fact, non-responses were observed (HDV RNA decline≤1Log IU/mL at week 24 of treatment). To date, it is not clear if therapy failure is linked to HDV genotype/subtypes, viral resistance, or host factors. Moreover, the treatment should be prolonged for life, and some adverse events could arise. We analyze clinical and virological parameters such as HBsAg, HBcrAg, HBcAb, HDV RNA viral load, and HDV polymorphisms that could be associated with the success of BLV therapy in patients chronically infected HBV/HDV.
Method: Patients with chronic HBV/HDV infection treated with BLV were enrolled in this study (n = 30). Sequential serum/plasma samples were collected at T0 (baseline), at 4 weeks, 12 weeks, 24 weeks, and 48 weeks to measure virological and clinical parameters. HBV core-related antigen (HBcrAg) and anti-HBc IgG (HBcAb) levels in the serum were quantified using Lumipulse G600II system (Fujirebio). HBV RNA levels were analyzed using the HBV RNA Quantitative Fluorescence Diagnostic Kit (Sansure Biotech Inc., LOD 100copies/ml), and HDV full genome was analysed by Sanger sequencing.
Results: HDV RNA levels decreased from 4.6 (IQR1-IQR3, 3.8–5.7) Log cp/ml at baseline to 2.9 (IQR1-IQR3, 0.0–4.0) Log cp/ml at week 48 ($p < 0.001$). A virological (v) response, defined as either achieving undetectable HDV RNA or a reduction of more than 2 Log from baseline, was observed in 33.3% patients at W24 and in 58.3% patients at W48. Three patients showed an increase in viral load indicative of a viral breakthrough. HBcrAg levels did not statistically differ between v-responder (vr), v-non-responder (vnr), and patients with viral breakthrough. The median HBcAb values were lower in vr compared to vnr: at T0, vr had a median value of 39.25 COI, while non-responders had a median value of 283.7 COI. At W24, responders had a median of 36.7 COI, while non-responders had 266.35 COI ($p = 0.0001$). Finally, the HBcAb levels did not differ statistically during

treatment for both groups, with p = 0.77 for responders and p = 0.44 for non-responders. ALT and AST levels declined in 90% patients at W48. HDV strains: 79% patients harbored HDV GT1e, 2 patients GT1b, 1 patients GT1c, one GT1a, and 3 patients have undetermined HDV1 subtype. Among vnr patients, 7 out of 8 harbored GT1e, the other patient had an undetermined GT1 subtype. In the RBD1 domain, the position N22 showed high variability in vr (50%) whereas in nvr (10%). In addition, certain substitution were observed exclusively in v-responders N22 V (GT1e) and N22 T (GT1a). The amino acid change V16 T (GT1e) was present only in nvr.
Conclusion: Baseline HBcAb values showed the greatest predictability of vr. No conclusive observations could be made regarding the sensitivity of GT1 subtypes to BLV, as most strains were GT1e, and no specific HDV amino acid mutations could be associated to BLV therapy failure.

WED-318
Ethnicity and socioeconomic disparities in diagnostic and hepatic event incidences in patients with chronic viral hepatitis
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Background and aims: Ethnicity and socioeconomic status significantly influence the diagnosis and outcomes of chronic viral hepatitis. This study evaluated the secular trends in diagnostic rates of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and the incidences of hepatic events, focusing on disparities by ethnicity and socioeconomic region over two decades.
Method: Patients were identified from a territory-wide database. Socioeconomic status was classified based on indigenous degree, individual productivity, populous grassroots, and young age, with regions grouped into four clusters (low, middle, high, upper-middle) using time series clustering. Diagnostic rates were stratified by race (Chinese, non-Chinese) and socioeconomic region and calculated based on the number of individuals tested annually. HCV rates were determined using census population data. Incidences of hepatic events, including hepatocellular carcinoma, decompensating events, and liver transplantation, were calculated among HBV and HCV-infected patients.
Results: A total of 234,865 individuals were diagnosed with HBV. Diagnostic rates for Chinese individuals increased from 0.43% [0.42%–0.44%] in 2000 to 3.58% [3.51%–3.65%] in 2020. Non-Chinese diagnostic rates rose from 0.20% [0.18%–0.22%] in 2000 to 2.31% [2.13%–2.49%] in 2020. Regions with low socioeconomic status showed the most significant rise in diagnostic rates, reaching 3.58% [3.48%–3.69%] in 2020, while high socioeconomic regions had consistently lower rates, peaking at 2.56% [2.26%–2.85%] in 2020. HCV diagnostic rates remained low throughout the study period, with a slight increase among both ethnic groups. Hepatic event incidences also showed significant disparities, with non-Chinese individuals experiencing an increase from 0.15% [0.08%–0.22%] in 2000 to 3.07% [2.31%–3.83%] in 2020, and Chinese individuals rising from 0.35% [0.32%–0.37%] in 2000 to 4.73% [4.49%–4.97%] in 2020. Regions with low socioeconomic status had the highest increases, with rates rising from 0.41% [0.35%–0.46%] in 2000 to 6.53% [5.90%–7.15%] in 2020.
Conclusion: Socioeconomic disparities have a substantial impact on HBV diagnostic rates and hepatic event incidences in Hong Kong. Regions with lower socioeconomic status faced the greatest burden. Reducing socioeconomic disparities is essential to decrease health inequalities and support hepatitis elimination efforts.

WED-319
Ten-year follow-up after 96 weeks treatment with peginterferon plus tenofovir in hepatitis D (HIDIT-II)
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Background and aims: Chronic delta hepatitis represents a major health burden. Until recently, pegylated interferon-alfa-2a (PEG-IFNa) therapy was the only treatment option for patients infected with hepatitis D virus (HDV). The aim of this study was to evaluate long-term clinical and virological outcomes after 96 weeks of treatment with PEG-IFNa with or without tenofovir disoproxil fumarate (TDF).
Method: We performed a retrospective follow-up study of the Hep-Net-International-Delta-Hepatitis-Intervention-Study 2 (HIDIT-2 trial). Patients had received 96 weeks of treatment with either PEG-IFNα-2a plus TDF or PEG-IFNα-2a alone. Patients were included if they had completed the 96-week treatment period and had at least one follow-up visit (PEG-IFNα-2a plus TDF; n = 51, PEG-IFNα-2a alone; n = 56). Liver-related complications were defined as liver-related death, liver transplantation, hepatocellular carcinoma (HCC) and hepatic decompensation defined as ascites, variceal bleeding and/or hepatic encephalopathy.
Results: Patients who received PEG-IFNα-2a plus TDF were younger (37 vs 42 years), no significant differences were observed in other baseline characteristics between the two treatment groups. The mean follow-up period was 8.4 years (with a range of 1.8 to 13.1 years). A total of 26 patients (24%) developed one or more liver-related endpoints after a mean time of 6.0 (1.4–12.6) years. Twenty-two patients were re-treated with IFN and 41 with Nucs. Histological cirrhosis was detected in 42 patients (39%) at baseline and another 29 patients progressed to cirrhosis after a mean time of 1.8 (0.9–6.8) years. At the end of treatment 48 patients had undetectable HDV RNA, of whom 59% patients experienced a relapse during the mean follow-up of 8.5 years. Fifteen patients lost HBsAg; none of them developed an event (p = 0.01). No significant differences were observed between the two treatment arms with regard to HDV RNA relapse, HBsAg loss, re-treatment administration, or progression to cirrhosis. However, patients who received PEG-IFNα-2a alone demonstrated a significantly greater incidence of clinical complications (p = 0.01). The development of clinical complications was further found to be associated with non-response to therapy (HDV RNA and HBsAg), high values of HBV DNA at EOT, age and baseline cirrhosis, as well as baseline values of platelets, AST, GGT, bilirubin and albumin using a Cox regression model. In multivariate analysis baseline cirrhosis, age, undetectable HDV RNA at EOT and high values of HBV DNA at EOT were significantly associated with endpoints.

Conclusion: The 10-year follow-up of a large randomized clinical trial demonstrates that HDV RNA response to PEG-IFNα-2a treatment and loss of HBsAg are associated with an improved clinical long-term outcome. Furthermore, concomitant therapy with TDF seems to be independently associated with a favorable clinical course.

WED-320

Serum hepatitis B surface antigen decline combined with the quantification of hepatitis B virus antigen and hepatitis B surface antibody at the end of treatment of pegylated Interferon predict hepatitis B surface antigen loss at 96 weeks after withdrawal

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Background and aims: Functional cure is the ideal goal recommended by chronic hepatitis B (CHB) management guideline. Pegylated interferon alpha (Peg-IFN alpha) therapy could help CHB patients achieve HBsAg loss. This study aims to explore the predictive factors involved in predicting HBsAg loss at follow up 96 weeks after 96 weeks of nucleos(t)ide analogues (NUCs) and Peg-IFN alpha combination and sequential therapy.
Method: This is a multicenter prospective study named of OCEAN study (NCT03358108), in which 170 NUCs experienced patients received a combination treatment of NUCs (ETV or TDF) and Peg-IFN alpha for 48 weeks, followed by Peg-IFN alpha monotherapy for another 48 weeks, and then withdraw the antiviral therapy. All patients were followed up every 24 weeks after the discontinuation of anti-virus therapy, and HBV related indicators were tested. Finally, a total of 114 patients completed the 96 weeks follow up after discontinuation of medication. The indicators predicting HBsAg loss at follow up 96 weeks (FU 96 weeks) were identified by univariate and multivariate analysis, then the nomogram model was constructed and internally validated. The primary endpoint analyzed in the study was HBsAg loss at the end of follow up (EOF), defined as serum HBsAg loss and HBV DNA undetected up to 96 weeks after withdrawal, with or without seroconversion to HBsAb.
Results: After 96 weeks of discontinuing antiviral therapy, there were 28.07% (32/114) patients with HBsAg negative. The univariate and multivariate analysis showed that the serum quantification of HBcrAg ≤4.25 log10U/mL, HBsAb >20 IU/L at EOT and HBsAg decline more than 630 IU/mL from baseline to week 24 during treatment could predict HBsAg loss at 96 weeks after discontinuation. The nomogram model was developed based on the risk factors, and the internal validation was conducted using Bootstrap method, with a concordance index (C-index) of 0.829. Meanwhile, the calibration curve and decision curve of the nomogram model also performed well. The joint indicators could predict HBsAg loss at FU 96 weeks with the areas under the ROC curves (AUROC) = 0.834 ($p < 0.0001$).
Conclusion: Serum HBsAg decline more than 630 IU/mL from baseline to week 24 combined with the quantification of HBcrAg and HBsAb at the EOT of Peg-IFN predict HBsAg loss at FU 96 weeks after withdrawal for CHB patients. We provide novel and effective predictive factors to predict functional cure at follow up 96 weeks after Peg-IFN withdrawal.

WED-321

Impact of hepatic steatosis on hepatitis B virus infection and antiviral treatments

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Background and aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis B (CHB) often co-occur. The interactions between these conditions and their effects on HBV infection and antiviral treatment outcomes are not well understood. This study investigates the impact of hepatic steatosis on HBV prognosis and antiviral treatment efficacy.
Method: A total of 608 chronic HBV-infected patients were categorized into two groups: CHB+MASLD (241 patients) and CHB-only (367 patients). All participants received antiviral therapy, including nucleos(t)ide analogs (NAs), pegylated interferon α-2b (PegIFNα-2b), or a combination. MASLD severity was classified based on the Controlled Attenuation Parameter (CAP) score (mild, moderate, severe). Baseline virological characteristics and antiviral responses at weeks 24 and 48 were analyzed. Kaplan-Meier (KM) survival analysis and Cox regression were used to assess the impact of MASLD on treatment outcomes.
Results: The CHB+MASLD group had lower baseline serum pgRNA levels (2.48 vs. 2.99, $p < 0.05$) and a lower proportion of HBeAg-positive patients (22.0% vs. 33.2%, $p < 0.05$) compared to the CHB-only group. In non-fibrotic CHB+MASLD patients (n = 164), increasing MASLD severity correlated with lower pgRNA ($p < 0.001$) and HBsAg levels ($p = 0.003$). In fibrotic CHB+MASLD patients (n = 77), HBV markers (HBV DNA, HBsAg, pgRNA) decreased from mild to moderate MASLD but increased from moderate to severe MASLD. Liver stiffness (LSM), APRI, and FIB-4 indices increased with worsening MASLD, though not significantly. At weeks 24 and 48, the CHB+MASLD group had higher HBsAg response rates than the CHB-only group (24w: 11.5% vs. 3.8%, $p = 0.026$; 48w: 24.4% vs. 8.4%, $p = 0.001$), and higher pgRNA response rates at week 48 (48w: 48.8% vs. 28.3%, $p = 0.049$). In non-fibrotic patients, CHB+MASLD patients had higher HBsAg response rates (24w: 22.4% vs. 8.1%, $p = 0.028$; 48w: 30.4% vs. 8.1%, $p = 0.003$). No significant difference was found in the fibrotic subgroup. KM survival analysis revealed that in non-fibrotic patients, median time to HBsAg response was significantly shorter in the CHB +MASLD group (HR = 10.05, 44.81 weeks vs. 47.07 weeks, $p = 0.002$). Cox regression identified predictors of HBsAg response: younger age (HR = 0.947, $p = 0.012$), combination therapy with NAs and PegIFNα-2b (HR = 3.90, $p = 0.005$), lower baseline HBsAg (HR = 0.606, $p = 0.005$), and MASLD presence (HR = 3.321, $p = 0.002$).
Conclusion: Hepatic steatosis is associated with reduced viral markers in non-fibrotic CHB patients. In patients with liver fibrosis, moderate MASLD may represent a threshold where viral replication and fibrosis progression are balanced. In non-fibrotic CHB patients, MASLD enhances antiviral response. Predictors of a favorable response include younger age, combination therapy, lower baseline HBsAg levels, and MASLD presence.

Viral Hepatitis B and D – New therapies, unapproved therapies or strategies

TOP-268

Up to 2 years' functional cure in response to bepirovirsen therapy in B-Clear Not-on-NA responders: B-Sure third report

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Background and aims: Bepirovirsen is an investigational unconjugated antisense oligonucleotide, currently in Phase 3 clinical trials for the treatment of chronic hepatitis B virus (HBV) infection. Data from a Phase 2b study (B-Clear; NCT04449029) indicated that a subset of participants achieved a response at the end of bepirovirsen treatment, which was sustained for 24 weeks off-bepirovirsen treatment. This occurred in participants 'on' and 'not-on' background nucleos(t)ide analogue (NA) therapy (On-NA and Not-on-NA). Participants who achieved a complete (CR) or partial (PR) response at the end of B-Clear were eligible for this long-term durability study (B-Sure; NCT04954859; ongoing). Here we present data on the durability of response and functional cure (FC) in B-Clear Not-on-NA complete responders (CRs) and partial responders (PRs) who entered B-Sure (duration of follow-up: 2.5 years).
Method: CR was defined as hepatitis B surface antigen (HBsAg) <0.05 IU/mL and HBV DNA < lower limit of quantification (LLOQ), and PR as HBsAg <100 IU/mL and HBV DNA < LLOQ at the end of B-Clear. Following entry into B-Sure, participants are assessed at baseline and at Months 3, 9, 15, 21, 27 and 33. Participants maintaining a CR at Month 3 (i.e., at least 9 months off bepirovirsen), were considered to have achieved FC. Adverse events were recorded, with physical examinations and blood tests performed at each visit for safety and efficacy, including time from achieving response in B-Clear to loss of response in B-Sure.
Results: Overall, 17 B-Clear Not-on-NA participants (11 CRs, 5 PRs and 1 non-responder) were enrolled into B-Sure. Participants had a mean age of 44.1 years. All participants were hepatitis B e-antigen (HBeAg)-negative and 9/17 (53%) had HBsAg ≤1000 IU/mL at B-Clear baseline. For CRs, at 3 months of B-Sure follow-up, 8/11 (73%) participants maintained a CR, thus achieving FC. All 8 participants maintained FC for at least 18 months. Of these 8, 6 maintained FC for 24 months. The 3 participants who did not achieve FC had HBsAg reversion by 3 months of B-Sure; 1 of these participants subsequently experienced HBsAg loss (Month 15) and this was maintained through to the latest available data. For PR participants, only 1/5 maintained a PR at 3 months and through 27 months of B-Sure follow-up. Two PR participants started NA treatment after B-Sure enrollment. There were no new safety signals.
Conclusion: These data provide evidence of longer durability of FC observed with bepirovirsen.
Funding: GSK (206882; NCT04954859).

THURSDAY 08 MAY

THU-240

30% of inactive HBsAg carriers achieved clinical cure at 48 weeks with Pegylated Interferon alpha-2b therapy: a multicenter real-world study (STARHB Project in China)- 2.5 years data update

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Background and aims: This study aimed to investigate the efficacy and safety of achieving functional cure (HBsAg loss) using Pegylated Interferon alpha-2b (PEG IFNα-2b) treatment in inactive HBsAg carriers (IHC).
Method: The STARHB Project (The STUDY ON TREATMENT FOR INACTIVE CARRIERS OF HEPATITIS B) is a multicenter real-world study in China focused on the functional cure of IHC, aiming to onboard approximately 25,000 patients (ChiCTR2200061541). Based on patient preferences, participants were assigned to a control group (without antiviral treatment) or treatment groups (NAs group and PEG IFNα-2b ± NAs group). The basic treatment duration was 48 weeks, extendable to 96 weeks as needed.
Results: As of Nov. 2024, 15,070 individuals were screened, and 10,894 eligible IHC patients were included in the mITT population baseline analysis. This cohort was 64.9% male with a mean age of 43 years; 6.3% were under 30 years old, and 41.5% had fatty liver. The mean HBsAg level was 223 IU/ml, with 81.8% below 500 IU/ml. The mean HBV DNA level was 220 IU/ml, with 58.5% having undetectable HBV DNA at baseline. The mean ALT was 22 U/L. Liver biopsies were performed on 60 patients at baseline, with 33.3% showing significant liver necroinflammation and/or fibrosis (≥G2 and/or ≥S2). At present, 729 patients have completed the 48-week follow-up. In the control group (n = 11), 4 achieved virological response (VR), with 1 achieved HBsAg loss. In the NAs group, the VR rate at 48 weeks was 100% (17/17), with 1 achieved HBsAg loss. Among those treated with PEG IFNα-2b ± NAs, the VR rate at 48 weeks was 91.01% (638/701), with an HBsAg loss rate of 30% (210/701). ROC analysis indicated that baseline HBsAg levels, 12-week and 24-week HBsAg levels, and 12-week AST levels could predict HBsAg loss at 48 weeks.
Conclusion: PEG IFNα-2b therapy can effectively achieve functional cure in IHC patients, with a 48-week HBsAg loss rate of 30%. Lower baseline, 12-week, and 24-week HBsAg levels, along with higher 12-week AST levels, are predictors of functional cure at 48 weeks. Thus, the IHC population is a favorable group for pursuing clinical cure for hepatitis B.

THU-241

Combination treatment of TLR7 agonist and anti-PD-L1 reconstitute protective immunity in virally suppressed chronic hepatitis B patients

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Background and aims: The combination treatment of Toll-like receptor (TLR) 7 agonist TQ-A3334 and PD-L1 inhibitor TQ-B2450 has been demonstrated to induce a remarkable decline of HBsAg in viral-suppressed chronic hepatitis B (CHB) patients with good safety and tolerability in a pilot RCT phase II study (OCEAN cure05 Study). In this study, we aimed to characterize the immunological features responsible for the efficacy of combination therapy.
Method: Totally 24 nucleos(t)ide analogues (NUCs)-treated CHB patients were randomized to receive Entecavir (ETV) monotherapy (n = 6), ETV+TQA3334 dual therapy (n = 9) or NA+TQA3334+TQB2450 triple therapy (n = 9) for 24 weeks and then followed up for 24 weeks. Serum and Peripheral Blood Mononuclear Cells (PBMCs) were collected at indicated timepoints. The serum levels of Interferon Stimulating Genes (ISGs) and cytokines were analyzed by Quantitative Polymerase Chain Reaction (qPCR) and Meso Scale Discovery (MSD) electrochemiluminescence assay, respectively. HBV specific CD8+T cell responses were determined by flow cytometry. Then PBMCs from NUCs-treated CHB patients were treated in HBV peptides conditioned culture system in vitro for further validation.
Results: Compared to NA monotherapy and dual therapy, triple therapy was associated with greater HBsAg reduction at the end of treatment (EOT). After 12 weeks of treatment, expression level of MX1 and ISG15 significantly elevated among patients received triple therapy. The patients receiving triple therapy displayed significantly higher level of IFN-γ, IP-10 and sPD-1 as well as lower sPD-L1 at week 12. While after 24 weeks of treatment, the IL-21 level in patients with triple therapy significantly increased and was the highest among the three treatment groups, the sPD-L1 level reduced to the lowest. Significantly elevated level of IFN-α was found in patients with dual or triple therapy, and was comparable at EOT between the two groups. In terms of HBV specific CD8+T cells, patients receiving triple therapy demonstrated stronger and broader HBV specific response. Both the production of IFN-γ and degranulation by CD8+T cells stimulated with core peptides pool in patients with triple therapy were significantly higher than those of patients in dual therapy and monotherapy group at EOT. And the elevation of core specific CD8+T IFN-γ remained significantly at 24w after EOT. In vitro, co-stimulation of TQ-A3334 and TQ-B2450 resulted in a significant increase in the frequency of core and polymerase pentamer specific CD8+T cell. In a co-culture system containing PBMCs and HepAD38 cell line, TQA-3334 in combination with TQB-2450 triggered obviously higher viral lysis rate of HepAD38 and strengthened viral control.
Conclusion: The combination of TLR7 agonist and anti-PD-L1 could reconstitute antiviral immunity in virally suppressed CHB patients by inducing the production of ISGs, antiviral cytokines, and reinvigorating HBV-specific CD8+T cell response, thus potentially favouring improved clinical outcome.

THU-242

Viral kinetics and sequence analysis of a phase I monotherapy study in subjects with chronic hepatitis B reveals a high barrier of resistance to the capsid assembly modulator ALG-000184

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Background and aims: The hepatitis B virus (HBV) Capsid Assembly Modulator (CAM) ALG-000184 demonstrated substantial reductions in HBV DNA, RNA and viral antigens during Part 4 Cohort B of the Phase I clinical trial ALG-000184-201, where 21 chronic hepatitis B (CHB) participants were treated with 300 mg ALG-000184 monotherapy for up to 96 weeks. No viral breakthrough as assessed by HBV DNA was observed. In this study, baseline samples of all 21 participants and the last available on-treatment sample with an HBV DNA viral load of ≥1000 IU/mL were sequenced to identify the presence of known CAM resistance mutations.
Method: Next-generation sequencing was performed on the baseline samples of all 10 HBeAg-positive and 11 HBeAg-negative participants; in addition, at least one on-treatment sample of the HBeAg-positive participants and one HBeAg-negative was analyzed. The minimum plasma HBV DNA concentration for sequencing was 1000 IU/mL. Sequences were compared to their respective genotype reference. Amino acid substitutions in the HBV core protein with a frequency of ≥1% are reported.
Results: All samples except one on-treatment sample were successfully sequenced, with an average read-coverage of >50,000. The three known main ALG-000184 resistance mutations, which mediate a ≥7-fold loss in antiviral activity in vitro, namely T33N, T33P and V124G were not detected (frequency <1%) in any of the samples. F23Y, which causes a 3-fold loss of activity in vitro, was detected in the baseline sample of one subject at a frequency of 5.1%. I105L was detected in the baseline samples of two subjects, with frequencies of 1.98 and 11.2%, respectively. In one of the two subjects, I105T at a frequency of 6.52% was also found. I105L/T reduce the in vitro activity of ALG-000184 ≤2.1-fold. The viral load of the 3 subjects with F23Y, I105L or I105T reached the lower limit of quantification rapidly (HBV DNA 10 IU/mL) by Day 14 and no on-treatment plasma sample with a sufficiently high HBV DNA concentration was available for sequencing. Other resistance mutations, which significantly reduce the in vitro antiviral activity of other CAMs but not ALG-000184 were detected in baseline samples but not in any on-treatment samples. These include Y38F (frequency 97%), T109M (>99%) and Y118F (8.6%).
Conclusion: No viral breakthrough or non-response, as measured by HBV DNA levels was observed in the 21 CHB participants undergoing ALG-000184 monotherapy for up to 96 weeks. Consistently, none of the major ALG-000184 resistance mutations identified in vitro (T33N, T33P and V124G) were detected in any of the baseline or on-treatment samples, indicating a high barrier to resistance. The lack of viral breakthrough and emerging resistance, combined with the significant reduction in HBV DNA, positions ALG-000184 as a promising candidate for further clinical development as a potential backbone of therapy for chronic viral suppression.

THU-243

SOLSTICE week 24 subgroup analysis: impact of baseline viral parameters and cirrhosis status on virological and biochemical responses in participants with chronic hepatitis delta virus infection treated with tobevibart and elebsiran

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Background and aims: The phase 2 SOLSTICE study is investigating the antiviral activity and safety of the monoclonal antibody tobevibart alone and in combination with the small interfering RNA (siRNA) elebsiran in chronic HDV infection (NCT05461170).
Method: Participants with chronic HDV infection, with or without compensated cirrhosis on NRTI therapy, were randomized 1:1 to receive either tobevibart 300 mg plus elebsiran 200 mg subcutaneously (SC) every 4 weeks (tobevibart + elebsiran Q4W *de novo*) or tobevibart 300 mg SC every 2 weeks (tobevibart Q2W) for 96 weeks. Here we present a subgroup analysis of the week 24 preliminary results based on cirrhotic status, HDV viremia and hepatitis B surface antigen (HBsAg) at enrollment from N = 32 participants receiving tobevibart + elebsiran Q4W *de novo* (56.3% cirrhotic CPT-A) and N = 33 participants receiving tobevibart Q2W (45.5% cirrhotic CPT-A).
Results: After 24 weeks of tobevibart+elebsiran Q4W *de novo* therapy, all participants demonstrated viral suppression (HDV RNA < limit of detection (<LOD, 14 IU/mL) or a ≥ 2 $\log_{10}$ decrease from baseline) with 75% achieving <LOD and 41% achieving target not detected (TND). The percentage of participants achieving TND within 24 weeks was similar regardless of baseline cirrhotic status, HDV viremia, or HBsAg. In contrast, 82% of participants receiving tobevibart Q2W demonstrated viral suppression with 58% achieving <LOD and 30% achieving TND; and fewer participants with baseline HDV viremia >10^5 IU/mL achieved TND. TND response rates were similar between non-cirrhotic and cirrhotic participants in both cohorts at week 24. ALT normalization was achieved by week 24 in 47% of participants receiving tobevibart + elebsiran Q4W *de novo* and 76% of participants receiving tobevibart Q2W regardless of the presence baseline compensated cirrhosis or baseline HDV viremia in both cohorts. Approximately 88% of participants receiving tobevibart + elebsiran Q4W *de novo* achieved HBsAg values <10 IU/mL by week 24 regardless of baseline HBsAg levels. In contrast, 22% of participants receiving tobevibart Q2W achieved HBsAg values <10 IU/mL at week 24 and the likelihood was decreased in participants with baseline HBsAg > 3,000 IU/mL. Treatment-emergent adverse events (TEAEs) were primarily Grade 1–2 and transient in nature, with the most common being influenza-like syndrome, myalgia, headache, and chills. There were low rates of treatment discontinuation.
Conclusion: In preliminary 24 weeks data, participants receiving tobevibart+elebsiran Q4W *de novo* therapy achieved high rates of viral suppression, regardless of baseline viral parameters or the presence of compensated cirrhosis, whereas participants receiving tobevibart Q2W with high baseline HDV viremia showed a trend towards decreased viral response. These results support continued development of tobevibart in combination with elebsiran for chronic HDV infection.

THU-244
Tissue virological response is the main predictor of hepatitis D relapses

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Background and aims: Chronic hepatitis delta (CHD) infection is the most aggressive form of viral hepatitis, leading to early development of cirrhosis, cirrhosis-related complications, and primary liver cancer. The only effective treatment for CHD patients is bulevirtide (BLV) with or without pegylated interferon alfa (PEG-IFN). Assessing the response to antiviral therapy in CHD patients relies on detecting and quantifying hepatitis delta virus (HDV) RNA in blood serum using PCR testing. However, achieving and maintaining undetectable HDV RNA during antiviral treatment predicts sustained virological response (SVR) in only 63% of patients; relapse occurs in one-third of patients after the end of treatment (EOT). The optimal time for discontinuing treatment remains debated, as undetectable HDV RNA at week 12 or 24 of antiviral therapy is not a strong predictor of SVR, defined as the absence of HDV RNA for 48 weeks in blood serum after EOT. This study aims to demonstrate that the presence of HDV RNA in liver tissue is a marker of active replication and a predictor of relapse post-EOT. Despite long periods of aviremia during antiviral therapy, lasting 36 to 96 weeks, most patients relapse after the EOT.
Method: The study included 24 CHD patients treated with combined antiviral therapy of PEG IFN and BLV 2 mg/day for 48 weeks, followed by BLV 2 mg/day monotherapy until 96–144 weeks. All patients achieved and maintained undetectable HDV RNA (complete virologic response) until EOT, with undetectable HDV RNA by PCR for at least 48 to 96 weeks of therapy. At EOT, liver biopsies were conducted for all patients. In addition to histological response assessment, HDV RNA detection by PCR in liver tissue was performed.
Results: Among the 24 patients maintaining undetectable HDV RNA (complete virological response) in serum, HDV RNA was detected in the liver tissue in 16 patients. All 16 patients relapsed within 24 weeks post-EOT.
Conclusion: In CHD patients who achieved and maintained undetectable HDV RNA during antiviral therapy with PEG IFN and BLV, the absence of tissue virologic response (detection of HDV RNA in liver biopsy by PCR) at EOT is the main predictor of HDV relapse post-EOT. Therefore, antiviral treatment should be prolonged based on the risk of relapse, which can be predicted by positive HDV RNA testing in liver tissue (tissue virologic response - tVR) obtained at EOT.

THU-245
Safety, tolerability, pharmacokinetics, and pharmacodynamics of RO7565020, a novel monoclonal antibody that targets the hepatitis B surface antigen: results from a phase 1 single ascending dose study in healthy volunteers and participants with chronic hepatitis B

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Background and aims: RO7565020 (RG6449) is a neutralizing human IgG1 monoclonal antibody (mAb) targeting the antigenic loop present in all forms of hepatitis B surface antigen (HBsAg). A neonatal Fc receptor (FcRn) affinity-enhancing Fc mutation was introduced to improve the pharmacokinetic (PK) properties. In vitro and in vivo studies of RO7565020 showed potent and cross-reactive neutralization against the main hepatitis B virus (HBV) genotypes (A-D). Here, we report the safety, tolerability, PK, and pharmacodynamics (PD) results of the first-in-human study of RO7565020 (NCT05763576).
Method: Part 1 is a randomized study in healthy volunteers (HVs), including 5 single ascending dose (SAD) cohorts and 1 ethnic bridging cohort, each with 8 participants (in a 6:2 ratio of active treatment to placebo). Part 2 is an open-label, active treatment-only study in virologically suppressed participants with chronic hepatitis B (CHB) treated with nucleos(t)ide analogues, including 3 and 2 SAD cohorts (each with 6 participants) with baseline low or high HBsAg (cutoff: 3000 IU/mL). Participants were followed for 24 to 36 weeks post-administration.
Results: Across 6 cohorts in Part 1, 32/48 (67%) participants reported 91 adverse events (AEs), all were Division of AIDS (DAIDS) Grade 1 or 2. Six (7%) treatment-related AEs and 1 unrelated serious adverse event (SAE) were reported. Across 2 of the 5 cohorts in Part 2 (the first 2 dose levels in participants with baseline low HBsAg), 3/12 (25%) participants reported 7 AEs, all were DAIDS Grade 1. One treatment-related AE was reported. No SAEs or evidence of immune complex disease. No dose-related trends in AEs or safety lab parameters were observed. Low anti-drug antibody titers were observed in 6 (13%) HVs and 1 (8%) participant with CHB, without impact on PK parameters. In Part 1, a single dose of RO7565020 was absorbed with a median Tmax ranging from 11 to 28 days and had a mean half-life of approximately 90 days. Exposure (Cmax and AUCinf) increased in a dose-proportional manner. PK profiles were similar between Asian and Caucasian participants. In both cohorts of Part 2, the median Tmax was 11 days and the half-life was dose-dependent. A clear temporal relationship between the increase in total serum active RO7565020 concentrations and the decrease in serum HBsAg levels was observed. The mean (SD) HBsAg reduction from baseline reached its nadir at Day 8, with similar values in both cohorts: 1.38 (0.54) log10 IU/mL for cohort 1 and 1.43 (0.29) log10 IU/mL for cohort 2. By Day 57, the reduction appeared more sustained in cohort 2 (1.06 (0.39) log10 IU/mL) than in cohort 1 (0.68 (0.60) log10 IU/mL). Additional data from these cohorts will be presented.
Conclusion: RO7565020 administered as a single dose was generally safe and well-tolerated. It demonstrated proof-of-mechanism with rapid reductions in serum HBsAg in participants with CHB who had baseline HBsAg ≤3000 IU/mL.

THU-246

Safety, tolerability and immunogenicity of GS-2829 and GS-6779, a novel arenaviral vectored therapeutic hepatitis B vaccine: results from a phase 1a study in healthy participants

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Background and aims: Achieving a functional cure for hepatitis B virus (HBV) infection may require novel combinations of agents that target viral replication and generate a sustained immune response. One approach to elicit such a response is therapeutic vaccination. Nonreplicating arenaviral vectors GS-2829 and GS-6779 were engineered to express highly conserved HBV proteins. Here, we present the results from a Phase 1a study evaluating the safety, tolerability and immunogenicity of GS-2829 and GS-6779.
Method: This randomised (4:1), blinded, placebo-controlled Phase 1a study (NCT05770895) was conducted at 1 centre in New Zealand in healthy participants. Cohorts (C)1 and C2 received a total of 2 intramuscular (IM) administrations of either a low dose of GS-2829 (C1), or GS-6779 (C2) once every 8 weeks (W). Alternating IM doses of GS-2829 or GS-6779 every 4 weeks (e.g. GS-2829 at W0, followed by GS-6779 at W4) were evaluated in multiple cohorts: C3, four total low doses; C4, four total high doses; C8, six total high doses. Safety and tolerability, including treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory abnormalities, were monitored throughout the study. Immunogenicity was evaluated via interferon-gamma ELISpot analysis of HBV-specific T cells and anti–hepatitis B surface antigen (HBsAg) antibody titres.
Results: A total of 51 participants were enrolled and treated: C1–4, n = 10 per cohort; C8, n = 11. The median age was 33 years, 49% were male, 35% were Asian, 41% were White, 4% were Native Hawaiian or Pacific Islander and 20% were other races. Both single and alternating vector administrations were safe and well tolerated. TEAEs occurred in 98% (50 of 51) of participants and were Grade 1 or 2 and nonserious, except for one Grade 3 unrelated SAE (Lisfranc fracture due to a road collision). Commonly reported TEAEs were injection-site reaction (55%, 28 of 51) and flu-like symptoms (headache [43%, 22 of 51], fatigue [41%, 21 of 51] and malaise [25%, 13 of 51]), that were transient in nature. No AEs led to discontinuation of the study drugs or death. Vaccine-elicited immune responses were dose dependent; in several participants (C8), addition of doses 5 and 6 further increased the magnitude of T cell responses. Participants generated HBV-specific T cells to all vaccine-encoded HBV antigens and high-magnitude, durable anti-HBsAg titres.
Conclusion: Alternating doses of GS-2829 and GS-6779 were safe and well tolerated in healthy participants. Common TEAEs were consistent with the vaccines as a drug class. Immunogenicity was dose-level dependent, and vaccine-elicited T cell responses were progressively increased with additional vaccine doses. These data support further investigation of GS-2829 and GS-6779 in participants with chronic HBV infection in this ongoing Phase 1 study.

THU-247

HBsAg declines, and T cell increases, observed in CHB patients: Interim results from P1b trial of VRON-0200, a novel checkpoint modifier, following prime only, and prime and boost dosing

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Background and aims: VRON-0200 is a therapeutic vaccine for CHB functional cure that expresses a genetically encoded checkpoint modifier, fused with HBV core and pol (but not S) antigens, designed to enhance, broaden, and prolong $CD8^+$ T cell responses. This is the first report of HBsAg and immunogenicity of i.m. prime and boost doses of VRON-0200.
Method: CHB patients (pts), virologically suppressed on nucleos(t)ide analogues and with HBsAg ≤500IU/mL, are randomized to receive i.m. VRON-0200 1×10^{10}vp(Cohort 1) or 5×10^{10}vp(Cohort 2). Cohort 1a/2a receives a prime, followed by a boost, on D91; Cohort 1b/2b receives prime only. Safety, virologic, and immunologic assessments are performed. T cell frequencies are assessed pre-tx (2 timepts) and at multiple post-tx timepts, via IFN-γ ELISpot(LLOD<30 SFU/1e6) from PBMCs using 3 peptide pools (core & pol representing the vaccine peptides, and S antigen peptides). All pts who received VRON-0200, with PBMC results, for the analyses are included.

Immunologic responders are defined as 2 consecutive core plus pol ELISpot values at D28 above the avg of the 2 pre-tx values. A one-sided paired t-test assessed if there was a difference between pre-tx and D28 values. A D91 response was defined as a core plus pol ELISpot value on D91 that is above the avg of the 2 pre-tx values. HBsAg levels were assessed in patients with results at their most recent study visit ≥ D91; declines ≥ 0.4 $\log_{10}$IU/mL are reported.

Results: 25 pts were included in this analysis (13-Cohort 1;12-Cohort 2): 80% male, 85% Asian, mean age, 46yrs, median BL HBsAg, 179 IU/mL (range:10–623). As of November 26, 2024, 5,830 pt safety days were evaluable, with 30 AEs reported in 15 patients (24-Grade 1;6-Grade 2). The frequency and severity of AEs were not related to dose or additional boost dosing. ELISpot results through D28, 91 and 154 were evaluable in 22,16 and 5 patients, respectively. At BL, most pts (n = 20;91%) had either one or both pre-tx ELISpot values to core or pol below LLOD. At D28, responses to core and pol increased 2.2-fold overall (p = 0.02) and 5.5-fold higher among the 7 responders.10/16 pts (63%) were determined to have a D91 response, with 5 of 6 (83%) D28 responders having a D91 response. Of the 22 pts with HBsAg evaluable at their last study visit, 5 pts (23%) had −2.3, −0.8, −0.6, −0.4 and −0.4 $\log_{10}$IU/mL declines. ELISpot and HBsAg responses following boost dosing are ongoing and will be reported.

Conclusion: In a CHB pt population with limited preexisting HBV immunity, VRON-0200 was safe, well tolerated, and significantly increased T cell responses and reduced HBsAg levels in >20% of patients, reflecting restored broad HBV-specific immune responses (vaccine does not contain S). VRON-0200 is a potential simple, easy-to administer, IFN-sparing immunotherapy, alone or in combination, for HBV functional cure. Immunologic, clinical, and safety analyses are ongoing.

THU-248

Preliminary safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of AB-101, a small-molecule PD-L1 inhibitor, in healthy and chronic hepatitis B subjects

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Background and aims: Programmed death 1 (PD-1)/ programmed death-ligand 1 (PD-L1) checkpoint inhibition using immune checkpoint inhibitor antibodies (ICI Abs) has been associated with HBsAg loss and seroconversion in chronic hepatitis B (CHB) subjects with low baseline HBsAg. A concern with the use of ICI Abs in CHB subjects is the development of immune related adverse events (irAEs). AB-101 is an oral small-molecule PD-L1 inhibitor being developed for the treatment of CHB infection in combination with other agents. As AB-101 is expected to have a shorter half-life than ICI Abs, dose modification or discontinuation may mitigate unanticipated safety issues. Better tissue penetrance leading to high concentrations in the liver by AB-101 may also permit lower doses to be used in CHB subjects compared to ICI Ab doses used in oncology patients. A Phase 1a/1b study is ongoing to assess the characteristics of AB-101 in healthy subjects (HS) and nucleos(t)ide analogue (NA)-suppressed CHB subjects. Preliminary results of completed single ascending dose (SAD) and multiple ascending dose (MAD) cohorts in HS are reported.

Method: AB-101-001 (NCT05960240) is a randomized, double-blind, placebo-controlled 3-part study evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of AB-101 in HS and HBV DNA-negative CHB subjects on NA therapy. In Part 1, HS were randomized 6:2 to receive single doses of AB-101 or placebo (PBO) and in Part 2, HS were randomized 8:2 to receive AB-101 or PBO once daily (QD) for 7 days. Part 3 in CHB subjects dosed with AB-101 or PBO for 28 days is ongoing. Safety was monitored throughout the study via adverse event (AE) reporting, vital signs, physical examination, ECGs, and laboratory assessments. Blood samples for single and repeat dose PK and PD were collected. PD was assessed via measurement of PD-L1 levels from peripheral cells (receptor occupancy [RO]).

Results: To date, HS SAD cohorts up to 40 mg and MAD cohorts up to 25 mg QD for 7 days are complete and the 40 mg QD for 7 days cohort is in follow up. All subjects in Parts 1 and 2 were male with an overall mean age of 29.6 years (SD 7.2). AB-101 was well tolerated with no serious adverse events (SAEs), irAEs, Grade 3 or 4 treatment emergent adverse events (TEAEs) or discontinuations due to TEAEs reported. All AB-101 related TEAEs (N = 6) were Grade 1. No clinically significant laboratory, vital sign, or ECG abnormalities were reported. There were dose-related increases in AB-101 C_{max}, AUC, and RO. RO >30% was observed after single doses of AB-101, with no obvious increase with repeat dosing at the same dose level. Mean maximal RO was 48%, 83%, and 94% for 10 mg, 25 mg, and 40 mg QD for 7 days, respectively.

Conclusion: Single doses of AB-101 up to 40 mg and repeat doses up to 40 mg QD for 7 days were well tolerated in healthy subjects. Preliminary PD data shows AB-101 RO at doses ≥10 mg, with dose-related increases in RO observed. Dosing in Part 3 in CHB subjects is ongoing and available data, including RO and HBV virologic biomarkers, will be presented.

THU-253

IM-PROVE I: Rapid loss followed by transient increases in HBV RNA in chronic hepatitis B subjects during treatment with imdusiran and pegylated interferon alfa-2a is associated with HBsAg seroclearance

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Background and aims: Functional cure (FC) of chronic hepatitis B (CHB) requires suppression of viral replication, reduction of HBV antigens and induction of anti-HBV immune responses. Imdusiran (IDR) is a *N*-Acetylgalactosamine–conjugated, pan-genotypic small interfering RNA therapeutic that blocks all HBV RNA transcripts, including HBV X protein, resulting in suppression of viral replication

and all viral antigens. IM-PROVE I is an ongoing Phase 2a study assessing 24 weeks (W) of IDR lead-in followed by 12W or 24W of pegylated interferon alfa-2a (IFN) with or without additional IDR doses in 43 nucleos(t)ide analogue (NA) treated CHB subjects. Exploratory HBV biomarker profiles of subjects who achieved FC are compared to subjects who did not achieve FC but who had HBV DNA <LLOQ or experienced HBsAg seroreversion after NA discontinuation during follow-up.

Method: Longitudinal plasma and serum samples were collected from subjects who attained FC (n = 6) and compared to subjects who did not achieve FC but who had HBV DNA <LLOQ (n = 3) or experienced HBsAg seroreversion during follow-up (n = 1). HBsAg (LLOQ = 0.05 IU/mL), anti-HBs antibodies (LLOQ = 1 IU/L), HBcrAg (LLOQ = 1.0 kU/mL) and HBV DNA (LLOQ = 10 IU/mL) were quantified using chemiluminescent immunoassays or molecular assay. HBV RNA, HBsAg isoforms and immune complex were assessed using the Abbott HBV RNA v2.0 assay (LLOQ = 0.49 Log_{10} U/mL or 3.09 U/mL) and exploratory assays.

Results: All subjects in IM-PROVE I with quantifiable HBV RNA at baseline (n = 36) showed declines during IDR lead-in, with mean (± standard deviation) maximal log_{10} changes from baseline of −1.06 (0.20), −0.99 (0.19), −0.80 (0.21) and −1.04 (0.18) in Cohorts A1, A2, B1 and B2, respectively. In 5/6 FC subjects and 2/3 subjects who had HBV DNA <LLOQ but did not attain FC, HBV RNA declined to undetectable during IDR lead-in; in contrast, HBV RNA undetectability during IDR lead-in was not achieved in one subject who lost HBsAg and later seroreverted. Transient increases in HBV RNA were observed during IFN treatment in 5/6 FC subjects which occurred prior to or concomitant with HBsAg loss. In contrast, subjects who had HBV DNA <LLOQ but did not achieve HBsAg loss or later seroreverted also experienced increases in HBV RNA, but these were associated with transient increases in HBV DNA off treatment. In the HBsAg seroreversion subject, an increase in HBsAg was observed to follow a decline in anti-HBs antibodies, suggesting unmasking of HBsAg from immune complexes. Further assessment of HBcrAg, immune complex and HBsAg isoforms levels in these subjects will be presented.

Conclusion: Subjects who achieved functional cure after combination treatment with IDR + IFN showed rapid HBV RNA decline during IDR lead-in, with 5/6 subjects achieving HBV RNA undetectability during this period. Transient elevations in HBV RNA were observed to occur during the IFN treatment period which was associated with further HBsAg decline and loss in some FC subjects.

THU-254

First-in-human pharmacokinetics and pharmacodynamics of oral small-molecule PD-L1 inhibitor AB-101 and correlation to preclinical models

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Background and aims: Functional cure of chronic hepatitis B (CHB) requires suppression of viral replication, reduction of HBV antigens (particularly HBsAg), and induction of anti-HBV immune responses. The PD-1/PD-L1 immune checkpoint axis plays a key role in HBV immune tolerance, which is a critical driver of CHB persistence. AB-101 is an oral small-molecule PD-L1 inhibitor with favorable liver distribution in preclinical species and the potential to enable tunable on-target engagement while reducing toxicities associated with systemic exposure. Preliminary pharmacodynamic (PD) data from an ongoing Phase 1a/1b study of AB-101 dosing in healthy subjects is presented. PD association with pharmacokinetic (PK) data is described and compared to PK-PD relationships observed in preclinical efficacy models.

Method: AB-101-001 is a double-blind, randomized, placebo-controlled single- and multiple-dose Phase 1a/1b study evaluating the safety, tolerability, PK, and PD of AB-101 in healthy subjects and subjects with CHB infection. Receptor occupancy (RO) and target engagement in peripheral blood cells and plasma were assessed at multiple timepoints after single and multiple ascending doses in healthy subjects, and clinical PK and PD of AB-101 is presented and compared to AB-101 PK-PD association in humanized PD-1/PD-L1 adenovirus-associated HBV mice and a humanized PD-1/PD-L1 MC38 tumor mouse model.

Results: To date, single dose cohorts up to 40 mg and multiple dose cohorts up to 25 mg QD for 7 days have been completed, and a 40 mg QD for 7 days cohort is in follow-up in healthy subjects. Dose-responsive increases in RO were observed, with mean maximal RO of 48%, 83%, and 94% following AB-101 dosing at 10 mg, 25 mg, and 40 mg QD for 7 days, respectively, with data through 7 days of follow-up. Increases in RO paralleled the increases in AB-101 plasma concentrations. AB-101 plasma concentrations rapidly declined after reaching a T_{max} at ~1 h post-dosing, indicating rapid distribution into tissues. Similar plasma PK profiles of AB-101 were observed in preclinical mouse efficacy models, which were associated with concomitantly high AB-101 concentrations (≥5 × serum-shifted EC_{90}) in liver and tumor with demonstrated RO and target engagement.

Conclusion: AB-101 was safe and well-tolerated in both single- and multiple-dose administrations in healthy subjects. Dose-responsive increases in RO were observed in peripheral blood cells, which correlated with dose-dependent increases in AB-101 plasma concentrations. The clinical plasma PK profile of AB-101 to date indicates rapid distribution into tissues, mirroring the plasma profiles seen in preclinical efficacy models, which exhibited high liver biodistribution and target engagement.

THU-255

The safety and efficacy of PD-1 antibody combined with pegylated interferon-α therapy to promote the clinical cure in nucleoside (acid) analogues-suppressed chronic hepatitis B patients

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Background and aims: The clinical cure of chronic hepatitis B (CHB) is an ideal goal of therapy, which is associated with improved long-term outcome. Studies have shown that PD1 antibody therapy can reduce HBsAg in patients with CHB. This study was used to evaluate the efficacy and safety of a novel strategy, PD-1 antibody combined with Peg-IFNα, in NAs-treated CHB patients.

Method: This study was designed as two cohorts. Cohort 1 was a prospective, multicenter, open-labled, randomized controlled study. Total 45 viral suppressed CHB patients with NAs treatment (HBeAg and HBV DNA nagetive, HBsAg ranged from 200 to 1000 IU/mL) were enrolled and randomly assigned to Peg-IFNα group, PD-1 antibody group and Combined group. Cohort 2 was a prospective, multicenter, single group assignment study. Fifty patients with HBsAg <200 IU/ml were treated with PD-1 antibody for 12 weeks and then efficacy was evaluated. If the HBsAg reduction of patients was less than 0.5log, Peg-IFNα-2b therapy was added, otherwise, the original treatment regimen was continued. The primary endpoint was rate of HBsAg loss at 24 weeks and 48 weeks, while safety was evaluated by the adverse events (AEs) profile.

Results: By the time this abstract was submitted, 12 eligible CHB patients were enrolled in cohort 2 and randomized to Peg-IFNα group (n = 3), PD-1 antibody group (n = 5) or Combined group (n = 4), and 11 patients were enrolled in cohort 2. The decline in levels of HBsAg

from baseline in combined group of cohort1 was 0.04 log10 IU/ml (range – 0.69–0.10) after 6–9 weeks treatment (n = 3), in PD-1 group was –0.05 log10 IU/ml (range –1.02–0.01) after 3–18 weeks treatment (n = 5) and in Peg-IFNα group was –1.96 log10 IU/ml (range –2.37 – –0.01) after 9–24 weeks treatment (n = 3). The media decline in cohort 2 was –0.21 log10 IU/ml (range –2.51 – –0.02) after 6–18 weeks treatment (n = 11). One patient obtained HBsAg loss only receiving 2 doses of PD-1 antibody in cohort 2. All 22 patients were included in the safety analysis. In total, 51 AEs were reported in 100% (3/3), 20% (1/5) and 75% (3/4) patients in Peg-IFNα group, PD-1 antibody group and Combined group of cohort1, respectively. In cohort 2, 17 AEs were reported in 30% (3/10) patients during firsts 12weeks PD-1 antibody therapy. Peg-IFNα was added to 3 patients at the 12-week evaluation, and 10 AEs were reported in all these 3 patients. There was no study drug-related serious adverse event (SAE).

Conclusion: PD-1 antibody or combined with Peg-IFNα was shown to be safe and well-tolerated in CHB patients according to our preliminary data. And more comprehensive data in our study later will provide evidence to verify the safety and efficacy of this strategy in promoting clinical cure.

THU-256

The safety and antiviral effect of oral daily 300 mg ALG-000184 in combination with Entecavir for up to 96 Weeks in untreated HBeAg-positive subjects with chronic hepatitis B virus infection

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Background and aims: ALG-000184 is a prodrug of ALG-001075, a highly potent capsid assembly modulator-empty (CAM-E) that has been shown in vitro to induce the formation of empty capsids, inhibit hepatitis B virus (HBV) replication, and prevent the establishment/replenishment of cccDNA.

Method: ALG-000184-201 is a multi-part, multi-center, randomized clinical trial evaluating the safety, pharmacokinetics, and antiviral activity of ALG-000184 in healthy volunteers and subjects with untreated chronic HBV infection (NCT04536337). Here, we report safety and antiviral activity data from untreated HBeAg+ subjects who received 300 mg ALG-000184 plus entecavir (ETV) for ≤96 weeks.

Results: 15 subjects were enrolled from Chinese sites and randomly assigned to the active (ALG 000184 + ETV, n = 12) or placebo arm (placebo of ALG-000184 + ETV, n = 3) for 12 weeks of treatment, followed by open label daily 300 mg ALG-000184 plus ETV for ≤96 weeks in all subjects. All subjects were Asian (mean age 31.4 years, HBV genotype B or C). 7 of 15 subjects had persistent normal ALT levels during screening. The mean levels of HBV markers at baseline were HBV DNA 8.1 $\log_{10}$ IU/mL, HBV RNA 6.7 $\log_{10}$ copies/mL, HBsAg 4.4 $\log_{10}$ IU/mL, HBeAg 3.0 $\log_{10}$ PEI U/mL, and HBcrAg 8.3 $\log_{10}$ U/mL, respectively. The mean reduction of HBV DNA at Week 12 was higher in the active arm than in the control arm (5.1 $\log_{10}$ IU/mL vs. 3.8 $\log_{10}$ IU/mL with ETV alone). Adding 300 mg ALG 000184 to ETV after Week 12 led to similar HBV DNA reductions at Week 24 as in the active arm. Nine subjects in the active arm received at least 48 weeks of treatment. Among them, maximum mean reduction in HBV DNA was 7.0 $\log_{10}$ IU/mL. The numbers of subjects who achieved HBV DNA <10 IU/mL at Weeks 48, 72 and 96 were 3/9, 4/8, and 4/5, respectively. All subjects achieved HBV RNA suppression (<200 copies/mL) by Week 28. Maximum mean reduction of HBsAg was 0.9 $\log_{10}$ IU/mL, HBeAg 2.0 $\log_{10}$ PEI U/mL, and HBcrAg 2.3 $\log_{10}$ IU/mL. The safety profile was favorable with no serious adverse events reported. One subject experienced a Grade 3 TEAE of ALT elevation probably associated with underlying liver progression (cirrhosis) and/or concomitant medication with known potential for hepatoxicity, which led to withdrawal. ALT levels had improved before stopping ALG-000184, showing a similar pattern of fluctuations during follow-up. All other Grade ≥3 TEAEs of ALT elevation (n = 2), eGFR decrease (n = 1), uric acid increase (n = 1), and neutropenia (n = 1) resolved during continued dosing.

Conclusion: ALG-000184, in combination with ETV for up to 96 weeks, was well tolerated and led to profound suppression of HBV DNA in untreated HBeAg+ subjects with high baseline HBV DNA levels. These results indicate the potential of ALG-000184 in different combination therapies for chronic HBV infection. Full data for 96 weeks of treatment and 8 weeks of follow-up will be shared at the EASL conference.

THU-257

Genetic prediction of causality of immune cell-mediated plasma metabolites and acute hepatitis B: a Mendelian randomization study

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Background and aims: Plasma metabolites play an important role in the progression of acute hepatitis B (AHB). Several studies have shown that metabolic reprogramming of immune cells is a key factor in chronic liver inflammation and hepatocellular damage, leading to the persistence of hepatitis B infection. This Mendelian randomization (MR) study aimed to investigate the causal relationship between immune cell-mediated plasma metabolites and AHB.

Method: Genome-wide association study (GWAS) data on plasma metabolites, AHB and immune cells were obtained from public databases. Five methods were used for analysis: inverse variance weighted (IVW), weighted median estimation, Mendelian randomization (MR)-Egger regression, single model and weighted model. Among them, the IVW method was used as the main analysis method to determine the causal relationship between metabolites and AHB, sensitivity analysis was used to evaluate the reliability of the MR results, the stability of the MR results was assessed using the leave-one-out method, and mediation analysis was used to explore the mediating role of immune cells.

Results: Our analysis identified a causal relationship between 56 plasma metabolites and AHB. 4-methylguaiacol sulfate levels (OR_{IVW} = 1.517; 95% CI (2.0770–10.0109); P < 0.001) 1-methylnicotinamide levels (OR_{IVW} = 1.91; 95% CI (1.06–3.44); P = 0.032), Cortisone to cortisol ratio ($OR_{IVW=}$2.34; 95% CI (1.06–5.19); P = 0.032)), etc. 10 metabolites play a key role in the progression of acute hepatitis B. Further mediation analysis showed that CD38 on naive-mature B cell (mediation effect accounted for 7.37% of the total effect, 95% CI: –2.36%, 17.1%) partially mediated the effect of 4-methylguaiacol sulfate levels on AHB, CD4 on CD39+ secreting Treg (–6.1%, 95% CI: 0.738%, –12.9%) partially mediates the association between 1-methylnicotinamide levels and AHB, and HLA DR on CD14- CD16- (4.3%, 95% CI: –1.38%, 9.98%) partially mediates the association between Cortisone to cortisol ratio and AHB.

Conclusion: This MR study provides evidence supporting a causal relationship between immune cell-mediated plasma metabolites and AHB. Immune cell-mediated identification of plasma metabolites with potential causal effects on AHB has been proposed as a potential therapeutic target for acute hepatitis B.

THU-258

Patient characteristics and treatment patterns amongst hepatitis D patients: results from a real-world survey in Europe

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Background and aims: While data are readily available on antiviral drugs treating hepatitis B virus (HBV), real-world evidence on bulevirtide (BLV) – the first antiviral drug for the treatment of hepatitis D virus (HDV) – is lacking. We aimed to describe demographics, clinical characteristics, and treatment adherence of HDV patients receiving treatments including BLV.
Method: Data were drawn from the Adelphi Real World Hepatitis Disease Specific Programme™, a cross-sectional survey, with retrospective data collection, of physicians and patients with HDV in France, Italy, Spain and the United Kingdom (UK) from February 2024 to November 2024. Analysis focused on physician reported demographics, clinical characteristics and adherence for up to four consecutively consulting patients with chronic hepatitis D, with two prescribed BLV. Analyses were descriptive.
Results: Overall, 127 physicians reported data on 369 patients. Mean patient age was 45.9 (SD 13.0) years, 70% were White, 66% male. Mean (SD) time since diagnosis of HBV and HDV was 6.8 (9.1) and 4.7 (6.7) years, respectively. At survey, 65% of patients were reported to have mild HDV, 29% moderate and 6% severe. A third (33%) of patients in this study sample were not prescribed HDV treatment (No HDV Tx), 57% were treated with BLV monotherapy (mBLV), 6% had Peginterferon/interferon monotherapy (mIFN) and 2% had both therapies. Concomitant conditions were present in half of patients (mBLV: 53%; mIFN: 48%; No HDV Tx: 57%), including anxiety (mBLV: 13%; mIFN: 29%; No HDV Tx: 21%), chronic pulmonary disease (mBLV: 9%; mIFN: 10%; No HDV Tx: 10%) and diabetes without chronic complications (mBLV: 8%; mIFN: 5%; No HDV Tx: 7%). A similar range of patients had liver cirrhosis across the groups (mBLV: 15%; mIFN: 14%; No HDV Tx: 20%). The most common reasons for prescribing current treatment were long-term efficacy (mBLV: 64%; mIFN: 52%) reduction in viral shedding (mBLV: 58%; mIFN: 62%) and reduction in HDV transmission (mBLV: 53%; mIFN: 43%) Longer acting medication and less frequent administration were reported as treatment improvement areas for 24% and 23% of mBlV patients, respectively and for 19% and 5% of mIFN patients, respectively. Physicians stated most patients (mBLV: 80%; mIFN: 81%) were completely or mostly adherent to treatment, with only 15% of mBLV, and 14% of mIFN having poor adherence.
Conclusion: Analysis of physicians' data showed that half of the patients with chronic HDV had a high comorbidity burden, most HDV treated patients received BLV monotherapy, and the majority were adherent to treatment. Prescribers treat HDV with BLV or IFN due to their long-term efficacy in reducing viral shedding and transmission. Physicians reported a remaining unmet need for longer-acting medication with a less frequent dosing schedule and further research is needed into factors affecting high patient adherence to BLV.

THU-259

Up to 18 months' functional cure in response to bepirovirsen therapy in B-Clear On-NA responders: B-Sure third report

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Background and aims: Bepirovirsen (BPV) is an unconjugated antisense oligonucleotide currently in Phase 3 for the treatment of chronic hepatitis B virus (HBV) infection. Data from a Phase 2b study (B-Clear) indicated that a subset of participants (pts) achieved a response at the end of BPV treatment, which was sustained for 24 weeks. This occurred in pts on and not on nucleos(t)ide analogues (NA) (On-NA and Not-on-NA). Pts who had a complete (CR) or partial (PR) response at the end of the B-Clear (parent) study were eligible for the B-Sure long-term durability study (NCT04954859; ongoing). Here we present up to 2.5-year follow-up data on the durability of response for B-Clear On-NA complete responders (CRs) and partial responders (PRs) who entered B-Sure.
Method: CR was defined as hepatitis B surface antigen (HBsAg) <0.05 IU/mL and HBV DNA < lower limit of quantification (LLOQ, <20 IU/mL), and PR as HBsAg <100 IU/mL and HBV DNA <LLOQ at the end of B-Clear. If eligible, pts discontinued NA 3 months (mo) into B-Sure (≥9 mo from their last BPV dose) and were followed further to determine functional cure (FC) and durability of response off all HBV therapy. Adverse events (AEs) were recorded, with physical examinations and blood tests performed at each visit for safety and efficacy, including time from NA cessation to loss of response.
Results: In total, 44 pts (11 CRs, 29 PRs and 4 non-responders) were enrolled into B-Sure; 33/44 (75%) were male, with a mean age of 53.8 years, and 24/44 (55%) were Asian. At entry into B-Clear, the majority of pts were hepatitis B e-antigen (HBeAg) negative (34/44 [77%]), 19/44 (43%) had HBV duration of ≥20 years and 32/44 (73%) had HBsAg ≤1000 IU/mL. Of the 11 CRs, 9 (82%) discontinued NAs 3 mo after rollover into B-Sure; 7/9 (78%) maintained a CR to 6 mo post–NA cessation, thus achieving FC, and all 7 maintained FC to 24 mo post–NA cessation. Of the 2 pts who did not achieve FC at 6 mo post–NA cessation, 1 had restarted NA therapy by 24 mo post–NA cessation. Of the 29 PRs, 23 (79%) discontinued NAs 3 mo after rollover into B-Sure. 3/23 (13%) achieved delayed FC 6 months post–NA cessation and were maintaining FC at 24 months post–NA cessation. 5/23 (22%) maintained PR status at 6 mo post–NA cessation, 3/23 (13%) at 9 mo post–NA cessation and 2/23 (9%) at 24 mo post–NA cessation; all 3 losses of PR beyond 6 mo post NA cessation were due to HBV DNA reversion. Among 23 PRs who discontinued NAs, 13 had restarted NA therapy by 24 mo post–NA cessation. Of all CRs/PRs who discontinued NAs, 5 had alanine aminotransferase (ALT) ≥2x upper limit of normal (ULN). After NA cessation, no pt who continued without needing to restart NA had an ALT increase of >5 × ULN. Post–NA cessation 3 pts reported AEs of ALT increased (2 with mild severity, 1 with moderate severity). There were no new safety signals.
Conclusion: These data provide evidence of longer durability of FC observed with BPV.
Funding: GSK (206882; NCT04954859).

THU-260

IM-PROVE I: characterization of chronic hepatitis B (CHB) subjects with functional cure or HBV DNA suppression after completion of imdusiran plus short courses of pegylated interferon alfa-2a (IFN) and discontinuation of nucleos(t)ide analogue (NA) therapy

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Background and aims: Baseline (BL) characteristics of study subjects and biomarker levels at key timepoints that predict functional cure (FC, defined as sustained HBV DNA <LLOQ and HBsAg loss 24 weeks after treatment cessation) in subjects who complete finite courses of experimental treatment for CHB remain unclear. Low levels of HBsAg at BL (specifically <1000 IU/mL) appear to be associated with increased HBsAg loss and FC rates, but other factors have not yet been identified.

Method: The IM-PROVE I study was a Phase 2a proof-of-concept study in 43 NA-suppressed, HBeAg-negative CHB subjects who received 4 doses of imdusiran (60 mg every 8 weeks) prior to randomization to 24 weeks or 12 weeks of IFN with or without additional imdusiran doses. Eligible subjects discontinued (d/c) NA therapy 24 weeks after end-of-treatment. Six subjects in this study achieved functional cure after NA d/c; 3 additional subjects had HBV DNA <LLOQ with low HBsAg levels during NA d/c follow-up. Further characterization of these subjects including all available demographic and baseline characteristics, HBV treatment history, and additional HBV biomarkers such as HBV and IL28b genotypes (GT), hepatitis B core-related antigen (HBcrAg) via Fujirebio Lumipulse G (LLOQ = 1.0 kU/mL), and HBV RNA via Abbott v2.0 RUO assay (LLOQ = 0.49 log10 U/mL or 3.0 U/mL), are presented at key timepoints during the study.

Results: Among the 6 subjects who achieved FC, mean (±SD) age was 51 (±2.8) years, 3/6 were male, 5/6 were Asian, and ongoing NA therapy at BL included 1/6 on entecavir and 5/6 on tenofovir based-therapy, with a mean (±SD) duration of current NA treatment of 7.8 (±2.6) years. HBcrAg was <LLOQ in 4/6 at BL (range <1.0–8.4 kU/mL) and at NA d/c (range <1.0–4.8 kU/mL); HBV RNA was <LLOQ in 1/6 at BL (range <3.0–478.6 U/mL) and in 5/6 at NA d/c (range <3.0–8.31 U/mL). HBsAg at BL was <1000 IU/mL in 5/6 subjects, and at time of NA d/c was ≤LLOQ in the same 5 subjects; all 5 had anti-HBs levels >25 mIU/mL. Two of the 6 subjects had IFN dose reductions to 90 mcg/week with dose interruptions of 6–8 weeks due to ALT increase and/or neutropenia, while the other 4 had no dose adjustments. The BL characteristics of the 3 subjects with HBV DNA <LLOQ/low HBsAg after NA d/c were similar with the exception of HBsAg and anti-HBs at time of NA d/c (0/3 were HBsAg <LLOQ and 1/3 had anti-HBs > 25 mIU/mL). HBV GT was B or C in those with available data, and host IL28b genotype (rs12979860) was C/C in 5/6 and 2/3 in FC and HBV DNA <LLOQ subjects respectively, but the majority of study participants were C/C (26/36 with available data).

Conclusion: Within this small group of subjects who achieved FC or HBV DNA<LLOQ after NA discontinuation in the IM-PROVE I study, HBsAg at baseline and at the time of NA d/c appear to be the only factors associated with FC, with no apparent differences in other baseline characteristics or HBV biomarkers collected, including HBcrAg and HBV RNA. Additional analysis of this dataset is ongoing, and these BL characteristics and HBV biomarkers should continue to be evaluated in larger trials.

THU-261

Monotherapy with the novel capsid assembly modulator ALG-000184 for up to 96 weeks results in profound and sustained HBV DNA suppression in untreated subjects with chronic HBV infection

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Background and aims: ALG-000184 is a prodrug of ALG-001075, a highly potent capsid assembly modulator-empty (CAM-E) that has been shown in vitro to induce the formation of empty capsids, inhibit hepatitis B virus (HBV) replication, and prevent the establishment/replenishment of cccDNA.

Method: ALG-000184–201 is a multi-part, multi-center, randomized clinical trial evaluating the safety, pharmacokinetics, and antiviral activity of ALG-000184 in healthy volunteers and in subjects with untreated chronic HBV infection (NCT04536337). Here, we report safety and antiviral activity data in untreated HBeAg+ and HBeAg- subjects who received open-label monotherapy with 300 mg ALG-000184 for ≤ 96 weeks.

Results: 21 subjects (n = 10 HBeAg+, n = 11 HBeAg-) received 300 mg of ALG-000184 monotherapy for ≥ 48 weeks and ≤ 96 weeks. HBeAg+ subjects were younger, with more Asian patients, and lower BMI than HBeAg- subjects. Higher baseline levels of HBV markers were seen in HBeAg+ subjects vs HBeAg- subjects, with a mean HBV DNA level 8.0 vs 4.3 $\log_{10}$ IU/mL, HBV RNA 5.3 vs 2.0 $\log_{10}$ copies/mL, HBsAg 4.3 vs 3.5 $\log_{10}$ IU/mL, and HBcrAg 8.3 vs 3.2 $\log_{10}$ U/mL, respectively. The mean baseline level of HBeAg in HBeAg+ subjects was 2.6 $\log_{10}$ PEI U/mL. By Week 96, maximum mean reductions in HBV DNA were 7.3 (HBeAg+) and 3.4 $\log_{10}$ IU/mL (HBeAg-), with individual maximum reductions of 8.0 and 4.4 $\log_{10}$ IU/mL, respectively. At Weeks 48, 72 and 84, 60% (6/10), 8/9 (89%), and 7/7 (100%) subjects achieved sustained HBV DNA < 10 IU/mL (lower limit of quantification, LLOQ). All HBeAg- subjects (11/11) achieved sustained HBV DNA < LLOQ by Week 24, and 10/11 achieved HBV DNA < 4.29 IU/mL (lower limit of detection) by Week 48. The maximum mean reductions from baseline in HBsAg was 1.2 $\log_{10}$ IU/mL; HBeAg 1.7 $\log_{10}$ PEI U/mL; and HBcrAg 2.6 $\log_{10}$ U/mL in HBeAg+ subjects. A maximum mean reduction of 0.4 $\log_{10}$ U/mL from baseline in HBcrAg was observed in HBeAg- subjects. No clinical viral breakthrough, as assessed by HBV DNA levels, occurred in any subject. Treatment was well tolerated with no serious adverse events (AEs) reported and without any discontinuations due to treatment-emergent AEs (TEAEs). Grade 3 TEAEs were reported in four subjects: asymptomatic ALT elevations (HBeAg+: n = 3; HBeAg-: n = 1) and cholesterol/triglycerides increase

(n = 1), all resolving with continued dosing. All Grade 3 ALT elevations occurred along with a significant decline in HBV DNA, without associated changes in other liver function parameters.
Conclusion: ALG-000184, in combination with ETV for up to 96 weeks, was well tolerated and led to profound suppression of HBV DNA in untreated HBeAg+ subjects with high baseline HBV DNA levels. These results indicate the potential of ALG-000184 in different combination therapies for chronic HBV infection. Full data for 96 weeks of treatment and 8 weeks of follow-up will be shared at the EASL conference.

THU-262
Quality of life in HDV-infected patients prior to bulevirtide treatment: chronic hepatitis versus compensated cirrhosis
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Background and aims: Delta hepatitis is endemic in Romania and, until recently, lacked effective treatment options, making it the leading indication for liver transplantation in the country. This study evaluates the quality of life (QOL) in HDV-infected patients prior to initiating bulevirtide therapy, comparing those with chronic hepatitis and compensated cirrhosis.
Method: Patients meeting the criteria for bulevirtide treatment were enrolled in the study. Before therapy initiation, participants completed a standardized quality of life questionnaire – HQLQv2™. Demographic data, along with HBV and HDV viral loads, were collected. Statistical analyses were conducted using SPSS IBM 29.0.
Results: A total of 45 patients were included (mean age 52.1 ± 12.6 years); 80% had compensated cirrhosis, and 20% had chronic hepatitis. Undetectable HBV viremia was observed in 53.7% of patients (58.8% in cirrhotics vs. 20.8% in CHD, p = 0.219), with a mean HDV RNA level of 1,186,550 ± 3,316,474 IU/mL. Although no significant differences were found in overall health status, 39.1% of cirrhotics reported limitations in daily activities, compared to none in CHD (p = 0.153). Emotional symptoms, including melancholia (54.8% vs. 0%, p = 0.046), discouragement (41.8% vs. 11.2%, p = 0.082), stress (60.6% vs. 11.1%, p = 0.02), and frustration (51.3% vs. 0%, p = 0.082), were more prevalent among cirrhotics. Conversely, CHD patients reported feeling energetic (77.8% vs. 49.8%, p = 0.013) and viewing life positively (88.9% vs. 52.1%, p = 0.103) more frequently. Correlations were identified between cirrhosis and melancholia (p = 0.005), illness susceptibility (p = 0.05), frustration (p = 0.069), and social difficulties (p = 0.094). Detectable HBV viremia was linked to increased illness susceptibility (p = 0.096), and higher HDV RNA levels correlated with functional impairments, such as difficulty carrying a shopping bag (p = 0.031), walking 1 km (p = 0.106), and expecting disease progression (p = 0.048).
Conclusion: Patients with compensated cirrhosis exhibit a poorer quality of life compared to those with chronic hepatitis, with significant correlations between clinical markers and QOL parameters. A reassessment of QOL after six months of bulevirtide treatment is strongly recommended to evaluate the therapy's impact.

THU-263
Besifovir reduces hepatocellular carcinoma risk compared to Tenofovir Disoproxil Fumarate: large-scale cohort study
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Background and aims: Besifovir dipivoxil maleate (BSV) is a newly developed acyclic nucleotide phosphonate derivative. A recent study using a predictive model highlighted a significantly reduced hepatocellular carcinoma (HCC) risk with BSV. This study aims to further evaluate whether BSV reduces HCC incidence compared to TDF, utilizing clinical big data from the Korean healthcare system.
Method: A total of 32,383 individuals were analyzed, comprising 2,358 patients in the BSV group and 30,025 in the TDF group. To minimize confounding effects, propensity score matching was conducted in a 1:3 ratio.
Results: The incidence rate ratio for HCC was 1.59 (95% CI: 1.20–2.12, p = 0.001). The hazard ratio (HR) for HCC in the TDF group compared to the BSV group was 1.703 (95% CI: 1.282–2.262, p < 0.001). In Cox regression analysis, the HR for cirrhosis in the TDF group was significantly lower than in the BSV group, with an HR of 0.670 (95% CI: 0.597–0.753, p < 0.001).
Conclusion: This analysis suggests that BSV is more effective than TDF in reducing the incidence of HCC.

THU-264
Safety and pharmacokinetics of bepirovirsen, delivered subcutaneously by vial, or prefilled syringe fitted with a safety syringe device in healthy adult participants, and syringe device ease of use: a randomised phase 1 trial
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Background and aims: Bepirovirsen is an unconjugated antisense oligonucleotide in Phase 3 development for the treatment of chronic hepatitis B virus infection. Currently, bepirovirsen is supplied in clinical trials as a clear glass vial for subcutaneous injection. A ready-to-use prefilled syringe (PFS) assembled with a safety syringe device (SSD) has been developed to make administration more convenient (vs vial) and facilitate patient self-administration. The formulation of bepirovirsen is identical between the vial and the PFS SSD. This study aimed to evaluate the safety, tolerability and relative bioavailability of bepirovirsen when delivered by subcutaneous injection from a vial or PFS SSD, and the ease of use of the PFS SSD for self-administration. Here, we report safety, topline pharmacokinetic (PK) and PFS SSD ease-of-use data.
Method: In this Phase 1, open-label, randomised, parallel group study, 160 healthy adult participants were randomised 3:3:2:2 to receive a single 300 mg dose of bepirovirsen from a vial by a healthcare professional (HCP; Group 1), or PFS SSD administered by an HCP (Group 2), or self-administered PFS SSD with training from an HCP (Group 3), or self-administered PFS SSD without training (Group 4). Participants in Groups 3 and 4 were also provided with instructions for use. All participants were monitored for adverse events (AEs) and had PK samples collected. Participants in Groups 3 and 4 completed an ease-of-use questionnaire, which contained multiple-choice questions relating to the ease of self-administration of the PFS SSD.
Results: Of the total population, 159/160 participants were included in the safety population, and 153/160 participants were included in the PK population. In total, 94% (150/159) of participants reported AEs, with similar proportions of participants reporting AEs across all treatment groups (88–100%). There were no serious or fatal AEs. AEs of special interest made up the majority of AEs reported, largely due to injection site reactions (148/159 [93%]). Most AEs were Grade 1/2 in severity. The majority of participants reported that the PFS SSD for

self-administration was very easy or easy to use both with and without HCP training (81–100% and 67–94%, respectively). Bepirovirsen PK was similar across all treatment groups.
Conclusion: Participants were able to self-administer bepirovirsen using the PFS SSD, and it had a similar safety profile whether administered by an HCP or a participant, with no new safety concerns identified for bepirovirsen. The use of PFS SSD is a viable alternative for bepirovirsen administration in patients. The PK of bepirovirsen was similar across all treatment groups.
Funding: GSK (study 219239).

THU-269

Interim results of a phase I/II study to determine the safety, immunogenicity and efficacy of therapeutic hepatitis B virus synthetic long peptide vaccination

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Background and aims: Immunotherapy is emerging as a pivotal component of HBV cure strategies as it may both increase on-treatment response and off-treatment durability of response obtained with novel antivirals. Synthetic long peptide (SLP) vaccines represent an innovative approach to stimulating robust T-cell responses. These vaccines contain carefully designed peptides representing viral epitopes capable of inducing both CD4+ and CD8+ T-cell responses. By targeting conserved and immunodominant regions of the hepatitis B virus (HBV), SLP vaccines have the potential to be included in a multidrug combinatorial treatment regime to overcome immune tolerance and re-establish effective viral control. We aimed to study safety and immunogenicity of SLP vaccination in virally suppressed patients with chronic hepatitis B (CHB).
Method: This ongoing single-center, double-blind, placebo-controlled, dose-escalation Phase I/II clinical trial investigates the safety, tolerability, and immunogenicity of 12 SLPs, along with the TLR1/2 ligand-based adjuvant Amplivant® in 24 patients. Eligible participants are HBeAg-negative CHB patients without significant fibrosis who have been on nucleos(t)ide analog (NUC) therapy > 1 year and have undetectable HBV DNA at time of screening. The trial includes three dose-escalation cohorts, each testing a different vaccine dose (10 µg, 20 µg, or 40 µg) Each cohort will consist of eight participants, with six receiving the vaccine and two receiving a placebo.
Results: In the first 9 patients (qHBsAg 1237 IU/ml ± SD 1302) dosed with 10 ug, 20 ug or placebo (n = 2–3 out of 9) possible TAEA events observed were: injection site adverse events (n = 6), fatigue (n = 2) and pyrexia (n = 1). Baseline and Post-vaccination T cell responses to the vaccine were measured by overnight IFN-y ELISpot in blood samples from the first 6 patients included (receiving either 10ug of vaccine or placebo (max n = 2 out of 6)). Increased IFN-y responses relative to baseline were observed in 2 out of these 6 patients. Result will be updated as they become available.
Conclusion: Preliminary results from this ongoing trial suggests that this SLP vaccine has a favorable safety profile, with the main TEAE injection site reactions. Potential induction of an IFN-y immune response was observed in a subset of patients. These results support further escalated dosing and efficacy evaluation of this promising new treatment modality. Further analysis of the induced immune response will provide data on the best combinatorial regime to fully realize the potential of this immunotherapeutic approach in re-establishing antiviral immunity and achieving functional cure.

THU-270

HBV genotype association with response to xalnesiran in nucleos(t)ide analogue treated participants with chronic hepatitis B infection in the Piranga phase 2 platform study

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Background and aims: The global distribution of hepatitis B virus (HBV) genotype (GT) varies significantly among patients with chronic hepatitis B (CHB). HBV GTs are associated with disease severity and response to approved antiviral therapy. Therefore, the early identification of HBV GTs that could impact the efficacy of novel direct-acting antivirals is essential. The Piranga phase 2 platform study (NCT04225715) assessed the efficacy and safety of multiple combinations of new molecules in nucleos(t)ide analogue treated participants (pts) with CHB. We report the association between HBV GT and HBsAg response to treatment with xalnesiran, a GalNAc-conjugated small interfering ribonucleic acid targeting HBsAg transcripts.
Method: Data from 126 pts were pooled across 4 arms of Piranga, which started with a 12-week period of treatment with xalnesiran 200 mg Q4W monotherapy. Pts were recruited in 11 countries across Asia-Pacific, Europe, and North America. HBV GT was determined using HBV RNA sequencing, HBsAg serotyping, and/or medical history. HBV RNA sequencing was performed using Illumina short-read sequencing and HBV GT was determined by homology with reference sequences. HBsAg serotyping was performed using the IMMUNIS® HBV genotype enzyme immunoassay which detects GT-specific epitopes in the preS2 region. GT-specific distributions of baseline and change from baseline in HBsAg levels after 12 weeks of treatment with xalnesiran were evaluated in all pts and stratified by low (<1000 IU/mL) vs. high HBsAg at screening.
Results: HBV RNA sequencing and HBsAg serotyping failed in 102 (81.6%) and 19 (15.2%) of 125 tested samples, primarily due to poor RNA amplification and HBsAg <3 IU/mL, respectively. The concordance rate between assays was 20/22 (91%). Among 126 pts, 6 GTs were observed, the most frequent being C (61, 48.4%), B (27, 21.4%), and D (18, 14.3%). The distribution of HBV GTs across regions matched with known global distributions. The mean of HBsAg at baseline was lower for GT B (2.57 $\log_{10}$ IU/mL) than for GTs C and D ($p < .01$). Among pts with low HBsAg at screening (18, 22, and 7 pts in GTs B, C, and D, respectively), the reduction of HBsAg after 12 weeks of treatment with xalnesiran was lower for GT D than for GTs B and C: 0.60 vs. 1.35 and 1.15 $\log_{10}$ IU/mL, respectively ($p < .001$). This association was significant in the overall group as well, with reductions of HBsAg of 0.84 vs. 1.26 and 1.17 $\log_{10}$ IU/mL for GTs D vs. B and C, respectively ($p < .01$).
Conclusion: Treatment with xalnesiran led to a marked reduction in HBsAg levels across all GTs. In this exploratory analysis with limited sample size, GT D was associated with a smaller reduction in HBsAg after 12 weeks of xalnesiran treatment than for GTs B and C, mainly among pts with low HBsAg. HBV GT should be considered a potentially important factor in studies testing novel direct-acting antivirals aiming to achieve functional cure.

Viral Hepatitis C – Clinical aspects including follow up after SVR

TOP-266

Association between sustained virological response and adverse liver-related outcomes in patients with decompensated HCV cirrhosis

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Background and aims: Sustained virological response (SVR) improves prognosis in chronic hepatitis C virus (HCV) infected patients with compensated liver disease, but whether similar benefit can be obtained in patients with decompensated cirrhosis is controversial. Therefore, we studied whether SVR was associated with a reduced risk of liver-related events (LREs) in patients with decompensated HCV cirrhosis.
Method: We conducted an international multicenter retrospective cohort study including patients with decompensated HCV cirrhosis (Child-Turcotte-Pugh (CTP) ≥7 and/or history of decompensation) treated with direct-acting antivirals (DAA). Survival analyses were used to assess the association between SVR and LREs (defined as a composite of further decompensation, hepatocellular carcinoma (HCC), liver transplantation (LT) or death) in the overall population and stratified by baseline MELD score. Additionally, the association between SVR related change in MELD score with LREs was assessed.
Results: In total, 914 patients were included with a median age of 54.7 (IQR 48.8–60.8) years, 68% was male, 45% had (a history of) alcohol abuse, 87% was CTP-B, and the median MELD score was 12.1 (IQR 10.0–14.5). SVR was achieved in 834 (91.2%) patients during the study period. Median follow-up time was 28 (IQR 13–39) months. In the overall population, the 3-year cumulative incidence of LREs was lower in patients who attained SVR compared to those who did not (47.5% vs. 58.6%, $p < 0.001$). Findings were consistent in multivariable analysis (adjusted hazard ratio (*a*HR): 0.692, 95%CI 0.52–0.92, $p = 0.011$). Stratification by baseline MELD revealed that SVR was associated with a reduced 3-year incidence of LREs amongst patients with a baseline MELD <15 (44.4% vs. 57.6%, *a*HR: 0.601, 95%CI 0.43–0.85, $p = 0.004$), but not amongst patients with a baseline MELD ≥15 (62.8% vs. 58.9%, *a*HR: 0.936, 95%CI 0.56–1.56, $p = 0.801$). Amongst patients with SVR, 23.4% achieved a decrease in MELD score of ≥2 points. A ≥2 point decrease in MELD score was not associated with a reduced 3-year incidence of LREs compared to patients with a stable or increased MELD score (52.1% vs. 50.7%, $p = 0.473$). Findings were consistent in multivariable analysis (*a*HR: 0.730, 95% CI 0.49–1.09, $p = 0.122$), and in the subset of patients with a MELD score ≥15 at baseline.
Conclusion: Amongst patients with decompensated HCV cirrhosis, SVR was associated with a reduced risk of LREs in patients with a MELD score <15, whereas no clinical benefit was observed in those with higher MELD scores despite an SVR associated decrease in MELD. These findings provide important guidance for the timing of DAAs versus potential liver transplantation in decompensated HCV cirrhosis.

TOP-267

Refining HCC risk prediction in non-ACLD chronic hepatitis patients after antiviral therapy: insights from a multicenter study

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Background and aims: Hepatocellular carcinoma (HCC) surveillance is recommended for chronic hepatitis C (CHC) patients with advanced liver disease (ACLD) after achieving sustained virological response (SVR). However, the risk of HCC persists in non-ACLD CHC patients, who are often outside the current surveillance scope. This study aimed to identify high-risk HCC patients within a non-ACLD population using a simple stratification algorithm feasible for primary care settings and validated in external cohorts.
Method: CHC patients who achieved HCV eradication with direct-acting antiviral agents (DAA) and had pre-therapy FIB-4 scores <3.25 were enrolled from Chang Gung Memorial Hospital, Linkou Medical Center. ACLD was defined as FIB-4 ≥3.25. All patients underwent liver ultrasonography and AFP assessments every 6–12 months. HCC was diagnosed using dynamic liver imaging and/or histological confirmation. Cox regression analysis was performed to identify independent risk factors for HCC occurrence in non-ACLD patients. A predictive score (SFA score) was developed based on adjusted hazard ratios from multivariate Cox regression analysis of patients younger than 65 years and was validated in external non-ACLD cohorts from Chang Gung Memorial Hospital, Chia-Yi branch, and Chia-Yi Christian Hospital.
Results: The derivation cohort included 1902 non-ACLD patients (mean age: 59 years; 44% male; median FIB-4: 1.77, IQR: 1.26–2.36).

Validation cohorts included 3839 DAA-treated patients (mean age: 62 years; 46% male; median FIB-4: 1.71, IQR: 1.21–2.31). Over a median follow-up of 3.4 years, 29 HCC cases occurred in the derivation cohort, with annual and 5-year cumulative incidences of 0.49% and 2.8%, respectively. Multivariate Cox regression identified age ≥65 years [adjusted hazard ratio (aHR): 2.986; p = 0.005], male sex (aHR: 3.399; p = 0.005), and pre-therapy AFP ≥6 ng/mL (aHR: 10.370; p < 0.001) as independent predictors of HCC. Patients aged ≥65 years had an annual HCC incidence of 0.8%, exceeding the updated threshold for HCC surveillance (0.7%/year). Among patients aged <65 years, those with an SFA score ≥3 (1×[male:1, female:0] + 2 × [FIB-4 ≥2.5:1, <2.5:0] + 1 × [AFP ≥6:1, <6:0]) had an annual/5-year HCC incidence of 2.9%/12.8%, compared to 0.1%/2.9% for those with SFA <3 (log-rank test, P < 0.001). The model demonstrated strong predictive performance (Harrell's C-index: 0.896 in the derivation cohort and 0.837 in the DAA-treated validation cohort) and was validated in external cohorts (HCC annual/5-year incidence for SFA ≥3 vs. <3: 1.5%/4.7% vs. 0.09%/0.2%; log-rank test, P < 0.001).
Conclusion: The SFA score effectively identifies high-risk HCC patients among non-ACLD CHC patients with SVR in primary care settings. Non-ACLD CHC patients aged ≥65 years or those aged <65 with an SFA score ≥3 should continue HCC surveillance after viral eradication.

THURSDAY 08 MAY

THU-207-YI
Clinical follow up in patients treated for hepatitis C

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Background and aims: Over 80,000 people have been treated for hepatitis C in the UK since 2015, as a result of the advent of direct-acting antivirals (DAAs) and the national hepatitis C virus (HCV) elimination programme. A proportion of these patient remain at risk of developing hepatocellular carcinoma (HCC) despite achieving sustained virologic response (SVR). EASL recently issued a position paper on clinical follow-up after HCV cure. Our study aims to determine the follow-up status of patients who achieved SVR in Barts Health NHS Trust, London, UK, in line with the guidance outlined in the EASL position paper.
Method: A retrospective service evaluation of patients treated for hepatitis C at Barts Health NHS Trust since 2016 was conducted. Patients with a baseline liver stiffness measurement (LSM) ≥8 kPa and/or APRI ≥1.0 and/or documented history of cirrhosis were included. Diagnosis of steatotic liver disease (SLD), cardiometabolic risk factors and harmful alcohol intake were also recorded. Post SVR LSM and current follow-up status was assessed. Rate of HCC development and hepatitis C recurrence were documented. Patients with a baseline LSM of <8.0 kPa, APRI <1.0 or no documented history of cirrhosis were excluded.
Results: 1346 patients treated for HCV from 2016 to 2024 were reviewed, with 262 meeting the inclusion criteria. 211 patients (80.5%) had a baseline LSM of ≥10 kPa or were identified as having cirrhosis, and 51 patients (19.4%) had a baseline LSM between 8 and 10 kPa. 125 (47.7%) had a post-SVR LSM available, with 66/125 (52.8%) having a post-SVR LSM of ≥8 kPa. 46 (17.5%) patients had a harmful alcohol history documented and 92 (35.1%) had a diagnosis of SLD. Only 79 (30.1%) patients remain under hepatology follow-up and HCC surveillance, with 55 (20.9%) patients discharged and 27 (10.3%) deceased. The remaining 107 (40.8%) patients have been lost to follow-up. 4 (1.5%) patients developed a hepatocellular carcinoma (HCC).
Conclusion: We found that a significant number of HCV patients had been discharged or lost to follow-up from the Hepatology service at Barts Health NSH Trust. Many of those would require long-term follow-up or a single non-invasive assessment of their liver fibrosis status, as per the EASL position statement. Services might be required to review discharge pathways after SVR.

THU-208
Post-treatment outcomes for patients with hepatitis C cirrhosis treated through west London operational delivery network

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Background and aims: Untreated chronic hepatitis C (HCV) can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Over the last decade, the treatment paradigm has shifted to direct-acting antivirals (DAAs), which are known to be effective, but their impact on long-term mortality and HCC risk in cirrhotic patients remains unclear. It is crucial to understand the role of cofactors influencing these endpoints to improve outcomes for local populations. This study aimed to assess mortality rates and factors affecting HCC development in cirrhotic patients with a sustained viral response (SVR) after DAA treatment as well as the regression of liver fibrosis using Fibroscan data.
Method: In this retrospective regional study, electronic patient records and National Health Service (NHS) HCV registries were used to collect data, including paired pre- and post-treatment Fibroscan scores, for patients with cirrhosis and SVR 12 weeks post DAA treatment received through the West London HCV Operational Delivery Network between 2015 and 2023. Data was analysed using multiple and simple logistic regression, Kaplan-Meier analysis, and comparative statistical tests.
Results: A total of 702 patients were included in the analysis. The mortality rate was 36.6 deaths/1000 person-years with factors such as harmful alcohol use identified as significant predictors of outcome. Mortality associated with HCC occurred at a rate of 23.2 diagnoses/1000 person-years and was significantly associated with genotype 3. Fibroscan scores for 377 patients were analysed. SVR at 12 weeks resulted in a median score reduction of 6.9 kPa ($p < 0.0001$). A significant reduction in HCC occurrence was detected between scores of ≤7 kPa and ≥11.5 kPa ($chi^2 = 4.17$; $p = 0.0101$).
Conclusion: This was one of the largest studies of outcomes in patients with HCV and cirrhosis in the DAA era. Alcohol misuse and HCC are significant drivers of post-treatment mortality, highlighting the importance of holistic follow-up care. Fibroscan score reduction may be associated with increased disease-free survival, but there is not yet enough evidence to guide screening decisions. Further prospective studies could evaluate the roles of serum biomarkers, duration of infection and metabolic dysfunction-associated steatotic liver disease on post-treatment outcomes.

THU-209
Impact of hepatitis C eradication with direct-acting antivirals on metabolic and liver-related outcomes in diabetic patients

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Background and aims: Data on the long-term impact of hepatitis C virus (HCV) eradication on metabolic and liver-related outcomes in patients with type 2 diabetes (T2D) and chronic liver disease (CLD) after direct-acting antiviral (DAAs) therapy remain scarce. This study aimed to evaluate these outcomes (primary endpoint) over an extended follow-up period and their impact on overall survival (OS).
Method: All patients with T2D and HCV-related CLD treated with DAAs from April 1st, 2014, to December 31st, 2016, followed up until September 31st, 2024 at the Medicine and Hepatology Unit of the University Hospital of Messina were enrolled in the study. Demographic, biochemical and clinical features were collected for each patient at baseline and during follow-up. Regression models were applied to identify predictors independently associated with metabolic and liver-related outcomes.
Results: One-hundred eighty-two patients [53.3% males; median age 71 years (41–97); 55.5% with cirrhosis] followed for a median of 56.5 months were included in the study. Forty-six of 182 patients (25.3%) maintained clinical stability over time, 31 (17%) died and 38 (20.9%) had liver disease progression [Liver decompensation (LD) and hepatocellular carcinoma (HCC)]. One-hundred-fifty patients (82.4%) developed T2D-related complications (89 macrovascular/61 microvascular). Significant improvements in liver stiffness ($p < 0.001$), glycated hemoglobin (HbA1c) ($p = 0.004$), serum gamma-globulins ($p < 0.001$), and aminotransferase ($p < 0.001$) levels were noted at the end of follow-up. LD was associated with higher liver stiffness ($p = 0.003$), bilirubin values ($p = 0.002$) and lower LDL-cholesterol (LDL-c) levels ($p = 0.017$), while HCC with higher liver stiffness ($p = 0.003$). Kaplan-Meier analysis revealed a significant difference in HCC onset between cirrhotic and non-cirrhotic ($p < 0.001$). Major cardiovascular events were related to higher BMI ($p = 0.024$) and low LDL-c ($p = 0.043$), while peripheral artery disease to higher HbA1c ($p = 0.036$), total cholesterol (TC) ($p = 0.006$) and triglycerides (TG) ($p = 0.045$) levels. Diabetic neuropathy was associated with higher fasting glucose levels ($p = 0.03$), T2D retinopathy with lipid-lowering therapy ($p = 0.036$) and higher TC ($p = 0.04$), while diabetic nephropathy to elder age ($p < 0.001$), higher serum creatinine and HbA1c values ($p < 0.001$; $p = 0.023$). Lipid-lowering therapy showed a protective role against T2D nephropathy ($p = 0.039$). Cox regression analysis showed that higher liver stiffness ($p < 0.001$), creatinine levels ($p = 0.007$) and lower TG levels ($p = 0.03$) were independent predictors of death.
Conclusion: DAA treatment of HCV infection significantly improves liver disease and the natural course of T2D. Early intervention is crucial, as the severity of hepatic disease before starting DAA therapy could impact liver-related outcomes and OS.

THU-210
Evaluation of transient elastography and platelets count for predicting hepatocellular carcinoma in patients with chronic hepatitis C and sustained virological response to direct-acting antivirals

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Background and aims: The risk of developing hepatocelular carcinoma (HCC) in chronic hepatitis C patients with advanced fibrosis and cirrhosis remains after sustained virological response (SVR) with direct-acting antivirals (DAA). Targeting patients at the highest risk of HCC would reduce healthcare costs. Our aim was to evaluate transient elastography (TE) and platelet count as prognostic markers for HCC after SVR.
Method: A bicentric retrospective longitudinal study included patients with SVR with a liver stiffness measurement (LSM) ≥10 kPa at baseline. Baseline and 1 year after the end of treatment (EOT) LSM and laboratory results were analyzed. A survival analysis was performed to identify the HCC associated factors.
Results: 425 patients (62 ± 10 years; 65.2% female; 56.5% white non-hispanic; 36.7% diabetics; 20% clinically significant portal hypertension) were included and followed for 48 months (SD ± 23). The median baseline and 1 year LSM were 15.0 kPa (11.8–23.2) and 12 kPa (7.9–19.9) respectively. In one year, there was a 27% (2.7–43%) reduction in the median LSM. At follow-up, 6% (n = 26) developed HCC. Among these 65.4% developed HCC after 24 months after EOT and 84.6% were F4 at baseline. A greater HCC-free survival was observed for baseline [LSM <20 kPa (log-rank 17.3; $p < 0.001$), LSM <25 kPa (log-rank 16.8; $p < 0.001$) and platelets ≥ 150.000 (log-rank 14.6; $p < 0.001$)] and also for 1 year post EOT, [LSM < 20 kPa (log-rank 14.9; $p < 0.001$), LSM < 25 kPa (log-rank 13.2; $p < 0.001$) and platelets ≥150.000 (log-rank 4.8; $p = 0.028$)]. The variation in LSM did not impact on survival ($p = 0.64$). At Cox Regression analyzes, baseline platelets (HR 0.98 CI95% 0.96–0.99, $p = 0.004$), 1 year EOT platelets (HR 1.01 CI95% 1.00–1.02, $p = 0.032$) and 1 year EOT LSM (HR 1.04 CI95% 1.01–1.07, $p = 0.003$) as well as age (HR 1.06 CI95% 1.01–1.11, $p = 0.012$) were associated with HCC occurrence. At 1 year post EOT, those who fulfilled Baveno criteria (LSM ≥20 kPa and platelets <150.000) were at higher risk of HCC (log-rank 15.0; $p < 0.001$) and those who presented a LSM <10 kPa and platelets ≥150 had a better prognosis (log-rank 13.1; $p = 0.001$). Considering 1 year post EOT LSM <10 kPa and platelets ≥150 as the best prognostic scenario, among the 6% of patients with HCC (n = 26) only 11% (n = 3) fulfilled the entire favorable criteria compared to 50% (n = 13) who didńt present any favorable component of the criteria and 38% (n = 10) who presented only one component.
Conclusion: In patients with a baseline LSM > 10 kPa, neither baseline LSM or LSM variation predicted post-SVR HCC development. The evaluation of 1 year follow-up LSM associated with a platelet count, specially a LSM <10 kPa and platelet ≥150 confered a lower risk for HCC and should be considered in post-SVR HCC risk stratification.

THU-211
PRO-Link HCV: automated detection and Re-engagement of hepatitis C patients lost to follow-up. A pilot study in southern Spain

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Background and aims: Hepatitis C is recognized as a major global public health challenge by the World Health Organization (WHO). In Spain, addressing "lost-to-follow-up" patients remains a pivotal strategy to achieve elimination goals. Despite multiple attempts, traditional methods have often demonstrated limited success in re-engaging these patients. This study evaluates the outcomes of an

innovative "opportunistic" retrieval strategy integrated within the healthcare system.
Method: This prospective pilot study was conducted at two hospitals in Andalusia, Spain: the Hospital Universitario Clínico San Cecilio (Granada) and the Hospital Universitario Juan Ramón Jiménez (Huelva). It assessed a novel "opportunistic" approach to re-engage patients lost to follow-up. A daily automated process was implemented within the Laboratory Information System (LIS), generating lists of individuals with a history of positive anti-HCV antibodies and a currently available serum sample, submitted for any clinical purpose. These lists were reviewed daily to analyze electronic health records (EHR) for evidence of sustained virologic response (SVR) or previous antiviral treatment. For patients without documented SVR, HCV RNA testing was conducted using the available serum sample to confirm active viremia. This approach facilitated immediate identification and evaluation without requiring additional sample collection or direct patient contact. Clinical outcomes and follow-up actions were subsequently analyzed.
Results: Between May 2023 and November 2024, a total of 2,789 patients with positive anti-HCV antibodies were identified. Among these, 89% (2,484/2,789) had documented SVR and no apparent reinfection risk. For the remaining 305 patients, HCV RNA testing was performed on 294, identifying 95 (31.1%) as viremic, representing 3.4% of the total screened population. The majority of viremic patients were male (69.15%), with a median age of 59 years (IQR: 54–68). Among the viremic patients, 67.4% had been lost to follow-up without achieving SVR, and 31.6% had no prior confirmatory viral load test. Patient referrals originated from Primary Care (65.3%), Hospital Care (18.9%), and Emergency Services (15.8%). All viremic cases were reported to the referring physicians for evaluation and potential treatment. Of the 95 viremic patients, 67.4% (64/95) attended follow-up appointments; 60.9% (39/64) initiated antiviral treatment, while 12 declined therapy and 19 missed their appointments.
Conclusion: This study highlights the feasibility and efficacy of an "opportunistic" retrieval strategy utilizing LIS automation to identify and re-engage patients with incomplete hepatitis C diagnostic workups. By focusing on patients undergoing care for unrelated conditions, this approach streamlines re-entry into the care continuum and makes a meaningful contribution to elimination efforts.

THU-212

Overweight, but not alcohol is associated with increased risk for advanced liver disease in patients with chronic hepatitis C infection- results from the german hepatitis C-registry (DHC-R)

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Background and aims: Obesity and alcohol are important risk factors for the development of liver cirrhosis. However, their impact in patients after chronic HCV infection (cHCV) remains unknown. Data are lacking weather the co-existence of both risk factors has a supra-additive effect on disease progression. We aimed to analyze the impact of obesity and alcohol consumption in cHCV patients.
Method: Patients from the German Hepatitis C-Registry were classified into four groups according to the presence of overweight (BMI≥25 vs. BMI<25) and the presence of alcohol consumption (none, vs. any alcohol). Primary endpoint was progression to liver cirrhosis. Secondary endpoint was mortality in combination with disease progression.
Results: In total, n = 5967 patients were included after antiviral treatment. Patients with BMI≥25/no alcohol (O/nA) had an increased risk for progress of liver cirrhosis compared to BMI<25/ alcohol (L/A). In a multivariate analysis, obesity and diabetes were independent risk factors for disease progression (OR for BMI > 35 2.833 (1.682–4.771), OR for diabetes 1.489 (1.004–2.208). O/nA patients also had an increased risk for overall mortality and disease progression compared to L/A. Multivariate analysis of the secondary endpoint identified again diabetes and obesity as the only independent cardiometabolic risk factors for disease progression and mortality. Interestingly, neither alcohol consumption alone nor in combination with obesity influences disease progression.
Conclusion: In conclusion, obesity increased the risk for disease progression after cHCV infection, while neither alcohol consumption alone nor in addition to obesity impacts disease progression. Therefore, weight management in patients after cHCV is important to prevent disease progression.

THU-213

HCC risk stratification scores: insights from large multi-center national cohort study

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Background and aims: More than four million Egyptians have successfully cleared the HCV virus during the national HCV elimination program, and about 20% of them require HCC surveillance. Consequently, there is unmet need for HCC risk stratification. Several HCC risk prediction scores have been developed to tailor HCC surveillance strategies more precisely. Our aim was to evaluate the discriminative ability and clinical utility of these scores in a large multi-center national study.
Method: We conducted a multi-center retrospective study across 58 HCC screening centers across 28 governorates affiliated with the National Committee for the Control of Viral Hepatitis (NCCVH) in Egypt from the period of January 2020 till June 2024. We evaluated the predictive performance and clinical utility of several HCC risk scores.
Results: Of the 33,797 SVR-HCV patients with advanced liver fibrosis and cirrhosis, 13,632 has all the parameters of the scores. We included 8,577 are valid for the evaluation. The cohort was 56% female, with a median age of 60 years (range 53–67) and a median follow-up duration of 24 months The ALBI score showed no statistical significance (log-rank test; P = 0.21) The cumulative incidence of HCC in low, intermediate and high were 0.10, 0.09, and 0.01

respectively. The aMAP had a log-rank p-value of 0.15 which is not statistically significant. The cumulative incidence of HCC in low, intermediate and high were 0.03, 0.06, and 0.14 respectively. The FIB-4 with a log-rank p-value of 0.10, which was not statistically significant. The cumulative incidence of HCC in low, intermediate and high were 0.05, 0.10 and 0.10 respectively. Notably, GES successfully stratified the patients into low (74%), intermediate (11%), and high (15%) risk groups, with highly significant log-rank p-value < 0.01 with cumulative incidence of HCC in low, intermediate and high 0.03, 0.12 and 0.31 respectively. AFP levels <10 ug/dl (97%), 10–200 ug/dl (3%).

Conclusion: GES and changes in the AFP levels demonstrated robust performance and highly significant discriminative ability, outperforming the suboptimal results of aMAP, ALBI, and FIB-4. Applying the EASL policy statement of liver cancer screening, GES classified over 70% of patients as low-risk suggesting that these patients could either be excluded from surveillance or screened at extended intervals. This outcome could minimize patients' physical and psychological harm and markedly reduce healthcare system costs.

THU-214

An innovative peer-led, smartphone-based intervention to enhance engagement for patients with untreated hepatitis C

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Background and aims: Individuals living with hepatitis C may experience barriers accessing treatment including constrained resources, lack of means of communication and negative healthcare experiences. This study aims to evaluate use of smartphones and peer support to improve engagement with treatment.

Method: In this peer led, structured support intervention in North Central London, patients with HCV deemed the most challenging to engage were offered a smartphone and 2-year contract, peer support and bespoke social support. Eligibility criteria included those delayed longest from diagnosis to treatment, patients leaving prison without a phone, and those deemed highest risk of disengagement by our outreach team. The smartphone contract was terminated if the participant was uncontactable. Replacement phones were offered to those demonstrating engagement. Engagement and treatment outcome data were collected, patient satisfaction was assessed via survey.

Results: 47 participants were enrolled over 18 months. Year of diagnosis ranged from 1999–2023; 53% were delayed > 1 year from diagnosis and 43% were delayed for ≥5 years. Nearly 1/3 had previously failed treatment. Following the intervention, 46 (98%) patients started treatment, 39 (83%) within one month of receiving the smartphone. Of those with sufficient time to do so, 32 out of 45 (71%) participants completed treatment. 13 out of 18 (72%) participants with adequate time who were delayed ≥5 years completed treatment. 10 out of 15 (67%) participants who had previously failed treatment completed treatment. Overall, 24 (65%) participants who were enrolled with enough time to achieve cure of HCV were successfully treated. At study completion, 29 (62%) patients had an active handset; 15 handsets were lost, stolen or broken and 10 patients had received a second handset. 81% of those who had a phone at the end completed a course of treatment and 56% who did not have a phone at the end completed treatment. Participants who completed the survey rated the project's helpfulness an average of 9/10 in supporting their treatment; all agreed that it improved their wellbeing and made their life easier.

Conclusion: This intervention has had a significant positive impact in patients considered the most difficult to engage. Although unable to match a group with similar barriers who did not have a phone, there is clear benefit with most patients maintaining engagement with treatment. Those delayed ≥5 years from time of diagnosis represent a particularly disengaged subgroup and a high proportion completed treatment. Each smartphone and contract costs £326.35. Given that cost of untreated HCV includes the burden of managing advanced liver disease, earlier deaths and societal impacts[1], we propose that this is a cost saving initiative warranting further health economic analysis. Our study indicates that a simple, inexpensive technology-based intervention improves treatment outcomes, however long-term patient engagement may require additional strategies.

THU-215

Characterising prevalence and unmet needs in the setting of funded hepatitis C therapy - automated hepatitis screening in australian emergency departments can assist

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Background and aims: With availability and full funding of curative therapies for hepatitis C (HCV) in Australia, patients may remain undiagnosed or untreated. We evaluate the use of universal, automated hepatitis screening in the emergency department (ED) to determine HCV Antibody (HCV Ab) prevalence, viraemia, treatment rates and the characteristics of the untreated population.

Method: A novel pilot clinical service utilising automated universal hepatitis screening in the ED, SEARCH 3X (Screening Emergency Admissions at Risk of Chronic Hepatitis 3 Extension) was implemented in five metropolitan hospitals in Sydney, Australia during 2023–2024. A computer algorithm automatically added HCV Ab tests when an adult underwent blood draw for routine biochemistry. Serology was performed in the biochemistry autoanalyser. Data was collected on patient demographics, risk factors, prevalence of HCV Ab and HCV RNA.

Results: Of 25,045 patients tested, 529 were positive of whom 92% were contactable, 73% had a HCV RNA test and 3% were medically unfit for follow up. HCV Ab was positive in 2.1% with a younger median age (54.3 years, 54.1–64.7) and higher proportion of males (64%) compared to the tested cohort (62.8 years, 40.8–79.3 and 46% male, p < 0.00001). HCV Ab prevalence was 1.4% in overseas born (195/14,028), 2.3% in non-Indigenous Australians (238/10,330) and 11.8% (81/687) in Indigenous Australians (p < 0.00001). The diagnosis was new in 16% (64/406), and rates similar across overseas born 18% (29/160), non-Indigenous 13% (24/183) and Indigenous cohorts 17% (11/63). Overseas born patients reported significantly lower intravenous drug use rates 46% (62/135) compared to Australian born (74%, 29/199, p < 0.00001) and Indigenous patients (95%, 56/59, p < 0.00001). Viraemia was detected in 17% (67/387). Viraemia was present in 0.27% (67/25,045) and similar across Indigenous, non-Indigenous, or overseas born cohorts. Of 67 viraemic, the diagnosis was new in 36% (24) and known in 64% (43). Of the known, 29% (13) reported past treatment and 12 were people who inject drugs (PWID) suggesting reinfection. Of the 277 "ever-eligible" for treatment, 81%

(223) had been treated previously and 54 were untreated, including 24 newly detected and 30 with known diagnosis. Current PWID were significantly more likely to be viraemic compared to non-viraemic patients (46%, 23/50 vs 28%, 54/193, p = 0.0175). Viraemic patients, were more likely to have diagnosed psychiatric conditions than non-viraemic patients, (61%, 41/67 vs 47% 142/300, p = 0.00434). Of the 67 viraemic patients, 54 initiated antiviral treatment, 6 were under assessment for treatment and 7 had medical contraindications.
Conclusion: ED screening revealed high HCV Ab prevalence, high treatment rates and relatively low viraemia rates (0.27%) suggesting a successful HCV treatment program. Nevertheless, the higher viraemic rates in some cohorts suggest PWID and those with mental illness are being left behind.

THU-216

A step toward eliminating recalls and follow-up testing: first australian implementation of hepatitis C RNA reflexive testing utilising a single blood sample collected in the emergency department setting

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Background and aims: Case detection remains a challenge for hepatitis C virus (HCV) elimination. Recognised plateauing of testing and diagnosis rates suggest the need for implementation of universal screening programs, however HCV diagnostic testing methods may be a barrier. Australian guidelines recommend a sequent approach to hepatitis C diagnostic testing with an initial hepatitis C antibody (HCV Ab) serology assay, followed by molecular confirmation of active infection using polymerase chain reaction (PCR) of hepatitis C RNA. The latter often requires patient recall for a new specimen collection. This multi-step process is complicated by instances of loss to follow up and introduces inefficiencies as many recalled patients may not have active infection. Laboratories may, at first blood collection, reserve a second blood tube in advance of an antibody test to reduce patient recall, however this is not a practical solution in the context of large-scale automated universal hepatitis screening programs. We have reported findings of a novel pilot Screening Emergency Admissions at Risk of Chronic Hepatitis 3 Extension (SEARCH 3X). In this paper we describe the outcomes of a novel hepatitis C RNA reflexive testing process.
Method: SEARCH operation at two tertiary hospital sites in Sydney Australia, a computer algorithm automatically added HCV Ab tests when an adult underwent routine biochemistry testing in the Emergency Department (ED). Initial positive HCV Ab serology results were identified and if sufficient volume available (minimum 650μL), specimens were retrieved from the Cobas e801 biochemistry analyser and aliquoted for PCR testing of HCV quantitative nucleic acid on Cobas 4800 instrument. Patients were recalled for a dedicated collection to confirm the validity of the HCV RNA results obtained by reflexive testing.
Results: SEARCH tested 9,521 patients of which 255 (2.7%) were HCV Ab positive specimens eligible for reflexive HCV RNA testing. The proportion successfully tested by the reflexive methodology was 100/255 (39%) of which, 13 (13%) were positive, 86 (86%) were negative and 1 invalid. Testing could not be performed on 155 (61%) due to insufficient sample volume. Of the 99 with valid results, 70 (71%) to date, have been recalled for a subsequent HCV RNA test on a dedicated tube. Of the 13 RNA positive specimens, 12 were confirmed (one patient died). Of the 86 RNA negative, 58 (67%) were confirmed and 21 (24%) are being followed-up. Four were lost to follow up and three declined further testing. No false positive or false negative results were identified using the reflexive HCV RNA single tube methodology.
Conclusion: Reflexive HCV RNA single tube methodology was efficient in establishing a complete HCV diagnosis in 99 patients, without the need for a second blood collection. The challenge of insufficient sample volume could be mitigated by using alternative validated PCR methods for HCV RNA testing.

THU-221-YI

Sex-related differences in patients with chronic hepatitis c virus infection treated with direct-acting antiviral drugs

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Background and aims: Sex is one of the known factors influencing the risk of hepatitis C virus (HCV) infection and the natural course of disease, characterized by a higher rate of spontaneous HCV elimination, less severe fibrosis and slower progression to cirrhosis compared to men. The aim of this study was to evaluate sex-related differences in the characteristics of HCV-infected patients and to assess the impact of female sex on treatment with direct-acting antivirals (DAAs) depending on age and menopausal status.
Method: The analysis used data of the consecutive 18,986 patients, 9,457 women and 9,529 men, treated with DAA for chronic HCV infection collected in the nationwide multicenter retrospective EpiTer-2 project. Women were divided into groups according to their menopausal status, defined by the recommendations of the World Health Organization, creating three age brackets: 15–44 years (pre-menopause), 45–55 years (menopause) and >55 years (post-menopause), which were compared with age-matched men.
Results: Regardless of age, women were characterized by a significantly lower BMI and a lower percentage of genotype (GT) 3 and a significantly lower incidence of cirrhosis compared to men. Comorbidities were reported significantly less frequently in youngest women compared to men of that age (p = 0.003), while in older age groups the percentages were comparable. Depression was more common reported among women, with differences reaching statistical significance in the 45–55 (p = 0.0003) and over-55 (p = 0.0007) age groups, while other psychiatric disorders were more frequent among men. HBV and HIV coinfections, as well as alcohol and drug addiction, were significantly less common in women than in men of all ages. Women in each age group were treated significantly more often with genotype-specific regimens as compared to men. Overall, the sustained virologic response rate was significantly higher in women compared to men and amounted to 98.4% and 96.6%,

respectively ($p < 0.001$). In all age groups, statistically significant differences in the effectiveness of therapy in favor of women were documented, although the oldest group achieved the relatively lowest SVR rate. Mild adverse events were reported significantly more often by women, regardless of age with highest percentage in the postmenopausal group, while serious events and deaths were reported more often in men.

Conclusion: Women chronically infected with HCV have lower BMI, less frequent GT3 infection, less frequent co-infection with HBV and HIV, and less advanced liver disease compared to men. DAA treatment is more effective in women compared to men, regardless of age, although in postmenopausal women the effectiveness is relatively the lowest and the rate of adverse effects is the highest. Antiviral therapy should be administered as soon as possible to avoid consequences related to the loss of protective sex hormones.

THU-222

Development of a hepatitis C infection integrated care model for prisoners in chinese population

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Background and aims: In the current era of highly effective direct acting antiviral (DAA) therapy, one of the remaining obstacles to elimination of hepatitis C virus (HCV) is identification of undiagnosed individuals. Prisoners or person-in-custody (PIC) are high-risk for HCV due to criminalization of drug use and engagement in criminal activity to fund illicit drug habits. Only 35% countries with national plans for hepatitis elimination outlined interventions for HCV among prisoners. We aimed to determine the prevalence of HCV among PICs in Hong Kong and evaluate the feasibility of a prison-based integrated care model.

Method: Since 2023, we initiated an outreach program to conduct site visits to prisons in Hong Kong, which are operated by the Correctional Services Department by the Hong Kong Government. Eligible participants watched an educational video on natural history, course and implication of HCV. We then performed point-of-care (POC) test for antibody to HCV (anti-HCV) by Oraquick®. PICs with positive POC test received reflex venipuncture for HCV RNA and on-site vibration-controlled transient elastography assessment by a portable version of Fibroscan®. PICs with confirmed active HCV viremia were treated with DAA in the prison under direct observation within 4 weeks. Sustained virological response 12 weeks after DAA completion (SVR12) was evaluated by onsite POC test for HCV RNA by Xpert HCV VL Fingerstick on the Cepheid GeneXpert ® system.

Results: In this interim analysis, 11 site visits were conducted and 346 PICs were screened: median age was 42 years old, 100% male, 36.1% primary level of education, 76.5% chronic smokers, 32.7% had tattoo, 2.4% admitted history of injection drug use and half of them practiced needle sharing. The most common route of illicit drug use was inhalational. The awareness of HCV was 0% and willingness to receive treatment was 100%. A total of 17 PICs had +ve anti-HCV (anti-HCV seroprevalence rate: 4.9%). Compared to PICs without HCV exposure, those with anti-HCV+ were older (56 vs 40 years old, $p < 0.001$), more likely to had primary level of education (76.5% vs 34%, $p = 0.002$), more likely to be chronic smoker (100% vs 75.3%, $p = 0.016$), had tattoo (70.6% vs 30.7%, $p = 0.002$), had intravenous drug injection (25% vs 1.2%, $p < 0.001$), longer time in the prison (9.3 vs 5.5 years, $p = 0.003$) and longer time from release (6.8 vs 3.2 years, $p = 0.001$). Among 16 PICs with RNA +ve (viremic rate 4.6%), only 1 had HBV co-infection and 0 had HIV co-infection. The most common genotype was 6 (47.1%), followed by 1b (17.6%) and 3 (11.8%). 5/16 (32.5%) had advanced fibrosis at diagnosis (defined as liver stiffness >9.5 kPa), with 8 (47%) noted to have raised ALT. DAA was started in all 16 subjects with good tolerance. Among 7 PICs who had post-treatment evaluation, SVR12 was achieved in 100%.

Conclusion: Micro-elimination is an effective strategy to identify PICs with HCV in Chinese populations where the overall prevalence of HCV in background population is low.

THU-223-YI

Implementation of a systematic hepatitis C screening program: insights from a regional approach and its impact on diagnosis and treatment outcomes

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Background and aims: Hepatitis C (HCV) is a curable chronic viral infection. Nonetheless, there is still a high proportion of undiagnosed cases. In 2016, WHO announced the goal of HCV elimination until 2030. In line with the World Health Organization, we have implemented in our region a global HCV screening programme in 2020.

Method: A systematic, opportunistic HCV screening was adopted in patients aged 18–70 who required blood work regardless of the clinical indication. Screening was integrated across hospital wards, emergency departments and primary care from January 2020 to December 2024 via electronic health record algorithms and oral opt-out consent. Viremic patients were identified either with reflex testing wherein positive HCV antibody tests triggered HCV core antigen confirmation on the same specimen or HCV viral load on a second sample.

Results: We screened 63,299 patients from January 2020 to December 2024, upscaling HCV and found 0.42% antibody prevalence ($n = 263$) and 0.13% ($n = 80$) viremia. When analyzing the provenance, almost two-thirds ($n = 160$) of HCV-positive cases were identified in the context of hospital emergency, followed by primary care settings (29%). Viremic patients were stratified according to non-invasive liver fibrosis scores with Fibrosis-4 Index for Liver Fibrosis (FIB-4), and the AST to Platelet Ratio Index (APRI). Approximately half of these patients were at low risk ($n = 38$), followed by intermediate and high risk. The majority ($n = 69$; 85%) had transaminase abnormalities at diagnosis. However, almost one-third ($n = 22$) had no risk factor identified and 11 patients did not have hepatic function test abnormalities. Treatment was successfully completed in 34 patients, with only one first-line therapeutic failure, and 85% achieved normalization of liver tests after sustained virologic response. On the other hand, 16 treated patients (47%) showed an elevation in their lipid profile.

Conclusion: Emergency departments appear to be the most effective setting for large-scale population screening. Nearly half of the viremic patients had a low fibrosis risk by non-invasive methods, and many patients exhibited no red flags, such as risk factors or abnormal test results. This underscores the importance of implementing screening programs that enable early disease detection.

THU-224-YI

Hepatocellular carcinoma risk scores and incidence during and after hepatitis C therapy with direct antiviral agents - data from the german hepatitis C-registry (DHC-R)

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Background and aims: Hepatitis C virus infection is a risk for hepatocellular carcinoma (HCC). After successful therapy with direct antiviral agents (DAA) risk stratification is needed to decide on individualized HCC surveillance. This analysis explores follow-up and HCC incidence of all German hepatitis C registry (DHC-R) patients.
Method: In this retrospective analysis all DHC-R patients were included, that had no HCC at baseline (BL) before therapy. Patients were prospectively followed for up to 7 years. HCC risk was calculated at BL with the HCC risk calculator (Ioannou et al., 2018) and aMAP score (Fan et al., 2020).
Results: The cohort included 8,508 patients with a median age of 53 (IQR 43–61) years and 60% of whom were men. Liver cirrhosis was present in 33% of patients. The mean aMAP score at baseline predicted medium risk (52.8 SD +/– 9 points, translating as HCC risk of 1.2–3% in 3 years). According to the HCC risk calculator overall median 5-year HCC risk was 2.1 (IQR 1.5–3.5) % at BL. During the 7 years of follow-up, 152 HCCs were diagnosed. The cumulative incidence of HCC was 1.15% after 3 years, 1.47% after 5 years and 1.77% after 7 years. After 24,222 patient years of follow-up, the annual incidence was 0.63% for all patients, with 0.55% for cirrhotic and 0.08% in non-cirrhotic patients. The actual HCC incidence was lower than predicted. More than half of HCCs were diagnosed in the first two years (52% of HCCs), but the incidence remained stable throughout follow-up visits. The number of patients that were followed declined with each year (from n = 7,190 year 1 to n = 937 year 7) irrespective of abundance of liver cirrhosis, diabetes mellitus or obesity (data not shown). Patients with HCC as compared to patients without HCC had more often liver cirrhosis (88%, 29%, Chi^2 test $p < 0.001$), diabetes mellitus (22%, 9%, $p < 0.001$), a BMI > 30 kg/m^2 (21%, 15%, $p = 0.0036$) and showed fewer sustained-virological response 12 weeks after end of treatment (88%, 95%, $p < 0.001$). Male sex and age were no significant risk.
Conclusion: Cumulative HCC incidence after 3 and 5 years in DHC-R patients was lower than predicted with the HCC risk calculator and aMAP score. DHC-R is an observational registry that primarily focuses on hepatitis C and is hence probably not completely covering HCC onset and screening for it.

THU-225-YI
Systematic screening for HBV, HCV and HIV in hospitalised psychiatric patients: a feasible approach on the road towards elimination of viral hepatitis

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Background and aims: Cost-effective screening strategies for hepatitis B and C virus (HBV/HCV) are important on the road towards elimination of viral hepatitis. People with serious mental illnesses are at increased risk of these infections and human immunodeficiency virus (HIV) has similar transmission routes. We aim to assess the prevalence of these blood-borne viruses (BBV) by means of a generalised screening approach in hospitalised psychiatric patients and identify associations between BBV infections and psychiatric diagnosis.
Method: This multi-center prevalence study was conducted between 2017 and 2024 in 6 Belgian psychiatric hospitals (PH). For all newly admitted adult patients who were willing to participate, psychiatric diagnosis according to DSM-IV criteria was documented, and BBV serum testing was performed. Patients with positive serology were referred to a hepatologist or infectious disease specialist. In addition, serological data were obtained retrospectively of two forensic psychiatric centres (FPC), as a generalised BBV screening was already in place here.
Results: A total of 2213 patients were included in the study [PH: 1634 (73.8%); FPC 579 (26.2%)]. HBsAg, HCVAb, HIVAb test results were obtained in 93.1%, 97.1% and 89.7% of included patients. Psychiatric diagnoses were obtained in 4 out of 6 psychiatric hospitals for 1061 patients. In total, 20.6% suffered from a psychotic disorder, 12.8% from intranasal or intravenous (IN/IV) drug dependency, and 12.9% from a personality disorder. In total, HBsAg seroprevalence was 0.68%. HBsAg seroprevalence was higher in the FPC group ($p < 0.0001$) and in the total study population ($p = 0.0003$), compared to the general Belgian population (0.27%). HCV seroprevalence was 3.44% (74/2149). HCV seroprevalence was higher in the total study population ($p < 0.0001$), and in the PH (36/1588, 2.27%, $p < 0.0001$) and FPC group (38/561, 6.77%, $p < 0.0001$), compared to the general Belgian population (0.22%). HCV seroprevalence was higher in the FPC group compared to the PH group ($p < 0.0001$). 22/62 patients tested HCV PCR+. HCV antibodies were more prevalent in patients with IV/IN drug dependency ($p < 0.0001$). Even in the patient population where IV/IN drug dependency was not the reason of admission, HCV seroprevalence was still higher than in the GBP (1.66%, $p < 0.0001$). No associations between HBV and HIV and any psychiatric diagnoses were identified. HIV antibodies were found in 9/1986 (0.45%) of patients. Prevalence of HIV was higher in the PH group ($p = 0.003$) and in the total study population ($p = 0.002$), compared to the general Belgian population (0.17%).
Conclusion: As the seroprevalence of HBV, HCV and HIV is significantly higher in the study population than in the general Belgian population, we recommend general screening in all psychiatric hospitals as an effective and feasible strategy on the road towards elimination of viral hepatitis.

THU-226
Hepatitis C treatment in arterial hypertension is safe and highly effective: real-world study

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Background and aims: There is a bidirectional relation between arterial hypertension (AH) and chronic hepatitis C, with the former exacerbating the risk of severe liver disease while the latter leading to cardiovascular complications. Therefore, it is essential to treat hypertensive patients infected with HCV, though the data on the effectiveness and safety of direct-acting antivirals (DAAs) is scarce. This study aimed to assess the effectiveness and safety of HCV treatment with DAAs in patients with (AH).
Method: This study employed a retrospective, real-world analysis of adult patients infected with HCV who were treated with direct-acting antivirals (DAAs) in Poland between 2015 and 2023. Data were extracted from national HCV treatment registries and collected across 22 national hepatology centers. The records included information on patient demographics, comorbidities, HCV genotype, liver disease status, treatment regimens, and outcomes.
Results: The analysis encompassed 18,968 patients treated with DAAs for chronic hepatitis, including 5,976 (31.5%) diagnosed with AH. These individuals were older, more frequently women, had a higher prevalence of obesity and other comorbidities, liver function decompensation, cirrhosis, and hepatocellular carcinoma, and were more commonly infected with genotype 1b. The percentage of patients achieving sustained viral response was high and did not differ between those with and without AH in the intent-to-treat and per-protocol analysis (94.8% vs. 94.2% and 97.6 vs. 97.6%, respectively). AH was not the independent predictor of treatment failure (OR, 95%: 0.87, 0.69–1.10). The predictors of treatment failure in AH patients included genotype 3 infection, decompensated liver function, cirrhosis, thrombocytopenia, and treatment with asunaprevir +daclatasvir. Adverse events (AEs), including fatigue and anemia, were more common in hypertensive patients, with one-fifth reporting AEs. Hypertensive patients were also more prone to therapy discontinuation and had higher mortality, though no deaths were attributed to antiviral therapy.
Conclusion: Although hypertensive patients were more prone to therapy discontinuation, the vast majority of them completed it, with only one-fifth reporting adverse events, mostly fatigue. The study shows that DAAs therapy is safe and effective in hypertensive patients and underscores the need for targeted screening strategies, particularly in hypertensive individuals, to optimize treatment success and reduce the long- term burden of HCV in this population.

THU-227
Relinking lost to follow up patients with hepatitis C: a modeling approach to assess liver-related outcomes

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Background and aims: Relinking patients with hepatitis C virus (HCV) who were lost to follow-up (LTFU) represents an accessible and effective strategy to enhance HCV elimination efforts. This study aimed to model the impact of relinkage to care among LTFU patients on key outcomes over a 10-year period follow-up, including the need for liver transplantation (LT), hepatocellular carcinoma (HCC) development, and mortality, under varying treatment uptake scenarios.
Method: We developed a Markov closed cohort state-transition model to simulate the natural progression of chronic HCV in 100,000 patients who were LTFU. The model compared the impact of relinkage strategies compared to no intervention. Transition probabilities and health utilities were derived from the literature and expert consensus. The analysis assessed the 10-year relative risk reduction (RRR) for the following outcomes under three scenarios: (1) LT need, (2) HCC development, and (3) mortality.
Results: Compared to a no relinkage to care program as the baseline scenario, a 10% relinkage rate (Scenario 1) achieved a 10-year RRR of 15% for LT need, 17% for HCC development, and 30% for mortality. Increasing the relinkage rate to 25% (Scenario 2) resulted in greater RRR: 27% for LT need, 31% for HCC development, and 53% for mortality. Achieving an ideal 100% relinkage rate (Scenario 3) would reduce the relative risk of LT need, HCC development, and mortality by 41%, 35%, and 78%, respectively.
Conclusion: Our model demonstrates that relinkage programs can significantly reduce liver-related complications and mortality, highlighting their potential as a transformative public health interventions.

THU-228
Effectiveness of automatic alerts from microbiology laboratories to liver units for linking to hepatitis C treatment

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Background and aims: Automatic alerts sent from Microbiology laboratories to requesting physicians upon detecting a positive HCV RNA have become widespread in recent years. These alerts aim to reduce the number of patients with hepatitis C not linked to treatment. Their effectiveness has been minimally studied, and the limited data available has shown modest impact (56%) (D. Morales-Arraez et al. Am J Gastroenterol 2020). Our aim was to analyze the effectiveness of automatic alerts for positive HCV RNA issued from the Microbiology laboratory when sent directly to the Liver Unit for linking to hepatitis C treatment.
Method: Observational, prospective, and single-center study that included all automatic alerts sent from the Microbiology Laboratory to the Liver Unit of our center. The case manager at the Liver Unit contacted the patient and informed them of the appointments. In a single visit, medical history, physical examination, liver elastography, laboratory tests, and initiation of antiviral treatment were conducted. Sociodemographic data, clinical factors and risk behaviours for hepatitis C transmission were collected.
Results: From 04/18/2023 to 09/30/2024, 87 alerts were issued. The majority were men (82.8%) with a median age of 46 years (range: 24–96) and foreign-born (57.5%). Forty-four cases (50.6%) were previously unknown infections, and among the known cases, 20/43 (46.5%) had never been referred for treatment. Thirty-seven (42.5%) did not have stable housing. Forty-one patients (47%) reported a history of drug use, and 25 (28.7%) reported high-risk sex. Ten cases (11.5%) were excluded from treatment due to advanced age or comorbidities, and 8 were already being treated in other centers. Ultimately, 58/69 (84%) were linked to treatment. Eleven cases (15.9%) were considered uncontactable. Homelessness was the only factor independently associated with failure to link to treatment ($p = 0.018$, OR: 14.5).

Conclusion: Automatic alerts for positive HCV RNA sent from the Microbiology lab to Liver Units help identify patients with hepatitis C and allow 84% of treatable cases to be linked to treatment. The effectiveness of the alerts is much lower in the homeless population, where specific strategies are needed.

THU-229-YI

Increasing risk of hepatic decompensation in patients with HCV related liver cirrhosis during long-term follow up after sustained virological response (SVR) - data from the german hepatitis C-registry (DHC-R)

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Background and aims: Hepatic decompensation leads to a substantial amount of morbidity and mortality in patients with liver cirrhosis and chronic viral hepatitis despite a sustained virological response (SVR). In this study, we aim to identify risk factors to predict hepatic decompensation after SVR in a large, multicenter real-world cohort.
Method: We retrospectively analyzed a total of 6,714 patients achieving SVR included in the well-established German Hepatitis C Registry (DHC-R) comprising 2,021 patients with liver cirrhosis. The diagnosis of cirrhosis was based on clinical, radiological, or histological findings, and hepatic decompensation was defined by the manifestation of ascites, hepatic encephalopathy, and/or variceal hemorrhage. Patients with a history of acute decompensation and/or hepatocellular carcinoma (HCC) were excluded from this study. Univariable Cox regression was performed to analyze risk factors for hepatic decompensation.
Results: After successful viral eradication, a total of 132 patients with compensated liver cirrhosis experienced hepatic decompensation during the seven-year follow-up period, with a median follow-up time of three years. The cumulative incidence of hepatic decompensation increased from 2.0% at follow-up year one to 6.7% at follow-up year seven. Age at SVR (HR: 1.02, 95%CI: 1.01–1.05, $p = 0.013$) and platelet count (HR: 0.99, 95%CI: 0.98–0.99, $p < 0.001$) as well as serum albumin (HR: 0.94, 95%CI: 0.91–0.96, $p < 0.001$) and MELD score (HR: 1.57, 95%CI: 1.45–1.7, $p < 0.001$) were identified as risk factors for acute decompensation in patients with compensated liver cirrhosis. Furthermore, post-treatment liver stiffness measurement (LSM) ≥25 kPa ($p = 0.01$) rather than change during treatment (LSM decrease ≥20%, vs. <20%, $p = 0.828$; LSM decrease ≥20% to final value <20 kPa, vs. others, $p = 0.555$) was associated with hepatic decompensation.
Conclusion: The findings suggest that demographic and laboratory data, in conjunction with LSM, may assist in the identification of patients with compensated HCV related liver cirrhosis and SVR who are at risk of hepatic decompensation and therefore may benefit from intensive surveillance.

THU-230

Predictors of hepatocellular carcinoma risk after hepatitis C viral clearance - data from the german hepatitis C-registry (DHC-R)

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Background and aims: Hepatocellular carcinoma (HCC) is the leading cause of death in patients with chronic viral hepatitis C after achieving a sustained virological response (SVR). Prediction models for HCC development after SVR still require further validation but are crucial for clinical practice. In this study, we aim to determine risk factors to predict HCC development after SVR as well as validate previously suggested HCC risk scores in a large multicenter, real-world cohort.
Method: We retrospectively analyzed a total of 6,714 patients achieving SVR included in the well-established German Hepatitis C Registry (DHC-R) comprising 4,693 patients with and 2,021 without liver cirrhosis, respectively. Patients with a history of HCC and/or acute decompensation of liver cirrhosis were excluded. Univariable Cox regression was performed to analyze risk factors for HCC development. Previously proposed risk scores, i.e., the aMAP score comprising age, gender, bilirubin, albumin and platelet count, were validated.
Results: Overall, 67 patients developed de novo HCC during the first seven years after SVR. The cumulative incidence rates at seven years after SVR were 3.6% in all patients, 7.4% in patients with liver cirrhosis, and 1% in patients without cirrhosis. Moreover, the aMAP risk score was associated with an increased risk for HCC development in the entire cohort and in patients with liver cirrhosis (HR: 1.15, 95%CI: 1.09–1.21, $p < 0.001$). Furthermore, evaluating differential risk factors for the onset of HCC after SVR, we observed that liver stiffness measurement (LSM) at SVR (HR: 1.05, 95%CI: 1.02–1.09, $p = 0.003$), age (HR: 1.06, 95%CI: 1.04–1.09, $p < 0.001$), body mass index (BMI) (HR: 1.07, 95%CI: 1.01–1.14, $p = 0.03$), diabetes (HR: 2.71, 95%CI: 1.55–4.76, $p = 0.001$), and platelet count (HR: 0.99, 95%CI: 0.985–0.993, $p < 0.001$) were factors associated with the incidence of HCC in the overall cohort, whereas within the subcohort of patients with liver cirrhosis, only LSM ($p = 0.045$), age ($p = 0.007$) and diabetes ($p = 0.033$) were significantly associated with de novo HCC. Interestingly,

α-fetoprotein (AFP) did not emerge as a risk factor for the development of HCC in patients with (p = 0.196) and without liver cirrhosis (p = 0.854).
Conclusion: These results emphasize LSM, age, BMI, diabetes and platelet count as predictors for the onset of HCC in patients with hepatitis C virus infection after SVR and highlight the aMAP score as an effective tool for predicting HCC development.

THU-231
Microelimination project for HCV in patients with elevated ALT using pooling PCR technique in a health area. Preliminary results
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Background and aims: Screening for Hepatitis C Virus (HCV) in patients with elevated ALT levels is a recommended clinical practice. However, various factors often prevent its routine implementation in clinical settings in primary care centers. Aim To implement a microelimination program for hepatitis C by screening for HCV RNA using a pooling PCR technique in all patients in the Valladolid West Health Area with elevated ALT levels and FIB-4 scores above 2.67. Also, to analyze the prevalence of active HCV infection in this population, and identify and treat positive cases, evaluating the efficiency of this screening strategy.
Method: The study included all blood tests ordered by primary and hospital care from January 1, 2024, to October 2024, excluding hospitalized patients. Samples with elevated ALT and FIB-4 >2.67 were forwarded to the Microbiology Department for HCV RNA detection using the pooling PCR technique. Initially, 10 pools were created, each containing 10 samples. Positive results were communicated to the ordering physician and the Hepatology Department, which scheduled patients for a high-resolution clinic visit, including FibroScan evaluation, prior to initiating treatment.
Results: Between January 1, 2024, and October 7, 2024, 1,300 samples with elevated ALT were analyzed, of which 25 (1.92%) tested positive for HCV RNA. The average age of patients was 67.60 ± 13.48 years, with no significant differences between positive and negative groups (p = 0.526). A significantly higher proportion of males were observed among HCV-positive patients compared to negatives (76.0% vs. 49.6%, p = 0.016). No significant differences were found in mean AST or ALT levels between positive and negative groups. FIB-4 scores were significantly lower in the positive group than in the negative group (4.17 ± 1.68 vs. 5.79 ± 12.30, p < 0.01), and this difference persisted across all age groups. Positive patients originated in similar proportions from primary and hospital care (1.9% in both settings).
Conclusion: Automating HCV RNA testing via pooling PCR for patients with elevated ALT demonstrated a 1.9% prevalence in this population. Pooling PCR is an efficient approach to support microelimination programs in patients with elevated ALT.

THU-232
Treatment of genotype 3 chronic hepatitis C infection: age reduces the efficacy of treatment with sofosbuvir and daclatasvir but the reduction is less marked with sofosbuvir and velpatasvir
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Background and aims: Generic antiviral medicines give resource poor countries an opportunity to eliminate HCV infection. However, the more potent NS5A inhibitors (e.g. velpatasvir) are more expensive than daclatasvir, which is less effective in people infected with genotype 3, particularly in those with cirrhosis. Given that genotype 3 infection dominates in the Indian sub-continent, including Pakistan, a simple, inexpensive means of understanding which patient populations can be effectively treated with daclatasvir, rather than velpatasvir would be beneficial and allow consideration of treatment stratification. We explored the efficacy of sofosbuvir/daclatasvir and sofosbuvir/velpatasvir in people with genotype 3 HCV infection and examined the effect of age.
Method: HepFreePak is an observational study of the impact of sofosbuvir/daclatasvir treatment in Pakistan that examines response to current standard of care (sofosbuvir/daclatasvir for 12 weeks in people with an APRI score of <1.5 or 24 weeks in those with an APRI score of >1.5 or other features of cirrhosis). We examined SVR12 in people treated in this program. The NHSE registry records treatment outcomes and strategies for people in England treated for HCV and we examined registry SVR data for people with genotype 3 receiving sofosbuvir/velpatasvir therapy to compare with data from Pakistan.
Results: 2,214 people treated with sofosbuvir/daclatasvir in Pakistan had documented SVR12 outcomes. Overall SVR12 was 87.1% (87.8% in those without cirrhosis (1,575/1,793) and 85.3% (359/421) in those with cirrhosis). 14,475 people from the English treatment registry received sofosbuvir/velpatasvir and overall SVR12 was 90.5% (11,116/12,135) in those without cirrhosis (91.60%) and 1,920/2,254 (85.18%) in those with cirrhosis) not significantly different from sofosbuvir/daclatasvir, although we did find a significant difference in response rates in those with self-declared origin in Pakistan (851/901, 94.45%, p < 0.001). Assessment of cirrhosis in resource poor settings is difficult (APRI is unreliable and fibroscan/biopsy are unaffordable) so we examined age (a surrogate marker for advanced fibrosis and multi-morbidity). In sofosbuvir/daclatasvir treated people there was a reduction in efficacy with age – SVR in those aged <40 was 89.49%, falling to 82.78% in those >60 years old. In sofosbuvir/velpatasvir treated patients this reduction was not seen in those > 60 years (SVR12 in <40 was 91.33%, SVR12 in >60 was 89.35%,) but SVR12 rates dropped to (86.92%) in people aged 70 or more.
Conclusion: Efficacy with sofosbuvir/daclatasvir reduces by a modest amount with increasing age in Pakistan. This reduction is less marked but also seen in people with genotype 3 treated with sofosbuvir/velpatasvir in England. This likely reflects the higher rate of cirrhosis and co-morbidity in the elderly. These data show minimal benefits from switching to expensive sofosbuvir/velpatasvir in a young population and limited benefits in a subset of elderly people.

THU-237-YI
Effectiveness and outcomes of routine opt-out screening for hepatitis C in a UK emergency department
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Background and aims: A national programme for Emergency Department (ED) opt-out blood-borne virus screening (BBV) started in England in 2022. Initially targeted at areas of high HIV incidence, universal screening for hepatitis B (HBV) and hepatitis C (HCV) was later implemented. Some areas of the UK have higher prevalence of HCV than HIV. James Cook University Hospital (JCUH) has implemented an ED opt-out screening programme for BBVs and syphilis. We sought to explore the demographic characteristics and outcomes of patients identified with HCV through our screening programme.

Method: All patients attending the ED at JCUH had routine testing for HIV, HCV IgG (with reflex HCV RNA if positive), hepatitis B surface antigen and syphilis serology unless they opted out. Positive HCV/HBV results were highlighted to the hepatitis team for MDT discussion, initiation of treatment and testing for sustained virological response (SVR) at the end of treatment. Data was collected using electronic patient records for demographic characteristics including deprivation index, number of ED attendances in the past year and outcomes of hepatitis C management.
Results: Over the study period 3,875 patients attending ED had samples tested for viral hepatitis. Of these 96 (2.5%) were positive for HCV and 4 (0.11%) were positive for HBV (2 known and 2 new diagnoses). The population of patients testing HCV positive in JCUH ED were predominantly male (73.8%) and white analysis (92.9%). They visited the ED more than the general ED population (mean ED visits 7.3 (SD 7.7) vs 3.4 (SD 4.6)). Logistic regression analysis showed significant associations between male sex (aOR 2.7 [95% CI, 1.41–5.16]), white ethnicity (aOR 2.9 [1.1–8.3]) and residence in highly deprived area (aOR 4.0 [1.9–7.3]) in those with HCV compared to general ED patients. 91 patients had sufficient documentation to assess their outcomes. 14 (15.4%) were newly diagnosed cases of HCV and have started treatment. 6 (6.6%) have completed treatment and have achieved SVR. 39 (42.9%) were previously treated under the hepatitis service and screening confirmed SVR. 2 (2.2%) patients had previously started treatment but were lost to follow up and had relapses confirmed and treatment restarted. 4 (4.2%) patients who had previously completed treatment with SVR were found to be re-infected and were re-treated. 2 (2.2%) patients had a false positive HCV IgG; for 30 patients (33%) testing HCV IgG+ it was not possible to trace them or perform confirmatory HCV RNA.
Conclusion: Opt-out BBV screening in EDs is an effective form of case-finding and engaging new cases of HCV, as well as those out of care, in hepatitis services. Additionally, it can confirm SVR or re-infection in patients previously treated by hepatitis services but out of care. This is particularly useful in a cohort of patients who may primarily seek healthcare via the ED with high levels of drug use and deprivation.

THU-238

Previous hepatitis B virus infection and the risk of liver-related complications in patients after HCV cure - Data on more than 6,000 patients from the german hepatitis C-registry (DHC-R)

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Background and aims: Our findings demonstrate that there is a clinical impact of previous HBV in patients with SVR. Occult HBV infection should be considered a contributing factor for adverse disease outcomes underscoring the need for accurate and frequent clinical follow-up assessments.
Method: We analyzed clinical endpoints (≥3-point increase in MELD score, esophageal variceal bleeding, ascites, encephalopathy, liver transplantation, death, with/without HCC; HCC alone) in patients cured from HCV. Data were obtained from the German Hepatitis C Registry. Patients after organ transplantation, a history of HCC, or HIV co-infection were excluded. Statistical analyses included Kaplan-Meier curves to analyze the influence of HBV serological markers and logistic regression to identify predictors of clinical endpoints.
Results: A cohort of 6,355 patients fulfilled inclusion criteria, the median time of follow-up was 2.5 years (range 0.04–8.01). Serological evidence of previous HBV exposure was present in 1,889 patients (HBsAg negative/anti-HBc positive) while 157 patients had active hepatitis B (HBsAg positive). Univariate analysis identified age 50–70 years (odds ratio [OR], 2.04), sex (OR, 1.38), cirrhosis (OR, 4.88), anti-HBc-positivity (OR, 1.49) and diabetes mellitus (OR, 2.71) as risk factors for LRE. Multivariate analysis confirmed male sex, older age, cirrhosis and diabetes as independent risk factors.
Conclusion: The clinical impact of previous HBV in HCV patients after SVR requires further investigation. We suggest that occult HBV infection should be considered a contributing factor for potential adverse disease outcomes also in Caucasian patients.

THU-239

Long-term prognosis and changes in liver function after direct-acting antiviral treatment in decompensated cirrhotic patients with hepatitis C virus

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Background and aims: The sustained virologic response (SVR) rate of decompensated cirrhotic patients with hepatitis C virus (HCV) is approximately 90% by direct-acting antiviral (DAA) treatment, and improvements in liver function and prognosis are expected in the short term. However, long-term changes in liver function and prognosis after DAA treatment in decompensated cirrhotic patients with HCV are unclear.
Method: A total of 206 decompensated cirrhotic patients with HCV treated with DAA between February 2019 and December 2021 at 31 Japanese hospitals were enrolled. Decompensated cirrhosis was defined as Child-Pugh class B or C at enrolment, or class A with a history of decompensating events. All patients were treated with 12 weeks of sofosbuvir and velpatasvir. SVR was defined as undetectable serum HCV-RNA at 12 or 24 weeks after the end of treatment (EOT). We assessed the changes in Child-Pugh class, and incidence rate of and factors associated with liver transplantation (LT)-free survival after DAA treatment.
Results: The median age was 68 years, 51% of the patients were male, and 40% had a history of hepatocellular carcinoma prior to DAA treatment. The percentages of patients with Child-Pugh class A, B, and C at baseline were 10%, 76%, and 14%, respectively. Seven patients had virologic failure, two had missing HCV-RNA levels, five died before SVR confirmation, four were lost to follow-up, and the SVR rate was 91.3%. The proportions of patients with Child-Pugh class A at baseline, EOT, 24 weeks after the EOT, 1 year after the EOT, 2 years after the EOT, 3 years after the EOT, 4 years after the EOT, and 5 years after the EOT were 10%, 32%, 45%, 44%, 48%, 40%, 35%, and 14%, respectively. During the 43.7 months after starting DAA, 43 patients died (30 died due to liver-related causes) and four underwent LT. The 5-year LT-free survival rate was 69.0%. In multivariate Cox proportional hazard analyses, virologic response and Child-Pugh class at 12 weeks after the EOT were significantly associated with LT-free survival. The 3-year LT-free survival rates in patients with SVR and virologic failure were 86.3% and 50%, respectively, and those in patients with Child-Pugh class A, B and C at 12 weeks after the EOT were 91.9%, 86.4% and 46.0%, respectively.
Conclusion: In decompensated cirrhotic patients with HCV treated with DAA, liver function improved up to 24 weeks after the EOT, but may deteriorate at 5 years after the EOT. The 5-year LT-free survival rate was 69.0%, and virologic response and Child-Pugh class at 12 weeks after the EOT were associated with LT-free survival.

Viral hepatitis C – Therapy and resistance

TOP-251

Efficacy and safety of Bemnifosbuvir and Ruzasvir after 8 weeks of treatment in patients with chronic hepatitis C virus (HCV) infection

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Background and aims: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent pan-genotypic inhibitors of the HCV NS5B polymerase and NS5A protein, respectively. The combination of BEM+RZR demonstrated strong synergistic antiviral activity in vitro. A Phase 2 open-label study was conducted to evaluate the efficacy and safety of BEM +RZR administered for 8 weeks in HCV-infected patients (NCT05904470).
Method: In this single arm study, direct-acting antiviral (DAA) naïve patients with chronic HCV infection received 550 mg BEM + 180 mg RZR once daily (QD) for 8 weeks. Patients without cirrhosis or with compensated cirrhosis were eligible. Objectives included assessment of safety (adverse events [AEs], laboratory abnormalities, ECGs) and efficacy (primary endpoint of SVR12). The primary efficacy population was the pharmacokinetic and pill compliant per-protocol (PK/PC-PP) population, which included those who were study drug adherent; corroborated by pill counts and plasma drug levels adjudicated by an independent clinical pharmacologist. A secondary efficacy evaluable per-protocol (EE-PP) population included patients regardless of drug adherence. Plasma HCV RNA was measured using the Roche cobas® HCV quantitative nucleic acid test for use on the cobas® 6800/8800 systems, with a lower limit of quantitation (LLOQ) of 15 IU/mL.
Results: 275 patients were enrolled in the study with the following HCV genotypes: GT1 (n = 189), GT2 (n = 7), GT3 (n = 77) and GT4 (n = 2). 13% (37/275) had compensated cirrhosis. 88% (240/274 with sequence data) had NS5A resistance-associated substitutions (RASs) at baseline. SVR12 was 98% (208/213) in the primary PK/PC-PP population and 95% (242/256) in the EE-PP population, which included 17% (43/256) who were treatment non-adherent. In the PK/PC-PP, SVR12 was 99% (178/179) in non-cirrhotic patients, with high efficacy across genotypes. SVR12 was 88% (30/34) in cirrhotic patients, with all achieving HCV RNA <LLOQ by end of treatment Week 8. Five patients (4 cirrhotic and 1 non-cirrhotic) experienced virologic failure (post-treatment relapse) in the PK/PC-PP. There were no clear patterns with respect to baseline or treatment-emergent RAS. There were no drug-related serious adverse events (SAEs) or premature treatment discontinuations due to AEs. AEs were mostly mild/moderate, and no clinically significant trends in laboratory or ECG abnormalities were observed.
Conclusion: In this population with NS5A RAS high prevalence at baseline, high efficacy was observed, regardless of treatment adherence. These data support that non-cirrhotic patients can effectively be treated for 8 weeks with BEM+RZR, while cirrhotic patients will require 12 weeks of dosing to maximize efficacy. The regimen was well tolerated with no drug-related SAEs or treatment discontinuations due to AEs. Data support prompt Phase 3 development of this regimen.

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WED-264

Glecaprevir/pibrentasvir in chronic HCV: an integrated analysis of patients on concomitant opioids, antipsychotics and cardiovascular medications

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Background and aims: Although glecaprevir/ pibrentasavir (G/P) is highly effective and has a well-documented safety profile, co-administration of G/P with concomitant medications that are substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3 may result in an increased plasma concentration of these drugs. While the effect of G/P on the exposures of these concomitant medications is expected to be small, herein we analyze the safety and tolerability of a subset of concomitant medications including antipsychotics (aripiprazole, quetiapine, risperidone, paliperidone, lurasidone, clozapine), cardiovascular agents (statins, beta-blockers, calcium-channel blockers, hypertensives) and opioids (fentanyl, oxycodone and hydrocodone).
Method: An integrated pooled analysis was carried out across 21 randomized controlled clinical trials in patients with chronic HCV genotype 1–6 infection with or without compensated cirrhosis receiving G/P for 8, 12 or 16 weeks.
Results: Among 6547 patients in this analysis, 136 patients were on antipsychotic medications, 219 received statins, 226 hypertensives, 94 beta-blockers and 44 calcium-channel blockers that had potential interactions with G/P; however, none of the patients experienced a treatment-related serious adverse event (SAE). Of the 133 patients on opioids with potential interactions, 1 patient experienced a treatment-related SAE. Treatment discontinuations due to any AEs were rare with only 1 discontinuation in the antipsychotics class, 3 in the cardiovascular class and 3 in the opioid class. High adherence (>94%, as defined by percentage of tablets taken versus expected) was observed across these specific concomitant medication classes. Sustained virologic response at 12 weeks post-treatment (SVR12) by modified intent-to-treat (ITT; excluding patients who failed to achieve SVR12 due to reasons other than virologic failure) was 99.2% when used concomitantly with antipsychotics, 99.5% with statins, 100% with beta-blockers, calcium channel blockers and antihypertensive agents and 96.9% with opioids.
Conclusion: This integrated pooled analysis demonstrated that G/P when concomitantly administered with medications such as those belonging to the antipsychotic (aripiprazole, quetiapine, risperidone, paliperidone, lurasidone, clozapine), cardiovascular (statins, beta-blockers, calcium-channel blockers, hypertensives) and opioid class, was safe, well tolerated, and demonstrated high efficacy and adherence.

WED-269

The annual incidence of HCV RNA positivity detected by rapid on-site RT PCR doesn't decrease and remains relatively high over the last 3 years among drug users

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Background and aims: The eradication of HCV infection requires the elimination of HCV infection among drug users (DU). However, the number of drug users screened and treated for hepatitis C remains low. Many DU are lost to follow-up after serological diagnosis. Measuring viral load by rapid PCR from capillary blood (Xpert® HCV Viral Load Finger stick) provides a result in 1 hour, and increases the percentage of PCR+ DU who could benefit from treatment. Measuring changes in the annual incidence of rapid PCR introduced since March 2021 was used to define the reduction in HCV infection in this population. The aim of this study was to measure the annual incidence of C viral load measured directly on site by rapid PCR, over the last 3 years in DU followed up in 3 addiction centers (CAARUD/CSAPA: 2 in Nice and 1 in Marseille).
Method: From March 1, 2021, the date of implementation of on-site rapid PCR, all HCV-positive DU (previously known or detected using a TROD targeting HCV, HBV and HIV) followed up in 3 CAARUD/CSAPA were offered rapid PCR (Xpert HCV Viral Load Finger stick), directly on-site. If the HCV PCR was positive, treatment was offered.
Results: From March 2021 to 2024, 413 DU were included: 183 in year 1, 120 in year 2 and 110 in year 3: 80% men with an average age of 43 years, 85 without social rights, 103 homeless, 198 declared having injected: heroin, crack, other, 175 having inhaled: cocaine, crack, other, and 235 excessive alcohol consumption, 185 were receiving substitution treatment. HCV serology was documented in 180 of the 183 DU followed up in year 1, in 118 of the 120 DU in year 2, and in 107 of the 110 DU in year 3. It was positive in 85 (47%), 60 (51%) and 49 (46%) of them respectively. 82/85 anti-HCV subjects in year 1, 59/60 in year 2 and 46/49 in year 3 agreed to undergo rapid PCR. The annual incidence of PCR positivity was 16%, 21% and 16% respectively in each of these 3 years. Anti-HCV treatment was initiated in 18 of 29 PCR+ DUs in year 1, in 12 of 25 PCR+ DUs in year 2 and in 12 of 18 PCR+ DUs in year 3. Six out of 11, 11 out of 13 and 4 out of 6 PCR+ DU in each of these 3 years could not be treated because they had no access to social rights.
Conclusion: The annual incidence of C viral load over a 3-year period from 2021 in DU followed up in 3 French addiction centers does not decrease and remains relatively high. While rapid on-site PCR almost always results in a virological diagnosis, in order to achieve viral eradication, it would be necessary to be able to treat all positive PCR drug users and in particular those who do not have access to social rights.

WED-270

A decade of hepatitis C virus management: insights from a large population-based cohort on treatment patterns, adherence, and outcomes

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Background and aims: The global effort to eradicate hepatitis C virus (HCV) has achieved remarkable progress; however, significant hurdles remain in achieving comprehensive elimination. This study leverages a large-scale, population-based cohort of HCV patients from Leumit Health Services (LHS) to derive insights into treatment patterns, adherence, and outcomes, aiming to improve patient care and inform public health strategies.
Method: A retrospective cohort study was conducted using the LHS database, encompassing data from 2015–2023. The cohort included HCV-infected patients identified by ICD-9-CM codes and serological confirmation. Extracted data included demographic, social, clinical, and laboratory variables, as well as fibrosis staging, treatment records, and therapeutic outcomes. Adherence was meticulously monitored through medication dispensation records and electronic visit logs, with outcomes analyzed across HCV subpopulations.
Results: A total of 1,380 patients were treated with direct-acting antivirals (DAAs). The cohort's mean age was 55.1 ± 7.7 years, with a male predominance (60.2%). HIV coinfection was present in 1.4% of patients, 1.3% had a concomitant diagnosis of hepatocellular carcinoma (HCC), and 44.7% were classified as having advanced fibrosis (F3–F4). Additionally, 22.9% of the cohort were obese, and 17.3% had diabetes. The rates of excessive alcohol use and intravenous drug use (IVDU) were 10.8% and 5.4%, respectively. Of the total cohort, 136 patients (9.9%) discontinued follow-up without post-treatment

HCV RNA testing. This subgroup exhibited significantly higher rates of moderate-to-low adherence (57.4% vs. 8.9%), minority ethnicity (5.9% vs. 3.7%), excessive alcohol consumption (22.8% vs. 9.5%), Alzheimer's disease (15.4% vs. 1.2%), and IVDU (17.6% vs. 4.0%) compared to those who completed follow-up. Among the 1,244 patients who completed follow-up, 94.5% achieved SVR. SVR rates were higher with newer pangenotypic regimens such as Epclusa (96.4%) and Maviret (96.2%) compared to older medications but markedly lower in DAA-experienced patients (85.0%) and those with moderate-to-low adherence (56.8%). Multivariate analysis identified major depressive disorder, dementia/Alzheimer's disease, IVDU, and excessive alcoholism as independent factors associated with moderate-to-low adherence.

Conclusion: This comprehensive decade-long analysis underscores critical insights into the management and outcomes of HCV in a large, population-based cohort, revealing that while high SVR rates are achievable, adherence remains a pivotal determinant of success. Our findings highlight specific subpopulations at risk for poor adherence and incomplete follow-up, emphasizing the need for targeted interventions to address these barriers in the pursuit of HCV eradication.

WED-271

8 weeks of Glecaprevir/Pibrentasvir is highly effective in patients with genotype 3 hepatitis C related cirrhosis, irrespective of the presence of clinically significant portal hypertension

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Background and aims: The final iteration of EASL HCV guidelines recommend that patients with genotype 3 (GT3) hepatitis C (HCV) infection and compensated cirrhosis may be treated with 8 weeks of Glecaprevir/Pibrentasvir (GP). This comes caveated that more data are needed to consolidate this recommendation. It highlights the lack of outcome data amongst those patients with cirrhosis and clinically significant portal hypertension (CSPH). We sought to examine the real world treatment outcomes of 8 weeks GP in patients with GT3 infection and cirrhosis, with or without CSPH.

Method: Patients with a diagnosis of GT3 HCV with cirrhosis, receiving 8 weeks of GP, were identified from a HCV database. Data on baseline demographics, opioid substitution therapy (OST), liver stiffness measurement (LSM), platelet count, Child's Pugh Score (CPS) and treatment outcomes were obtained. CSPH was ruled in according to Baveno criteria of LSM > = 25 kPa. SVR rates were calculated on an intention to treat (ITT) and a per protocol (PP) basis. PP analysis excluded those not achieving SVR due to missing blood tests or confirmed re-infection.

Results: 97 treatment episodes were identified, relating to 91 patients with cirrhosis and GT3 infection: median age 51 (7.7) years, 8 (8.2%) HIV co-infection, 29 (29.9%) on OST. 90 pre-treatment Fibroscans were performed, with a median LSM of 19.3 kPa (11.2 kPa), the remainder were diagnosed with cirrhosis based on imaging/clinical/laboratory characteristics. Median platelet count was 159 (93), and 42 (43.3%) of patients had platelets below 150. 3 (3.1%) patients had CPSB7/8, 32 (33%) CPSA6, and 62 (63/9%) CPSA5. 88/97 (90.7%) achieved ITT SVR. Excluding 5 patients with confirmed re-infection prior to SVR bloods and 3 with missing SVR data, the PP SVR was 87/88 (98.9%). 26 (26.9%) of patients had CSPH, amongst whom 25/26 (96.1%) achieved ITT SVR. Excluding one patient with missing SVR bloods, the PP SVR was 26/26 (100%). All 3 patients with CPSB7/8 cirrhosis, and 31/32 (96.9%) of CPSA6 achieved SVR. Excluding missing data the PP SVR was 31/31 (100%).

Conclusion: Our real-world data support the use of an 8-week regimen of GP amongst patients with GT3 infection and cirrhosis. In a cohort of patients where 1 in 4 patients had CSPH and 1 in 3 had CPS6 or higher, SVR rates remained excellent irrespective of these baseline factors.

WED-272

Real-world efficacy and safety of universal 8-week Glecaprevir/Pibrentasvir in CHC patients with early CKD or Pre-ESRD: insights from a nationwide HCV registry in Taiwan

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Background and aims: The eight-week glecaprevir/pibrentasvir (GLE/PIB) regimen is recommended for treatment-naïve patients with chronic hepatitis C (CHC). With the Taiwanese government's goal of hepatitis C elimination by 2025, this study aimed to gather real-world evidence on 8-week GLE/PIB for treatment-naïve patients with chronic kidney disease (CKD) through the Taiwan Association for the Study of the Liver HCV Registry (TACR).
Method: Data of CHC patients treated with an 8-week regimen of GLE/PIB were extracted from the TACR, managed by the Taiwan Association for the Study of the Liver (TASL). Treatment efficacy, measured as sustained virologic response at 12 weeks post-treatment (SVR12), was evaluated in the modified intention-to-treat (mITT) population, excluding those lost to follow-up or without SVR12 data. The safety profile was analyzed in the intention-to-treat (ITT) population.
Results: Of 1,072 CHC patients with CKD received at least one dose of GLE/PIB (ITT population), 1,054 had SVR12 data available (mITT population). The overall mITT SVR12 rate was 99.6% (1,050/1,054), with rates of 99.7% in pre-ESRD patients (571/573) and 99.6% in early CKD patients (479/481). Among specific subgroups, SVR12 rates were 100% for genotype 3 infection (21/21) and dyslipidemia (48/48), 99.5% for diabetes (368/370), 99.4% for cardiovascular disease (328/330), 96.9% for those with a history of cerebral vascular accident (31/32), and 95.5% for people who injected drugs and those with HIV coinfection (21/22). Adverse events (AEs) occurred in 16.8% (181/1,072) of patients, with nine patients (0.8%) experiencing serious AEs and eleven events (1%) leading to permanent drug discontinuation, although only two events were deemed treatment-related. Additionally, the estimated glomerular filtration rate (eGFR) significantly increased from 39.2 ± 16.5 ml/min/1.73 m² to 41.9 ± 21.8 ml/min/1.73 m² ($P < 0.01$) overall, with notable improvements in early CKD patients (from 53.5 ± 4.3 ml/min/1.73 m² to 57.1 ± 13.5 ml/min/1.73 m², $P < 0.01$) and pre-ESRD patients (from 27.1 ± 12.8 ml/min/1.73 m² to 29.2 ± 19.1 ml/min/1.73 m², $P < 0.01$) at SVR12.
Conclusion: Eight-week GLE/PIB therapy was effective and well-tolerated in treatment-naïve patients with early CKD or pre-ESRD. Additionally, there was a significant improvement in renal function at SVR12 for both early CKD and pre-ESRD patients.

WED-273

Exploring a hepatitis C elimination model among ex-drug users in community drug rehabilitation centers insights from Guangdong, China

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Background and aims: There is a lack of data on the prevalence of hepatitis C virus (HCV) infection among ex-drug users (EDUs) in community drug rehabilitation centers (CDRCs) in mainland China. This study aimed to evaluate the HCV burden in this population and develop a feasible screening-to-referral model. A micro-elimination approach tailored for EDUs was implemented and assessed in Shunde, Guangdong Province.
Method: This prospective observational study was initiated by Shunde Hospital of Southern Medical University, in collaboration with the Office of Drug Control (ODC), the Center for Disease Control (CDC), CDRCs. This novel four-party linkage model include EDUs recruitment, conducting surveys, performing HCV antibody (HCV-Ab) reflex testing, recalling HCV RNA-positive individuals for referral, initiating direct-acting antiviral (DAA) therapy, and treatment follow-up.
Results: Over one year, 11 free consultations across 10 CDRCs enrolled 246 EDUs, with a fingerstick HCV-Ab testing rate of 99.2% (244/246). The median age was 48 years (IQR: 43–52), with 91.8% male. Among participants, 79.1% had an education level of middle school or below, 25.4% lacked stable income, and 48.8% had a history of intravenous drug use. Additionally, 48.8% of participants had controlled attenuation parameter (CAP) values >238 dB/m, indicative of steatotic liver disease, while 39.3% and 14.3% were suspected of liver fibrosis and cirrhosis, respectively, based on liver stiffness measurements. The HCV-Ab positivity rate was 49.2% (120/244). Of these, 95.2% (119/125) underwent HCV RNA testing, with 84.3% (86/102) testing RNA-positive. The referral rate for RNA-positive individuals was 44.2% (38/86), and 89.5% (34/38) of referred individuals initiated DAA therapy. Among those treated, HCV genotype 6a was the most common (16/28), followed by genotypes 3b (6/28), 1b (4/28), and 3a (2/28), consistent with regional patterns. Currently, among those undergoing treatment, rapid virologic response (RVR) was achieved in 96.7% (29/30) of patients tested at week 4 of treatment.
Multivariable analysis revealed that low referral rates were significantly associated with poor disease awareness (86.8% vs. 43.8%, $p < 0.001$) and financial constraints (81.6% vs. 60.4%, $p = 0.034$). Overall, this approach increased the EDUs' HCV diagnosis rates from 46.4% (58/125) to 95.2% (119/125) and treatment rates from 22.4% (28/125) to 50.4% (63/125).
Conclusion: This study is the first to report an HCV elimination model for EDUs in CDRCs in mainland China. The HCV prevalence among EDUs is significantly higher than in the general population. The four-party linkage model effectively improved HCV screening, referral, and treatment rates. However, economic and awareness barriers remain significant challenges. Further optimization of the screening and referral process is essential to meet the WHO's HCV elimination targets.

WED-274

Real-world outcomes in patients with Voxilaprevir (VOX)/ Velpatasvir (VEL)/Sofosbuvir (SOF) treatment failure: a follow-up study

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Background and aims: The global elimination of hepatitis C virus (HCV) is feasible with highly effective direct-acting antivirals achieving SVR (sustained virological response) rates above 95%. However, eliminating HCV requires addressing difficult-to-treat patients, particularly those with failure to regimens like VOX/VEL/SOF. Data on the retreatment outcomes of VOX/VEL/SOF failures is limited. The characterization of these patients supports the development of salvage therapies to achieve SVR. This study aimed to follow-up patients with VOX/VEL/SOF failure and evaluated retreatment efficacies.
Method: We analyzed samples from 1420 patients included in the European Resistance Database (between the years 2014–2024) who experienced DAA treatment failure. NS3, NS5A, and NS5B regions were amplified and subjected to population sequencing, with resistance-associated substitutions (RASs) exhibiting >2-fold reduced DAA susceptibility being examined. Clinical and virological parameters were collected retrospectively.
Results: A total of 31 patients with virological failure to VOX/VEL/SOF retreatment were identified. Of those, 77% (24/31) patients were male, with a median age of 58.8 years. Cirrhosis was present in 58% (18/31) and 19% (6/31) had a history of hepatocellular carcinoma (HCC). 48% were infected with HCV genotype (GT) 3 (15/31), 27% (9/31) with GT1a and 21% (7/31) with GT1b. Most of the patients had been pre-treated with VEL/SOF (55%, 17/31), 13% (4/31) each had received G/P (glecaprevir/pibrentasvir) or GZR/EBR(grazoprevir/elbasvir) ± SOF and 10% (3/31) each had been pretreated with LDV (ledipasvir)/SOF or DCV(daclatasvir)/SOF. HCV RASs were uncommon in NS3 and NS5B after VOX/VEL/SOF failure. In contrast, NS5A RASs were detected in 80% of patients, with L31M and Y93H being most frequently observed, largely reflecting the pre-treatment resistance profile. During follow-up, 10% (3/31) of patients died from HCC, and 31% (10/31) did not receive salvage therapy due to HCC progression, being lost to follow-up, or return to home country. Salvage therapy was initiated in 58% of patients (18/31) and the most common administered regimen was G/P+SOF ± RBV (83%, 15/18), followed by VEL/SOF ± RBV (11%, 2/18) and one patient received G/P (6%, 1/18). SVR data were available for 94% (17/18) of patients. The modified intention-to-treat SVR-rate was 77% (13/17). Notably, two patients died from comorbidities during treatment, and one patient was lost to follow-up. Only one case of virological failure was observed after suboptimal retreatment with VEL/SOF+RBV, however, the patient finally achieved SVR after G/P+SOF+RBV.
Conclusion: The combination of G/P+SOF represents an effective third-line treatment option for difficult-to-treat patients, including those with cirrhosis, HCC, or HCV GT3 infection. These findings highlight the importance of tailored salvage therapy to achieve optimal outcomes in this challenging population.

WED-275

Retreatment of HCV in a large metropolis – implications for WHO elimination targets? The London experience

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Background and aims: Despite the high efficacy of direct acting antiviral (DAA) therapies in the treatment of chronic hepatitis C (HCV) infection, retreatment (ReTx) is required, due to treatment failures, poor compliance with the treatment regimen and reinfection. Previously identified risk factors requiring ReTx include patients with rare genotypes, people who are actively injecting drugs (PWID) and men who have sex with men. We examined these factors and the outcomes of retreatment in London, with a population of 9.7 M.
Method: All patients undergoing DAA therapy in 18 centres in London from 09/13–03/24 were registered centrally. This data was interrogated for those patients undergoing 2 treatment episodes > 6 months apart. Demographics and outcomes were compared with all patients undergoing a single treatment episode over the same period. Reinfection was defined as new HCV RNA positivity following a confirmed sustained virological response (SVR12), or a differing genotype in any individual lost to follow-up following their first treatment episode without a confirmed SVR12. All treatment outcomes are expressed as intention to treat.
Results: There were 16471 patients treated with DAA therapy, with ReTx occurring in 342 patients having 2 treatment episodes (2.1%) and 12 patients had 3 treatment episodes. The retreated patients were younger, (53 years old vs 64 years), more likely to be male (81.6% vs 69.8%), have HIV (11.3% vs 9.8%) and PWID (30.2% vs 12.3%) or have alcohol as a contributing factor to their liver disease (18.1% vs 10.7%). Reinfection accounted for 145 patients (115 having had an SVR12 and 30 patients with a different genotype). 29 had HIV (20%), 49 were

current PWID (33.7%). In the remaining 209 patients, the outcomes of their first treatment episode were relapse, breakthrough and 'non-response' in 77. No outcome was documented in 19, with 81 lost-to-follow-up, incomplete treatment in 4 and other reasons in 28. In this cohort, 11 had HIV (5.3%; p < 0.001) and 58 were current PWID (27.8%, p = NS). The median time between treatments was 697 days (IQR 425–1173). The median time between retreatments in the reinfected was 946 days versus 600 days in the non-reinfected cohort. The overall SVR12 rate in the retreated group was 60.1%. The SVR12 rates in reinfected were 64.8% and 56.9% in non-reinfected (p = NS). Seventy nine patients were retreated with the same drug regimen. The SVR12 rate in this group was 26/79 (32.9%). Thirty three of these were reinfection (14 PWID and 11 with HIV). SVR rates were higher in those treated with voxilaprevir-containing regimens (n = 107, 73.8%) and differing non-voxilaprevir-containing regimens 1(n = 167, 55.7%).

Conclusion: The need for retreatment of HCV occurs more commonly in treatment failures rather than reinfection. The reinfection risk was higher in patients with HIV rather than current PWID. Retreatment with the same drug regimen was associated with worse outcomes. Factors associated with 1st treatment episode failures should be modified prior to retreatment if possible.

WED-276

The SVR10K Hepatitis C study: final results show 98.9% SVR in 7,000 patients treated with SOF/VEL in Asia, Latin America, Middle East, Nordic and Southern Europe

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Background and aims: A previously published real-world data analysis demonstrated high effectiveness of sofosbuvir/velpatasvir (SOF/VEL) in > 6,000 HCV patients from 12 clinical cohorts across Australia, Canada, Europe & USA. Irrespective of age, male patients were more likely to have advanced fibrosis and infection with HCV GT 3, and median time to treatment initiation was numerically shorter in male patients across the age spectrum. The aim of this large real-world analysis was to evaluate characteristics and outcomes in an expanded pool of HCV patients treated with SOF/VEL across regions globally.

Method: A previously published real-world data analysis demonstrated high effectiveness of sofosbuvir/velpatasvir (SOF/VEL) in > 6,000 HCV patients from 12 clinical cohorts across Australia, Canada, Europe & USA. Irrespective of age, male patients were more likely to have advanced fibrosis and infection with HCV GT 3, and median time to treatment initiation was numerically shorter in male patients across the age spectrum. The aim of this large real-world analysis was to evaluate characteristics and outcomes in an expanded pool of HCV patients treated with SOF/VEL across regions globally.

Results: Overall, 7,027 patients were included, with a median age of 55 years [IQR 46–64], with patients over 50 y.o. representing two thirds (66%) of the overall population. Patients were mainly male (65%), with 72% females vs 62% males being > = 50 yo (p < 0.001). HIV/HCV coinfection was more prevalent in males (5.8% vs 2.1%, p < 0.001), as well as GT3 (35% vs 20%, p < 0.001), these differences were seen mostly in males > = 50 yo. TTI with the HCV therapy was shorter in females, with 40% treated in the first month, as compared to 25% of males, for both above and under 50 yo (p < 0.001). SVR was achieved in 98.9% of the treated population, with SVR rates ranging from 97.1% to 100% in all sites. SVR remained higher than 98% for males and females of all ages, and for patients with mental disorders or intravenous drug use. SVR remained higher than 97% in the concomitant presence of GT3 and a cirrhotic status.

Conclusion: Results on treatment effectiveness in diverse geographical regions did not differ from real world studies of patients in Western countries, reinforcing the effectiveness of pangenotypic/panfibrotic/pangeographic DAA therapy such as SOF/VEL and supporting the global applicability of HCV treatment guidelines.

WED-277

Efficacy and safety of glecaprevir/pibrentasvir in acute HCV participants with a history of prior infection(s)

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Background and aims: Reinfection is a major obstacle to hepatitis C virus (HCV) elimination, occurring mostly in people who inject drugs (PWIDs) and men who have sex with men (MSM), with reinfection rates of 4–30/100 person years and 7.3–15.2/100 person years (y), respectively. Oral, direct-acting antivirals (DAAs) such as the 8-week regimen of glecaprevir/pibrentasvir (G/P) are highly effective in curing acute or recently acquired and chronic HCV infection. Previously, high efficacy, safety and tolerability was confirmed in n = 286 acute HCV participants (AASLD 2024 abstract #5031). This analysis aims to confirm the efficacy and safety of G/P in persons with acute infection (AHC) with a history of prior HCV infection.

Method: A post-hoc analysis of safety, tolerability and efficacy of G/P was carried out in a subset of participants from a single-arm, prospective phase 3 study (NCT04903626) of adults with AHC and a history of prior HCV infection categorized by the number of prior HCV infections.

Results: Among 286 participants with AHC, 52 (18.2%) had ≥1 prior HCV infection: 32 had 1, 10 had 2, 6 had 3, 2 had 4, and 2 had 6 prior infections. A majority of the participants with prior infections had HCV/HIV-1 co-infection (92.3%), were MSMs (78.8%) or PWUDs (ongoing or history of illicit drug use, 69.2%) with a median age of 48.0 y (range 31–69). Risk behaviors for current AHC included unprotected sexual activity with multiple partners (59.6%), shared drug-injection equipment (28.8%), shared non-injection drug use equipment (19.2%). Treatment for prior HCV infections included IFN/PEG-IFN/RBV, G/P SOF/VEL or SOF-based regimens or other DAA-based regimens. Sustained virologic response at 12-weeks post-treatment (SVR12) rates in participants with one or more prior infections were 98.1% (ITT) and 100% (mITT: excludes participants who failed to achieve SVR12 due to reasons other than virologic failure). Safety demonstrated by treatment related (TR) adverse events (AEs) or serious AEs (SAEs) was similar between participants with ≥1 and no prior infections. In participants who had prior infections, TR-AEs

were reported in 9 participants (17.3%), with no TR-SAEs, no TR-AEs leading to G/P discontinuation, no deaths and only 1 AE-related treatment interruption. During treatment, none of the participants in the prior infection group experienced an elevation in alanine aminotransferase (ALT) ≥ Grade 2 or in total bilirubin ≥ Grade 3 that had worsened from their baseline grade, and non experienced ALT >3 × upper limit of normal (ULN) with total bilirubin >2 × ULN.
Conclusion: G/P is highly effective, safe, and tolerable when used for treating acute or recently acquired HCV regardless of a history of prior HCV infections. These data provide insight into the role of prior infections in the management of acute infections in populations critical for HCV elimination.

WED-278
Pharmacokinetics of bemnifosbuvir in participants with hepatic impairment
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Background and aims: Bemnifosbuvir (BEM, AT-527) is an oral double prodrug of a guanosine nucleotide analog with potent activity against coronaviruses and flaviviruses including hepatitis C virus (HCV). BEM in combination with ruzasvir (HCV NS5A inhibitor), is under clinical development for the treatment of chronic HCV infection. We report here results from a phase 1 study evaluating the effect of hepatic impairment (HI) on the pharmacokinetics (PK) of BEM (NCT05724693).
Method: HCV-negative participants with mild [Child-Pugh (CP) score 5–6, category A, N = 8], moderate [CP score 7–9, category B, N = 8], or severe [CP score 10–15, category C, N = 7] hepatic impairment, as well as healthy participants (N = 16) matched by gender, age (± 10 yrs) and body mass index (± 20%) were enrolled and received a single oral dose of 550 mg BEM under fasted conditions. Intensive PK sampling was performed over 120 h and plasma concentrations of BEM and metabolites were quantitated using validated bioanalytical methodologies. Plasma protein on BEM PK was determined at 0.5 h post dosing.
Results: Compared with the control group, maximum plasma concentration (Cmax) and area under the curve (AUC) of the parent BEM increased by approximately 30, 45 and 80% (Cmax), and 35, 50 and 160% (AUC) in participants with mild, moderate or severe HI, respectively. HI had reduced effects on the plasma exposure of AT-551, the L-alanyl intermediate metabolite (Cmax and AUC increased by up to approximately 35 and 60%, respectively), while had no effect on the plasma PK of AT-273, the inactive metabolite considered the surrogate of the active intracellular triphosphate of the drug. BEM was not highly bound to human plasma protein (about 80%) and the fraction unbound, ranging from ~20 to 27%, was not meaningfully affected by HI. There were few mild to moderate adverse events reported (in 3 of 39 subjects), with no safety patterns observed between HI and control groups.
Conclusion: BEM 550 mg was safe and well-tolerated in participants with impaired or normal hepatic function. Plasma exposures to the parent BEM, but not the metabolite AT-273, surrogate for the active triphosphate, increased as hepatic function worsened. These results provide PK support for dosing BEM 550 mg in HCV-infected participants with compensated or decompensated cirrhosis.

WED-279
No DDI between Bemnifosbuvir/Ruzasvir and Bictegravir/Emtricitabine/Tenofovir Alafenamide
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Background and aims: Bemnifosbuvir (BEM) and ruzasvir (RZR) are potent, pan-genotypic inhibitors of the HCV NS5B polymerase and NS5A protein, respectively. The combination of BEM 550 mg/RZR 180 mg once daily (QD) for 8 weeks was safe and achieved high SVR rates in the lead-in cohort (60 patients) of an ongoing Phase 2 study. We report clinical pharmacokinetic (PK) drug-drug interaction (DDI) results between BEM/RZR and co-formulated antiretroviral bictegravir (B) 50 mg/emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 25 mg (Biktarvy) in healthy subjects.
Method: Two groups of healthy male and female subjects (14/group) were enrolled. Group 1 received BEM/RZR QD alone from day 1 to day 7, with B/FTC/TAF QD added from day 8 to day 17, and then B/FTC/TAF QD alone from day 18 to day 24; Group 2 received B/FTC/TAF QD alone from day 1 to day 10, with BEM/RZR QD added from day 11 to day 17, and then BEM/RZR QD alone from day 18 to day 24. Dosing occurred on an empty stomach and PK samples were obtained over 24 h. Safety assessments included adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests. Plasma samples were quantitated for all study drugs/metabolites using validated LC/MS-MS methodologies.
Results: Study regimens alone and in combination were well tolerated in healthy subjects with no discontinuations, serious AEs, clinically significant changes in vital signs or ECGs. Steady-state plasma PK of BEM, its metabolites, including the guanosine nucleoside AT-273 representing the active intracellular triphosphate, and RZR were not affected by co-administered B/FTC/TAF. Similarly, steady-state plasma PK of B and FTC were not affected by BEM/RZR. Plasma exposure of TAF and tenofovir was about 50% higher in the presence of BEM/RZR, which was not considered clinically significant.
Conclusion: BEM/RZR and B/FTC/TAF, alone and co-administered, were well tolerated in healthy subjects with no clinically relevant PK DDI. These results support the enrollment of HCV/HIV-co-infected subjects receiving B/FTC/TAF in BEM/RZR clinical trials.

WED-280
Pharmacokinetics of bemnifosbuvir in participants with renal impairment
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Background and aims: Bemnifosbuvir (BEM) is an oral guanosine nucleotide prodrug with potent activity against coronaviruses and flaviviruses including hepatitis C virus (HCV). BEM in combination with ruzasvir (HCV NS5A inhibitor), is under clinical development for the treatment of HCV. We report here results from a phase 1 study evaluating the effect of renal impairment (RI) on the pharmacokinetics (PK) of BEM (NCT05618314).
Method: HCV-negative participants with mild [eGFR 60–<90 mL/min/1.73 m^2, N = 6], moderate [eGFR 30–<60, N = 6], severe [eGFR 15–<30, N = 6] renal impairment (RI), or end-stage renal disease (ESRD) requiring hemodialysis (N = 6), as well as healthy participants (N = 12) matched by gender, age (±10 yrs) and body mass index (±20%) were enrolled. Non-dialytic participants received a single oral dose of 550 mg BEM fasted. ESRD participants received a single dose of BEM 550 mg ~ 2 h prior to the start of a 4-h dialysis session, and a second

dose 15 days later, ~ 2 h after the completion of dialysis. Plasma and urine PK sampling were performed up to 120 h and concentrations of BEM and metabolites were quantitated using validated bioanalytical methodologies.

Results: Compared with control, plasma exposure to BEM was not affected by any degree of RI. BEM was not highly bound to human plasma protein (about 80%) and the fraction unbound, ranging from ~15 to 20%, was not meaningfully affected by RI. Plasma exposure to AT-551, the L-alanyl intermediate metabolite, was not affected by mild or moderate RI whereas its area under the curve (AUC) increased by ~110 and ~225% in the severe category and ESRD with post-dialysis dosing, respectively. The AUC of plasma AT-273, the inactive metabolite considered the surrogate of the active intracellular triphosphate of the drug, was similar between mild RI and control, but increased by ~100% and ~400% respectively in moderate and severe RI. In participants with ESRD, a 4-h dialysis removed (based on AUC) ~55% of AT-551 and 40% of AT-273 without affecting BEM. Cumulative urine excretion for BEM and metabolites was about 30% of dose and was similar between RI and normal. AT-273 exhibited high and renal function dependent renal clearance ranging from ~300 mL/min in mild RI and normal control to ~100 mL/min in severe RI. Reported adverse events (in 12 of 30 subjects) were generally mild, with no safety patterns observed between RI and control groups.

Conclusion: BEM 550 mg was safe and well-tolerated in participants with impaired or normal renal function. Plasma exposure to BEM was not affected by RI but increased with worsening renal function especially for the inactive nucleoside metabolite AT-273. The high renal clearance of AT-273 which exceeded GFR indicated the involvement of active transport in its renal elimination. Intermittent hemodialysis was effective in removing the BEM metabolites from circulation. These results provide PK support for dosing BEM 550 mg in HCV-infected participants with renal impairment.

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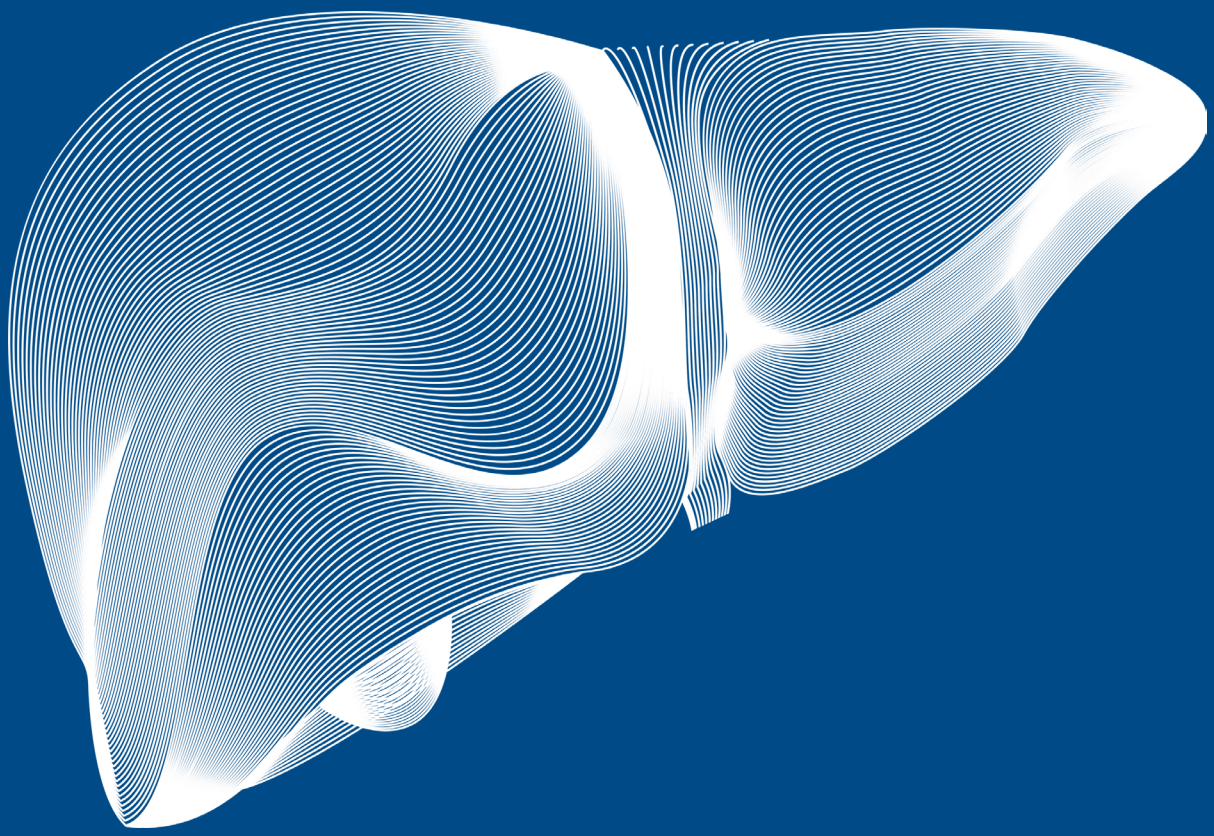

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