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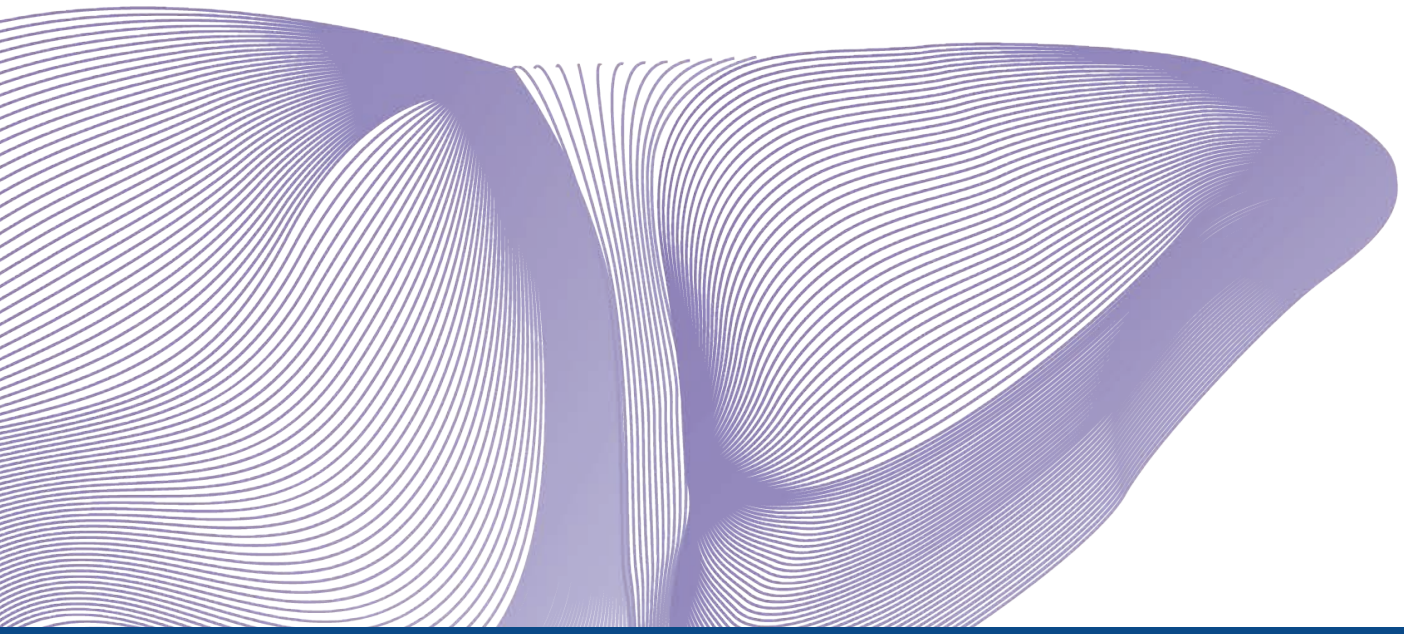

POSTGRADUATE COURSE

The role of vascular biology in chronic liver disease: Implications for clinical management

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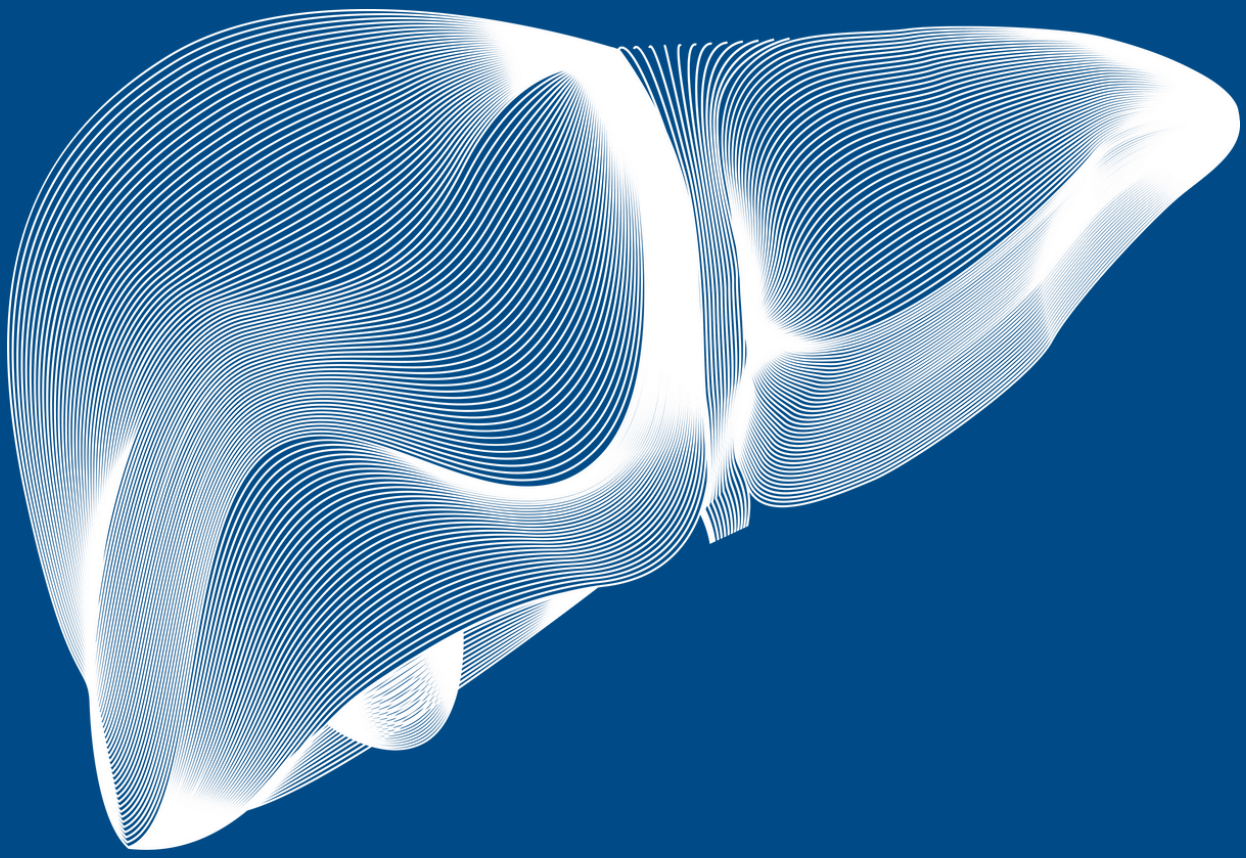

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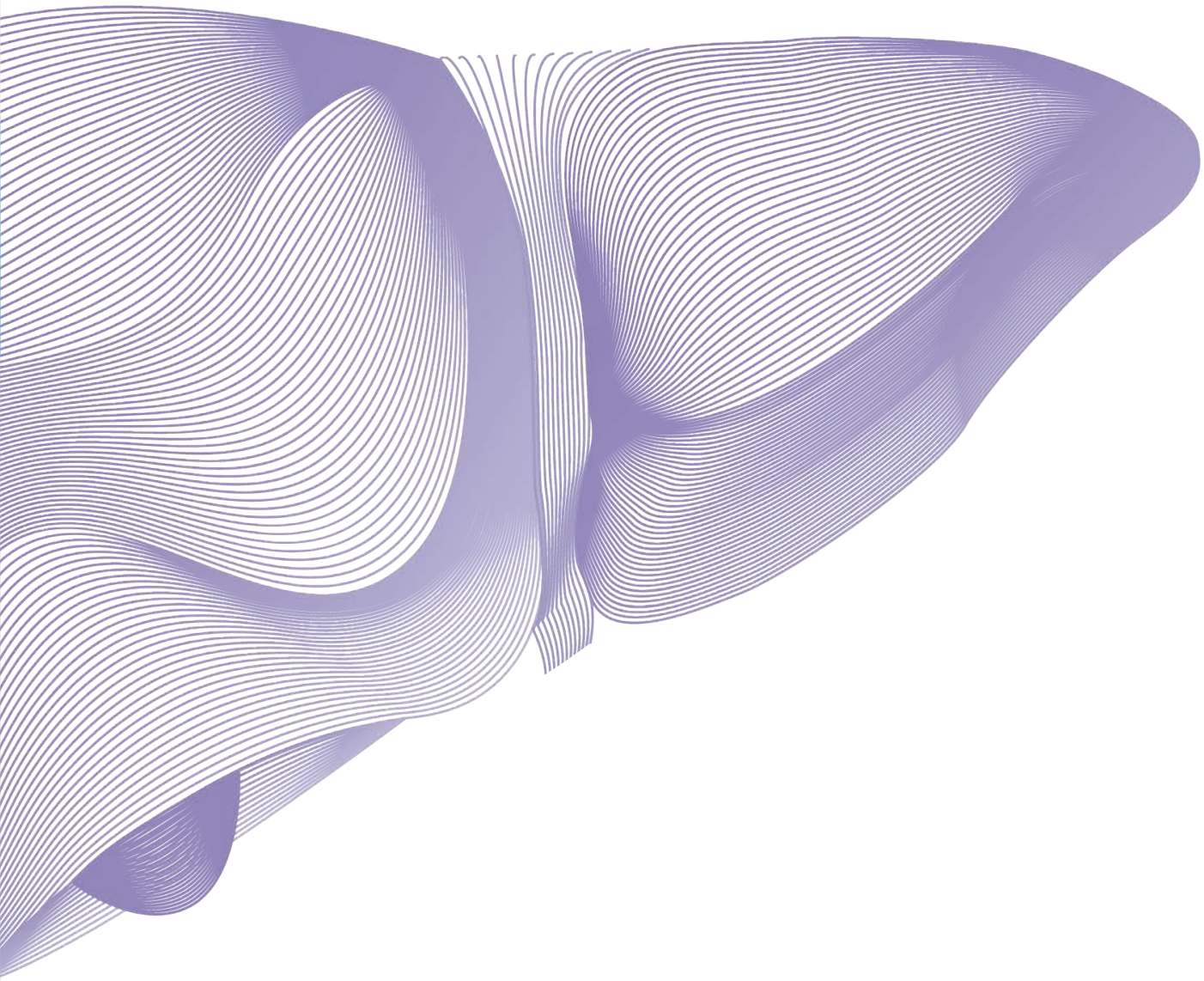

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Welcome message from the course organisers

Welcome to this postgraduate course on the role of vascular biology in chronic liver disease. The programme is divided into 4 blocks, all approaching vascular changes that can be observed in chronic liver disease. The first two blocks focus on portal hypertension and its complications in patients without and with cirrhosis. The third block focuses on haemostasis alterations associated with cirrhosis. The final block addresses extrahepatic complications of cirrhosis due to vascular changes, namely cardiopulmonary complications and hepatorenal syndrome. All sessions will address pathophysiology as well as practical management.

Ton Lisman
The The Netherlands

Pierre-Emmanuel Rautou
France

Cristina Ripoll
Germany

Programme

Postgraduate course: The role of vascular biology in chronic liver disease: implications for clinical management

WEDNESDAY, 5 JUNE 2024

Session 1: Vascular liver diseases

Chairs:
Virginia HERNANDEZ-GEA, *Spain*
Pierre-Emmanuel RAUTOU, *France*

08:30-08:45 **Porto-sinusoidal vascular disorders: how to diagnose, how to treat?**
Andrea DE GOTTARDI, *Switzerland*

08:45-09:00 **Medical management of portal vein thrombosis in patients without cirrhosis**
Aurélie PLESSIER, *France*

09:00-09:15 **Medical management of portal vein thrombosis in patients with cirrhosis**
Erica VILLA, *Italy*

09:15-09:25 **Interventional radiology for chronic portal vein thrombosis: Hepatologist**
Juan Carlos GARCIA-PAGAN, *Spain*

09:25-09:35 **Interventional radiology for chronic portal vein thrombosis: Radiologist**
Riad SALEM, *United States*

09:35-10:00 **Discussion**

Session 2: Management of portal hypertension in cirrhosis: what's new?

Chairs:
Thomas REIBERGER, *Austria*
Cristina RIPOLL, *Germany*

11:45-12:00 **Paradigm shifts in portal hypertension**
Thomas REIBERGER, *Austria*

12:00-12:15 **Non-invasive tools for assessment of risk in patients with compensated cirrhosis**
Annalisa BERZIGOTTI, *Switzerland*

12:15-12:30 **Portal-hypertensive gastro-enteropathy and GAVE syndrome: diagnosis and management**
Patrick S. KAMATH, *United States*

12:30-12:45 **TIPS: where are the limits?**
Christophe BUREAU, *France*

12:45-13:15 **Discussion**

Session 3: Coagulation changes in patients with cirrhosis: from concepts to practice

Chairs:
Ton LISMAN, *The Netherlands*
Erica VILLA, *Italy*

14:45-15:00 **Hemostasis in cirrhosis: what the clinician needs to know**
Ton LISMAN, *The Netherlands*

15:00-15:15 **Prevention of bleeding related to invasive procedures in patients with cirrhosis**
Nicolas INTAGLIATA, *United States*

15:15-15:20 **Management of bleeding related to invasive procedures in patients with cirrhosis: tips and tricks**

Case 1: Continuous oozing from a central line in a patient with ACLF
William BERNAL, *United Kingdom*

15:20-15:25 **Case 2: Bleeding after dental extraction**
Laure ELKRIEF, *France*

15:25-15:30 **Case 3: Bleeding after an invasive procedure in a patient with double antiplatelet agents**
Sarwa DARWISH MURAD, *The Netherlands*

15:30-15:55 **Discussion**

17:00-17:45

State-of-the-Art
Anticoagulation in patients with cirrhosis
Lara ROBERTS, *United Kingdom*
Chair: Ton LISMAN, *The Netherlands*

Session 4: Vascular consequences of cirrhosis outside the liver

Chairs:
Pierre-Emmanuel RAUTOU, *France*
Cristina RIPOLL, *Germany*

17:45-18:00 **Portopulmonary hypertension: diagnosis and management**
Laurent SAVALE, *France*

18:00-18:15 **Hepatopulmonary syndrome**
Sarah RAEVENS, *Belgium*

18:15-18:30 **Heart involvement in cirrhosis: where are we now?**
Lisa VANWAGNER, *United States*

18:30-18:45 **Diagnosis and management of AKI-hepatorenal syndrome**
Salvatore PIANO, *Italy*

18:45-19:15 **Discussion**

Abbreviations and Acronyms

AASLD	American Association for the Study of Liver Diseases
ABG	arterial blood gas
ACLF	acute-on-chronic liver failure
ADQI	Acute Disease Quality Initiative
AF	atrial fibrillation
AKI	acute kidney injury
ALAT	alanine aminotransferase
ALTA	Advancing Liver Therapeutic Approaches
APC	argon plasma coagulation
APTT	activated partial thromboplastin time
ASAT	aspartate aminotransferase
AT	antithrombin
AT2	alveolar type II
ATN	acute tubular necrosis
AV	arteriovenous
BMI	body mass index
cACLD	compensated advanced chronic liver disease
CBDL	common bile duct ligation
CCM	cirrhotic cardiomyopathy
CCMC	Cirrhotic Cardiomyopathy Consortium
CKD	chronic kidney disease
CLD	chronic liver disease
CLIF-C	Chronic Liver Failure-Consortium
CMR	cardiac magnetic resonance
CPGs	clinical practice guidelines
CSPH	clinically significant portal hypertension
CT	computed tomography
CTP	Child-Turcotte-Pugh
CVP	central venous pressure
DAMPs	damage-associated molecular patterns
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
EABV	estimated arterial blood volume
EASL	European Association for the Study of the Liver
eGFR	estimated glomerular filtration rate
ERAs	endothelin receptor antagonists
ERS	European Respiratory Society
ESC	European Society of Cardiology
EVL	endoscopic variceal ligation
FEV1	forced expiratory volume in the first second
FFP	fresh frozen plasma
FIPS	Freiburg Index of post-TIPS survival
FVC	forced vital capacity
FVL	factor V Leiden
GAVE	gastric antral vascular ectasia
GDMT	guideline-directed medical therapy
GGT	gamma-glutamyltransferase
GLS	global longitudinal strain
GMP	guanosine monophosphate
GVE	gastric vascular ectasia
HCC	hepatocellular carcinoma/ hepatocellular cancer
HCV	hepatitis C virus
HE	hepatic encephalopathy
HF	heart failure
HPS	hepatopulmonary syndrome
HR	hazard ratio
HR	heart rate

HRS	hepatorenal syndrome
HRS–AKI	hepatorenal syndrome–acute kidney injury
HRV	high-risk varices
HVPG	hepatic venous pressure gradient
ICA	International Club of Ascites
INR	international normalised ratio
IPVD	intrapulmonary vascular dilatation
ISTH	International Society of Thrombosis and Haemostasis
IVC	inferior vena cava
IVRT	isovolumetric relaxation time
LAVI	left atrial volume index
LF	liver failure
LMWH	low-molecular-weight heparin
LSM	liver stiffness measurement
LSPSS	large spontaneous portosystemic shunts
LT	liver transplant/transplantation
LVEF	left ventricular ejection fraction
MAFLD	metabolic-associated fatty liver disease
MAP	mean arterial pressure
MASH	metabolic dysfunction associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MELD	model for end-stage liver disease
MHE	minimal hepatic encephalopathy
mPAP	mean pulmonary artery pressure
MPN	myeloproliferative neoplasm
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCPH	non-cirrhotic portal hypertension
NGAL	neutrophil gelatinase-associated lipocalin
NGS	next-generation sequencing
NITs	non-invasive tools
NSAIDs	non-steroidal anti-inflammatory drugs
NSBBs	non-selective beta blockers
OHE	overt hepatic encephalopathy
OR	odds ratio
$P(A–a)O_2$	alveolar–arterial oxygenation gradient
PAH	pulmonary arterial hypertension
PAMPs	pathogen-associated molecular patterns
PaO_2	partial pressure of arterial oxygen
PAP	pulmonary artery wedge pressure
PCCs	prothrombin complex concentrates
PDE-5	phosphodiesterase type 5
PH	portal hypertension
PHG	portal-hypertensive gastropathy
PLT	platelet
PNH	paroxysmal nocturnal haemoglobinuria
POC	point-of-care
PoPH	portopulmonary hypertension
PRRs	pattern recognition receptors
PSVD	portosinusoidal vascular disorder
PT	prothrombin time
PVR	portal vein recanalisation
PVR	pulmonary vascular resistance
PVT	portal vein thrombosis
RAAS	renin–angiotensin–aldosterone system
RCT	randomised controlled trial
RHC	right heart catheterisation
ROTEM	rotational thromboelastometry

RRT	renal replacement therapy
SaO2	oxygen saturation
sCr	serum creatinine
SE	standard exception
SMV	superior mesenteric vein
SSM	spleen stiffness measurement
SVs	splenic veins
Tc-MAA	^{99m}Technetium-labeled macroaggregated albumin
TEG	thromboelastography
TIPS	transjugular intrahepatic portosystemic shunt
TPO-R	thrombopoietin receptor
TRV	tricuspid regurgitant velocity
TTE	transthoracic echocardiography
UO	urinary output
V/Q	ventilation–perfusion
VCTE	vibration-controlled transient elastography
VEGF	vascular endothelial growth factor
VET	viscoelastic test
VKA	vitamin K antagonist
VTE	venous thromboembolism
vWf	von Willebrand factor

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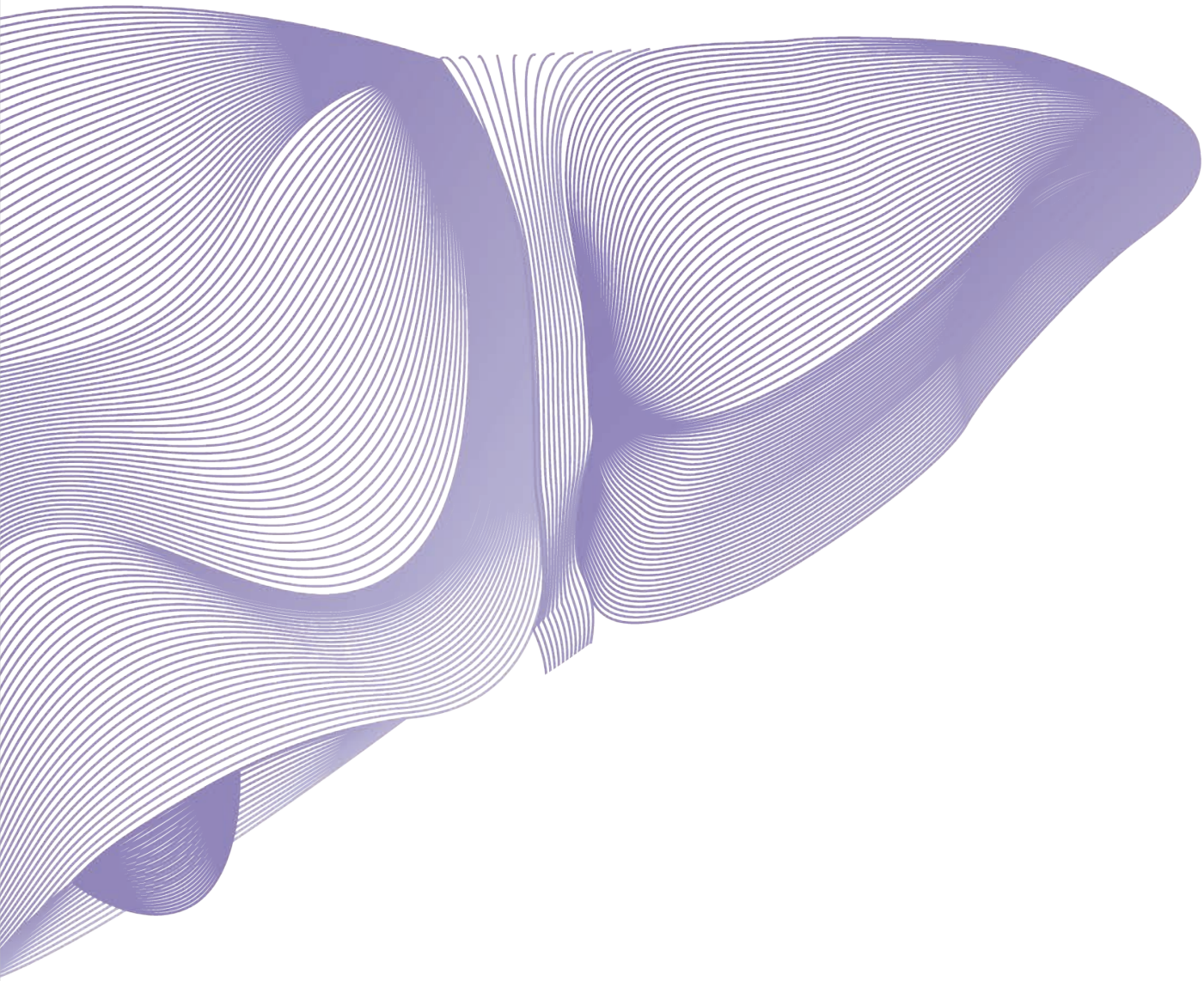
SESSION 1

VASCULAR LIVER DISEASES

WEDNESDAY 5 JUNE
08:30-10:10



Portosinusoidal vascular disorder: how to diagnose, how to treat?

Andrea De Gottardi[1, 2]

[1]Gastroenterology and Hepatology, Luzerner Kantonsspital, Luzern, *Switzerland*; [2]Università della Svizzera Italiana, Lugano, *Switzerland*

E-mail address: andrea.degottardi@luks.ch

Take-home messages

- The diagnosis of PSVD requires a liver biopsy and includes histological hepatic architectural changes associated or not with portal hypertension.
- Portal hypertension in patients with PSVD results from different histologic intrahepatic vascular alterations.
- PSVD may be associated with various immunologic disorders, infections, genetic conditions or pharmacologic treatments.
- Management includes anticoagulation, treatment of portal hypertension and liver transplantation.

Introduction

Non-cirrhotic portal hypertension (NCPH) includes a heterogeneous group of vascular liver diseases that lead to portal hypertension in the absence of cirrhosis.[1] It is associated with different histopathologic entities that have been referred to as obliterative portal venopathy, nodular regenerative hyperplasia or incomplete septal fibrosis/cirrhosis. The pathophysiology of idiopathic NCPH remains poorly understood and the management is essentially restricted to the complications of portal hypertension. However, it has recently gained increased attention in parallel with the increased use of immunosuppressive drugs for autoimmune and haematological disorders, conditions that are aetiologically linked to NCPH. Its complexity and unclear pathogenesis opened various controversies and gave rise to three main questions. First: what about the nature of NCPH before the development of portal hypertension, that is, in patients without any signs or complications related to portal hypertension? Second: should other chronic liver diseases, including viral hepatitis, metabolic dysfunction-associated steatotic liver disease or alcoholic liver disease, independently of their severity, be *a priori* excluded from the diagnosis of NCPH? Third: as portal vein thrombosis may be one of the causes, as well as a consequence of NCPH, should it exclude the presence of any form of NCPH?

Based on the observation that in patients with NCPH the changes occurring in the hepatic microanatomy, as observed on liver histology, are located in the lobular branches of the portal vein and in the sinusoid area, the name portosinusoidal vascular disorder (PSVD) has been proposed.[2]

Diagnostic criteria

The term PSVD was developed to group together several conditions that, despite diverse pathophysiology, are characterised by lesions in the sinusoids and small-sized portal veins. The main components of this definition include the absence of histological cirrhosis (liver biopsy is mandatory!) and the detection of histological findings with or without portal hypertension (Fig. 1).

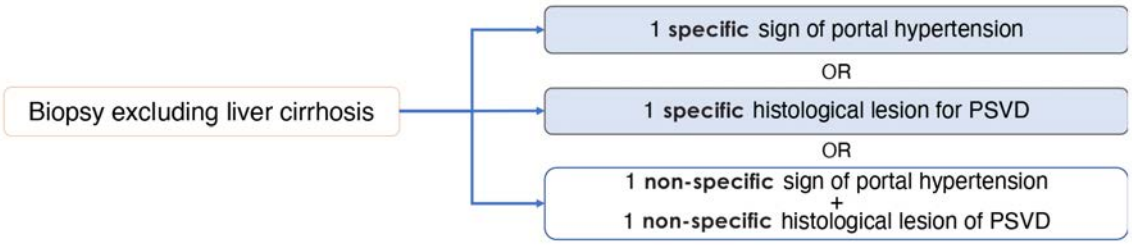


Fig. 1. Criteria to define portosinusoidal vascular disorder (PSVD)
The diagnosis of portosinusoidal vascular disorder (PSVD) requires the exclusion of cirrhosis on liver biopsy and the presence of one specific sign of portal hypertension or one specific histological lesion of PSVD or the combination of at least one non-specific sign of portal hypertension and non-specific histological lesion of PSVD.

The concomitant presence of causes for liver disease such as alcohol misuse, metabolic syndrome, or viral hepatitis, does not exclude PSVD, if liver biopsy shows specific findings indicative of PSVD.

Conditions affecting the hepatic veins (*e.g.* Budd-Chiari syndrome) or specific liver diseases that have been well characterised as causing microvascular damage such as sarcoidosis, congenital hepatic fibrosis, or sinusoidal obstruction syndrome are *a priori* excluded from the diagnosis of PSVD. Because of its most frequent secondary occurrence in PSVD patients, extrahepatic portal vein thrombosis does not preclude this diagnosis (Table 1).

Table 1. Diagnostic criteria for portosinusoidal vascular disorder (PSVD).

	Signs of portal hypertension	Histological lesions suggestive of PSVD
Specific	• Gastric, oesophageal or ectopic varices • Portal hypertensive bleeding • Portosystemic collaterals at imaging	• Obliterative portal venopathy (thickening of vessel wall, occlusion of the lumen, vanishing of portal veins) • Nodular regenerative hyperplasia • Incomplete septal fibrosis (also called incomplete septal cirrhosis); this latter feature can only be assessed on liver explants and not on liver biopsies
Non-specific	• Ascites • Platelet count < 150,000/mm^3 • Spleen size ≥13 cm in the largest axis	• Portal tract abnormalities (multiplication, increased number of arteries, periportal vascular channels, aberrant vessels) • Architectural disturbance: irregular distribution of the portal tracts and central veins • Non-zonal sinusoidal dilatation • Mild perisinusoidal fibrosis

Liver histology

Three types of histological lesions are recognised as specific for the diagnosis of PSVD. The first one is obliterative portal venopathy. This lesion has been reported previously under different names, hepatoportal sclerosis, phlebosclerosis or portal vein obliteration. The second specific lesion is nodular

regenerative hyperplasia, which is characterised by a diffuse micronodularity of the liver parenchyma without fibrosis. The third histological lesion is incomplete septal fibrosis/cirrhosis in which liver parenchyma is crossed by thin and incomplete fibrotic bands, generating incomplete nodules with approximation of the portal tracts and the centrolobular areas.

In the absence of specific histological lesions or specific signs of portal hypertension, the diagnosis of PSVD requires at least one non-specific sign of portal hypertension and one non-specific histological sign of PSVD as described in Table 1. These changes have an uneven distribution and can be very subtle. They may therefore remain under-recognised if the pathologist is not aware of them. However, they can also be found in other liver diseases and in other clinical contexts such as liver transplantation. Importantly, these histological lesions, specific and non-specific, have also been described in the absence of portal hypertension, therefore, they may potentially represent a preclinical condition before the development of portal hypertension.[3]

Additional diagnostic tools

PSVD is often misdiagnosed as liver cirrhosis. However, in patients with portal hypertension, some morphological imaging features, such as surface nodularity, anatomically dysmorphic liver with atrophy/hypotrophy of the right lobe, or abnormalities of the intrahepatic venous system, can support the correct diagnosis of PSVD.[4]

The catheterisation of hepatic veins can be used in patients with suspected PSVD to perform liver biopsy, to obtain venography images and to measure the HVPG. Patients with PSVD and evident clinical signs of portal hypertension usually show a normal or only mildly elevated HVPG (typically below 10 mmHg) because of a presinusoidal component of portal hypertension.

Values of liver stiffness measurement are in median 7.8–8 kPa, whereas spleen stiffness measurements are markedly increased in PSVD.[5]

Recent data suggest that isolated gamma-glutamyltransferase (GGT) values may be associated with PSVD also in the absence of portal hypertension.[6] New diagnostic biomarkers, including anti-endothelial cells antibodies and ADAMTS13, have been proposed as a possible parameter to differentiate PSVD from cirrhosis.

Moreover, metabolomic, transcriptomic, and genomic analyses show promising results for the differentiation of PSVD from cirrhosis, but these results need validation in further studies.[7]

Epidemiology

The overall prevalence of PSVD worldwide remains unknown. In India, the socio-economic status and sanitary/hygiene conditions have been suggested to be associated with the development of PSVD which accounts in some studies for 34% of all cases of portal hypertension. Males in their 30s and 40s have been predominantly affected. In Japan, PSVD with portal hypertension is most common in women aged 40–59 years with a ratio of 2:1. This predominance could be related to autoimmune disease being more common in women than in men and to hormonal factors related to pregnancies and premenopausal age. In Europe, PSVD appears to be rare, accounting for a lower proportion of cases of portal hypertension than reported in India or Japan. In the USA and Canada, this prevalence was 3–7%; men aged 60–69 years were predominantly affected.

Aetiology and associated conditions

Although the aetiology of PSVD has not been fully elucidated yet, in up to 50% of cases it is associated with rare conditions including drug exposure, immunological, coagulation disorders, infectious and congenital or familial defects (Table 2). PSVD has been related to prior exposure to immunosuppressive or antineoplastic agents such as azathioprine, oxaliplatin, as well as to numerous other drugs including didanosine and stavudine. Immune disorders, including acquired and congenital immune deficiencies and autoimmune diseases, have been detected in 10% of PSVD patients. Conversely, PSVD has been found in up to 84% of patients with common variable immune deficiency, hyper-IgM syndrome, primary antibody-deficiency syndromes such as Bruton's disease, and in Felty's syndrome. In patients with inflammatory bowel disease, the prevalence of PSVD was reported to be 6%. It has been proposed that the sinusoidal changes found in patients with conditions of disordered immunity, are related to intrasinusoidal cytotoxic T lymphocytes, granulomas, causing portal vein or sinusoidal endothelitis.

There is evidence that microthrombosis and platelet aggregation contribute to the development of PSVD. In fact, thickening or occlusion and obliteration of portal vein venules detected at liver biopsy, is generally regarded as indicating previous thrombosis. Moreover, prothrombotic conditions such as protein C deficiency have been associated with a higher risk of PSVD.[8]

Table 2. Conditions associated with portosinusoidal vascular disorder.

Drug/toxin exposure
• Didanosine • Azathioprine, 6-mercaptopurine • Tioguanine • Oxaliplatin, arsenic/vinyl chloride • Irradiation
Immunological disorders
• Common variable immune deficiency (significant hypogammaglobulinemia and bacterial infections) • Autoimmune hepatitis • Systemic lupus erythematosus • Scleroderma • Rheumatoid arthritis • HIV • Celiac disease • POEMS syndrome • Multiple sclerosis

Haemocoagulative disorders
• Aplastic anaemia • Myeloproliferative disorders • Hodgkin's lymphoma • Multiple myeloma • Protein C or S deficiency • Antiphospholipid syndrome • ADAMTS13 deficiency • MTHFR deficiency
Infectious
• Repeated gastrointestinal infections (*E. coli*)
Congenital, genetic, or familial
• Turner's syndrome • Adams-Oliver syndrome • TERT mutations • Cystic fibrosis • KCNN3 mutation • Noonan and Adams

Clinical manifestations

Patients with PSVD-related portal hypertension are usually asymptomatic until they develop complications of portal hypertension. Transaminases, alkaline phosphatase and GGT may be increased, but generally only moderately. The liver function is generally maintained with most patients showing normal serum albumin and bilirubin levels. Some patients develop complications of portal hypertension, mostly variceal bleeding, which is the initial manifestation in ~20–40% of cases, whereas ascites and encephalopathy are uncommon presenting symptoms. Indeed, the natural history of patients with idiopathic NCPH is characterised by the presence of large varices presentation in two-thirds of the patients with PSVD and portal hypertension and develops in 20% of patients within an average of 10 years of diagnosis.[9]

Within 5 years of diagnosis, portal vein thrombosis develops in around a third of individuals but is completely obstructive in only a third of patients. There is a substantial lack of data concerning the evolution of PSVD over time, although some authors have reported a low level of progression of liver function tests suggesting that PSVD is not evolving rapidly.[10]

PSVD may, however, occur in the absence of any signs of portal hypertension, such as splenomegaly, gastro-oesophageal varices, portosystemic collaterals, ascites, or hepatic encephalopathy, in up to 70% of cases. In such cases, altered liver tests may be the only laboratory features hinting towards the diagnosis of PSVD. Slightly impaired liver function tests, a higher rate of prothrombotic conditions, and immune diseases are likely to contribute to the progression to portal hypertension in these cases. The precise diagnosis, however, is established by specific findings at liver biopsy performed in patients presenting with asymptomatic abnormalities of liver laboratory parameters. The natural history and risk factors of PSVD without clinical features of portal hypertension remains largely unknown and only few data are available.

Management

The diagnostic workup in patients with a suspicion of PSVD is presented in Fig. 2.

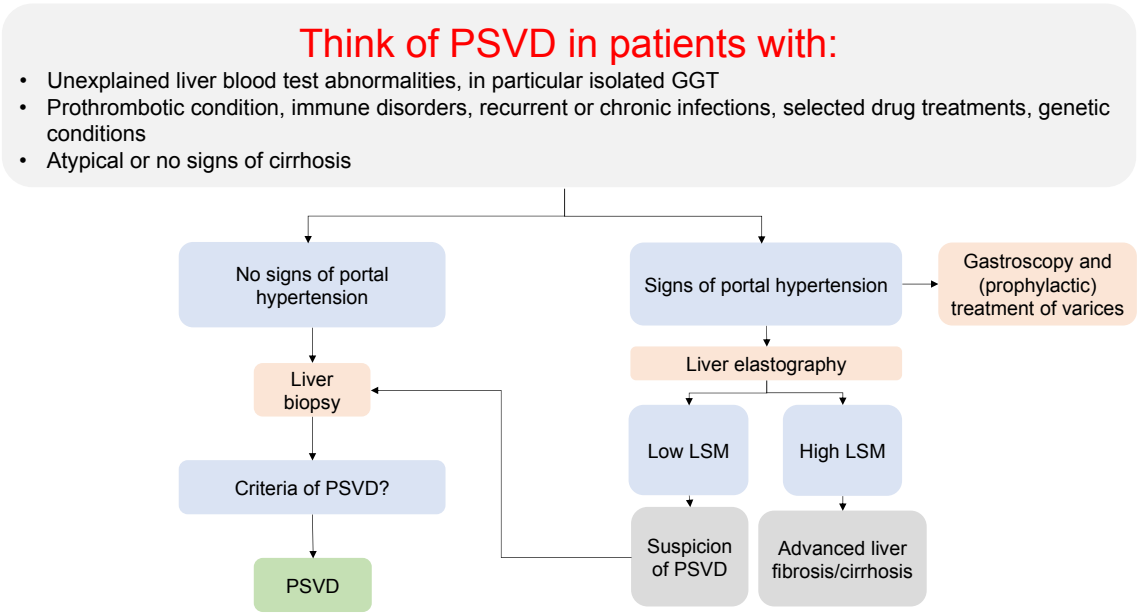


Fig. 2. Diagnostic workup in patients with a suspicion of portosinusoidal vascular disorder (PSVD).

The rationale for the use of anticoagulation in the setting of PSVD, even in the absence of portal vein thrombosis, includes the observation of thickening, narrowing, or obliteration of intrahepatic portal venules. Among explanted livers, portal venules were found to be obliterated in 100%, and large portal veins in 67%. Portal vein thrombosis occurs in 13–45% of patients with PSVD during follow up. Moreover, patients with PSVD commonly have underlying disorders associated with an increased risk of thrombosis. However, randomised trials are required to assess the benefit–risk ratio of prophylactic anticoagulation in patients of PSVD. Anticoagulation therapy is currently recommended for patients with high-risk prothrombotic disorders or those developing portal vein thromboses.

In patients with PSVD and portal hypertension, current practice guidelines propose treating varices following the recommendations for patients with cirrhosis. The effectiveness of this approach has been demonstrated. The cornerstone of therapy is beta-blockers, either carvedilol and propranolol, and endoscopic variceal ligation. Transjugular intrahepatic portosystemic shunts can be an effective treatment option in patients with PSVD and complications of portal hypertension such as variceal bleeding and refractory ascites. Scarce reported data has demonstrated that survival of PSVD patients after liver transplantation is favourable. Post-transplant (recurrent) PSVD has been reported, although its incidence is unclear.

References

References in **BOLD** are required reading

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Medical management of portal vein thrombosis in patients without cirrhosis

Aurélie Plessier[1, 2, 3]

[1]AP-HP, Hôpital Beaujon, Service d'Hépatologie, DMU DIGEST, Paris, *France*; [2]Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Clichy, *France*; [3]Université Paris-Cité, Inserm, Centre de recherche sur l'inflammation, Paris, *France*

E-mail address: aurelie.plessier@aphp.fr

Take-home messages

- Always screen for underlying thrombophilia even with local cause, or provoking factor, NGS can be helpful for diagnosis and prognosis.
- In recent PVT:
  - Urgently start anticoagulation, identify and treat the cause when appropriate, stop oestrogen-containing pill,
  - Prefer LMWH, then oral anticoagulation can be considered. DOACs can be considered as primary option in selected cases in the absence of so-called 'triple positive' antiphospholipid syndrome.
- In chronic PVT:
  - Initiate adequate portal hypertensive bleeding prophylaxis
  - Consider long-term anticoagulation. Haematopoietic NGS analysis, D-dimer concentration 1 month after anticoagulation interruption, factor VIII ≥150% and the 'provoked or unprovoked' characterisation of PVT, might be helpful to decide for anticoagulation interruption.
  - DOACs can be considered as the primary option in the absence of contraindication-dose adapted to cause.
- In patients who are symptomatic but not responding to standard of care, radiological intervention should be considered with a multidisciplinary approach in referral centres. Assess psychological and social context, propose patient's association support, and anticipate pregnancy.

Introduction – definition and classification

Non-tumoral and non-cirrhotic portal vein thrombosis is the most common cause of non-cirrhotic portal hypertension in the West. Portal vein thrombosis, the formation of a non-tumoral obstruction in the portal vein, can extend downstream to the right and left branches and to the intrahepatic segmental branches, and upstream to the splenic vein, and the superior or inferior mesenteric vein. Recent portal vein thrombosis is characterised by a newly formed thrombus in the portal vein or branches and tributaries, having occurred within the past 6 months.[1,2] Chronic portal vein thrombosis (PVT) is characterised by the presence of portal cavernoma or persistent obstruction of the portal vein, identified 6 months after an episode of recent PVT. Classification or staging of PVT, including initial site, extent, degree of luminal obstruction, and chronicity of clot formation is needed to anticipate and assess outcome. More than 20 classifications of portal vein thrombosis exist, according to the context (non-cirrhotic, cirrhotic), anatomical involvement and to the treatment (medical, radiology, surgery, liver transplantation). Presently, the American Association for the Study of Liver Diseases (AASLD) Baveno VII classification is regarded as the most widely accepted in clinical practice in non-cirrhotic PVT, aiming at assessing obstruction outcome correlation with treatment. The most common

complications of portal vein thrombosis include, in the recent stage, venous mesenteric ischemia or infarction, and in the chronic stage, gastrointestinal bleeding as a result of portal hypertension, hepatic encephalopathy from the shunt effect of portosystemic collateral circulation, and portal cholangiopathy resulting from ischemia/compression of the bile ducts by the cavernoma veins. In the chronic stage, mesenteric ischemia can still occur because of the extension of the thrombosis into the splanchnic venous system. These two clinical entities share the same causes, but their management differs.

Causes of portal thrombosis and aetiologic workup and treatment of the cause[3,4]

An inherited or acquired prothrombotic disorder (Table 1) is identified in approximately 50% of cases, and an exogenous or 'provoked' risk factor for venous thrombosis (hormonal, local cause, etc.) is present in about 35% of cases. Several factors are associated in the same patient in 15–36% of cases, which is more frequent than expected by chance alone. Patients with provoked PVT also seem to harbour high- or low-risk factors for thrombosis when systematic screening is performed, and when present are at higher risk of recurrent thrombosis. Therefore, identifying one risk factor should not halt the search for another, even in patients with 'provoked' PVT. Apart from cirrhosis and cancer, myeloproliferative neoplasm (MPN) is the most common cause of portal thrombosis. The diagnosis of MPN is now facilitated by the detection of the V617F JAK2 mutation in a peripheral blood sample. If negative, other mutations such as CALR or MPL mutations are identified less frequently. V617F JAK2 is present in 21–37% of patients with portal vein thrombosis outside the context of cancer and cirrhosis. Additional next-generation sequencing (NGS) for the presence of clonally expanded haematopoietic stem cells mutations identified variants associated with poor prognosis in patients with confirmed MPN.[5] Recent data have clarified the impact of viral infections such as acute cytomegalovirus (CMV) infection, or severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection and vaccine. Finally, in about 30% of patients with portal thrombosis, no cause is identified despite exhaustive investigations. Other data regarding haematopoietic stem cells mutations NGS has identified high risk of thrombosis recurrence variants in patients who had no identified risk factor.[6]

Table 1. Prevalence of risk factors for PVT in the absence of cirrhosis-diagnostic workup. CMV, cytomegalovirus; IVC, inferior vena cava; PVT, portal vein thrombosis; VKAs, vitamin K antagonists; DOACs, direct-acting anticoagulants.

Risk factor	Prevalence (%)	Diagnostic workup
Myeloproliferative neoplasm	**21–25**	Refer to expert haematologist; perform systematic testing of *JAK2* this belongs together and refers to the myeloproliferative neoplasm If negative: • Genetic testing of the *CALR* gene • Discuss next-generation sequencing • Discuss bone marrow biopsy
JAK2 V617F	15–21	
CALR mutation	1–2	

Risk factor	Prevalence (%)	Diagnostic workup
Inherited thrombophilic disorders		Genetic testing for prothrombin G202101A and factor V Leiden mutations; protein S, protein C, antithrombin activity assessed in the absence of VKA antagonist and DOACs
G20210A prothrombin gene mutation/ factor V Leiden mutation	5/8	
Antithrombin deficiency	5	
Protein C deficiency	1	
Protein S deficiency	2	
Acquired thrombophilic disorders		
Antiphospholipid antibody syndrome	5	Lupus anticoagulant, anticardiolipin, and antibeta2 glycoprotein 1 antibody testing *Repeat testing 12 weeks if positive*
Paroxysmal nocturnal haemoglobinuria	0–0.5	Flow cytometry analysis – Refer to expert centre
Behçet's disease	Uncommon	No specific testing, clinical diagnosis
Coeliac disease	0.7	Antitransglutaminase antibody +/– duodenal biopsies
Other systemic factors Auto-immune disease Inflammatory bowel disease, vasculitis, sarcoidosis, Connective tissue disease		Search clinical and/or laboratory features CMV IgM and CMV PCR
Exogenous or provoked factors CMV disease, COVID-19		(blood), perform COVID-19 PCR testing
Hormonal factors Oral contraceptive or pregnancy	**~20**	Especially if 6 months before TVP – Refer to gynaecologist
Local factors Pancreatitis, diverticulitis cholecystitis, appendicitis, intra-abdominal surgery	**20**	CT scan colonoscopy
No identified factor	15–40	

Moreover, in that setting of idiopathic PVT, central obesity is identified in 45% of patients compared with 25% of patients with one or more risk factor. To conclude, complete screening of risk factors is important as it may influence the decision to continue long-term anticoagulant treatment, the type and dose of anticoagulation.

In women, the risk of deep vein thrombosis is increased three to five times, with oestrogen-containing contraception, during pregnancy and post-partum. It is recommended to stop oestroprogestative oral contraception. Pregnancy needs to be anticipated and if possible, occur in stable conditions, having adjusted drug prescriptions.

Regarding treatment of aetiological factors, data are still limited. Studies assessing the impact of treatment of MPN are heterogeneous in terms of therapeutic target, and results are inconsistent. It is still not clear whether adding hydroxyurea to anticoagulation is beneficial for the risk of recurrent thrombosis. Preliminary data with ruxolitinib or pegylated-interferon in small series is promising. In patients with splanchnic vein thrombosis (including Budd-Chiari syndrome) associated with paroxysmal nocturnal haemoglobinuria (PNH), treatment with eculizumab significantly improved survival, and recurrent thrombosis in and outside the splanchnic veins.[7] In one case series, in 18 patients treated with C5 inhibition alone without therapeutic anticoagulation (interrupted in 12), two had recurrent thrombosis suggesting that discontinuation of anticoagulation in PNH patients well-controlled on terminal complement inhibition may be safe.[8] Other data in Behçet's disease and inflammatory bowel disease, suggest a role of anti-inflammatory therapy to prevent recurrent thrombosis.

At present, there are no uniform data supporting the cessation of anticoagulation therapy in patients with a managed aetiological factor.

Anticoagulation therapy

Indication, timing, and type of anticoagulation currently differs in recent and chronic PVT. Current recommendations urge the initiation of anticoagulation therapy at a therapeutic dose right after diagnosing recent PVT. The aims of anticoagulation therapy are to prevent the spread of thrombosis in the splanchnic veins and elsewhere, and to achieve repermeabilisation of the portal vein or the superior mesenteric and splenic veins. A large European study has shown that using low-molecular-weight heparin (LMWH) initially, followed by vitamin K antagonists (VKAs), led to a low incidence of mesenteric infarction (2%) and recanalisation of the portal vein in 40% of patients.[9] LMWH is generally preferred in these cases. Indeed, high incidence of heparin-induced thrombocytopenia in this group has been reported with unfractionated heparin. Although the evidence is limited, direct oral anticoagulants (DOACs) can be considered as a primary treatment option except for those with the 'triple positive' antiphospholipid syndrome or signs of intestinal ischemia. A recent retrospective analysis of 330 patients who were non-cirrhotic with recent PVT showed that DOACs had comparable rates of recanalisation to LMWH. After recent PVT, a treatment duration of at least 6 months is recommended. Long-term anticoagulation indication will vary according to the cause identified and the risk of bleeding.

In chronic PVT, prospective and retrospective, randomised and non-randomised studies suggest that anticoagulant treatment can reduce the risk of recurrent thrombosis within (mesenteric venous infarction, recurrent cavernoma vein thrombosis) or outside (phlebitis, pulmonary embolism, etc.) the splanchnic venous system, without increasing the risk of bleeding, particularly those caused by portal hypertension. In these cohorts, the anticoagulants used were either unfractionated or LMWH, VKAs, or DOACs. Data support long-term anticoagulation in patients with strong risk factors for recurrence such as personal or first-degree history of spontaneous venous thromboembolism, antiphospholipid

syndrome, MPN or high-risk thrombophilia. Recently, a randomised controlled study has shown that in the absence of these strong risk factors, interruption of anticoagulation was associated with a 20% patient year risk of deep vein thrombosis recurrence in the splanchnic and outside the splanchnic venous system.[10] Rivaroxaban 15 mg once daily significantly reduced thromboembolic events or death without increasing the occurrence of major bleeding in that setting. In patients in whom anticoagulation was discontinued, D-dimer concentration <500 ng/ml (Innovance technique, Siemens) 1 month after anticoagulation interruption, and provoked PVT predicted a low risk of recurrence. In a retrospective multicentre study evaluating risk factors for recurrent thrombosis in 64 patients with chronic idiopathic/local factor PVT factor VIII ≥150% was the only independent factor predicting recurrent thrombosis.[6]

Thus, recent recommendations support long-term anticoagulation in chronic PVT. Haematopoietic stem cells mutations NGS analysis, D-dimer concentration 1 month after interruption, factor VIII ≥150% and the 'provoked or unprovoked' characterisation of PVT, might be helpful, when anticoagulation interruption needs to be considered. When possible, follow up in therapeutic education programmes for anticoagulation or with anticoagulation expert centres is an important component of anticoagulation management.

Portal hypertension therapy

Episodes of gastrointestinal bleeding caused by rupture of oesophagogastric varices or from portal hypertensive gastropathy can occur unpredictably. The incidence of gastrointestinal bleeding is 12–20% per year and rebleeding occurs in up to 47% of the patients at 5 years. Varices responsible for the bleeding can belong to a portosystemic collateral circulation (oesophageal, gastric, or fundic varices) or to veins of the cavernoma (gastric antrum and duodenum).

Baveno VII recommendations for primary or secondary prophylaxis of variceal bleeding apply guidelines for cirrhosis. Screening endoscopy is needed in that setting, and oesophageal variceal band ligation can be performed safely without withdrawing vitamin K antagonists.[1]

Quality of life and conclusions

Although data are limited, quality of life (QoL) is often negatively impacted in cases of portal vein thrombosis, with a notable prevalence of anxiety, fatigue, and depression. Having these points in mind, diagnosis announce needs to be performed according to best practice, as it may have an impact on disease outcome and patient's compliance with therapy. Patient's association support is also part of management in rare diseases. Collaboration with expert centres in rare diseases, hepatology, internal medicine, haematology, and anticoagulation is invaluable in PVT.

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Medical management of portal vein thrombosis in patients with cirrhosis

Erica Villa[1]

[1]Chimomo Department, University of Modena and Reggio Emilia, Modena, *Italy*

E-mail address: erica.villa@unimore.it

Take-home messages

- Deterioration in liver function correlates with a shift towards a more thrombophilic state, rather than a haemorrhagic one, as a result of coagulative imbalance.
- Thrombotic complications, although not the primary cause of chronic liver disease progression, serve as one of several indicators of its advancement.
- Current evidence does not support the analysis of specific risk factors, whether inherited or acquired, for thrombosis in cirrhosis.
- The impact of portal vein thrombosis (PVT) on liver transplantation outcomes is variable; it does not alter long-term survival but may worsen short-term outcomes within the first year post-transplant.
- Anticoagulation is safe for patients with advanced cirrhosis. It works better than no treatment in achieving PVT recanalisation and may also improve survival.

Introduction

Portal vein thrombosis (PVT) is commonly associated with cirrhosis and its occurrence increases with the severity of liver disease. The one-year incidence rate escalates from 4.6% in patients at the Child-Pugh A stage to between 12.8% and 27.0% in those at the predominantly Child-Pugh B and C stages, as reported by Nery *et al.*,[1] Villa *et al.*,[2] and Maruyama *et al.*[3] Furthermore, evolving patterns in chronic liver disease aetiology, particularly the decline in hepatitis C virus (HCV) infections and the rise of metabolic-associated fatty liver disease (MAFLD) conditions, are likely to alter the interpretation of the natural course of PVT and management strategies in the foreseeable future.

Risk factors

The most significant and common risk factors for PVT include acquired factors such as Child-Pugh B–C classification, decompensated disease stage, and pronounced portal hypertension. Other relevant factors encompass prior variceal bleeding, decreased portal vein flow velocity, and interventional treatments such as varices endoscopic therapy, abdominal surgery, and injury to the portal venous system through methods such as surgical portosystemic shunting or transjugular intrahepatic portosystemic shunt (TIPS). Additional risk factors include liver or other organ cancers, sepsis, and a low platelet count.

As the recognition that patients with liver cirrhosis during the course of the disease are more likely to develop thrombotic rather than haemorrhagic complications[2] higher attention has been paid to the evaluation of thrombophilia as a predisposing factor to PVT. According to Middeldorp and van Hylckama Vlieg[4] thrombophilia may be defined as both a congenital or acquired abnormality of haemostasis predisposing to thrombosis.

Congenital factors such as deficiencies in protein C, protein S, antithrombin (AT), factor V Leiden (FVL) mutation, the prothrombin gene mutation G20210A, and the C667T mutation in the MTHFR

gene are not common. AT deficiency has a low prevalence (0.02–0.2%), but carries a high thrombosis risk. The C667T MTHFR mutation, although more prevalent (2–4%), carries a lower thrombosis risk. Philadelphia-negative myeloproliferative diseases also contribute, albeit less frequently. Individual small studies have given contrasting results.[5–7] Both Amitrano *et al.*[5] and Erkan *et al.*[6] found a significant association between thrombophilic genotype and PVT occurrence. Their results were not confirmed in a prospective study by Mangia *et al.*,[7] which prospectively evaluated 219 patients with cirrhosis, 43 of them with PVT. These authors found a similar proportion of the main prothrombotic mutations (FVL, G20210A of the prothrombin gene, MTHFR gene mutation) in patients with and without PVT. The main risk factors for PVT in this cohort were sclerotherapy or previous surgery. During follow up, only one patient with a thrombophilic profile developed PVT. In a larger and later study, Amitrano *et al.*[8] only partially confirmed their previous results, as the higher risk for PVT was confirmed only in a carrier of the prothrombin gene mutation G20210A.

Several meta-analyses have been carried out to try to elucidate whether there is a causal relationship between thrombophilic mutations and PVT. A meta-analysis performed on 3,000 patients from 12 studies showed that the pooled odds ratio (OR) for PVT was 1.90 (95% CI, 1.25, 2.90) in patients with FVL and 4.48 (95% CI, 3.10, 6.48) in patients with prothrombin mutation thus suggesting a causal association for these mutations in PVT.[9] A second meta-analysis from six studies showed that FVL mutation was significantly higher in patients with cirrhosis and PVT than in those without the event (hazard ratio [HR] = 2.55; 95% CI: 1.29–5.07; $p = 0.007$), whereas the prevalence of PTHR mutation was not different between both groups (HR = 2.93; 95% CI: 0.94–9.07; $p = 0.06$).[10] A more recent meta-analysis on nine studies including 1,929 subjects with cirrhosis of which 125 with PVT (overall prevalence 6.5%) confirmed that prothrombin G20210A mutation (OR, 2.43; 95% CI, 1.07–5.53; $p = 0.03$) and FVL (OR, 1.98; 95% CI, 1.06–3.68; $p = 0.03$) are significantly associated with PVT risk.[11] On the opposite, methyltetra-hydrofolate reductase C677T mutation was not associated with increased PVT risk.[11] Another meta-analysis found instead that patients with cirrhosis and PVT had significantly higher prevalence of homozygous MTHFR C677T mutation.[12] Overall, the findings of these meta-analyses remain inconclusive, likely because of significant variations in the populations studied and the methodologies used.

Few prospective studies have been performed. In a study enrolling 253 patients without PVT at baseline with confirmed cirrhosis-induced gastro-oesophageal varices with 2-year median follow up, a total of 47 (18.58%) patients without PVT at baseline developed PVT, 16 (6.32%) of them developed PVT within 1 year. Elevated factor VIII activity was associated with the occurrence and the severity of PVT. No other haemostatic biomarkers were tested apart from von Willebrand factor (vWf) antigen, and vWf activity.[13]

Turon *et al.*[14] performed a large single-centre prospective study in 369 patients with cirrhosis without PVT followed up for a mean of 48 ± 27 months. In the 310 patients who consented for blood sampling, an extensive evaluation of clinical, biochemical, inflammatory, and acquired/hereditary haemostatic profiles was performed. None of the tested biomarkers was significantly associated with PVT development. The composition of the cohort (>70% Child-Pugh A, more than half Hep-C positive with only 3.5% MAFLD) and the relatively short follow up for this category of patients, who have a low incidence of PVT,[1] suggest that further prospective studies investigating haemostatic alterations as risk factors for PVT are warranted. As for now, these findings indicate that screening for inherited or acquired thrombophilia is not indicated in the routine clinical practice.

Emerging evidence suggests a higher thrombotic risk in metabolic dysfunction-associated steatotic liver disease (MASLD) compared with other aetiologies. One of the first reports suggesting this relationship was in the transplantation context. Non-alcoholic steatohepatitis (NASH) cirrhosis was identified as

the strongest risk factor independently associated with a diagnosis of PVT at multivariable analysis (OR, 1.55; 95% CI, 1.33–1.81; p <0.001). Interestingly, NASH cirrhosis appeared to predispose a patient to PVT independently of other risk factors.[15] Stupia *et al.*[16] have examined the prevalence of PVT in patients with non-alcoholic fatty liver disease (NAFLD) compared with other aetiologies in a meta-analysis of five observational studies for a total of 225,571 patients, of which 26,840 (11.9%) had NAFLD. Even considering a relevant heterogeneity of the studies, patients with NAFLD and its advanced forms had a higher risk of prevalent PVT (OR, 1.34; 100% CI, 1.07–1.67; p <0.01) (Fig. 1). This meta-analysis suggests that patient with NAFLD/NASH have a higher risk of prevalent PVT than patients of other aetiologies. These data need to be further substantiated by prospective studies.

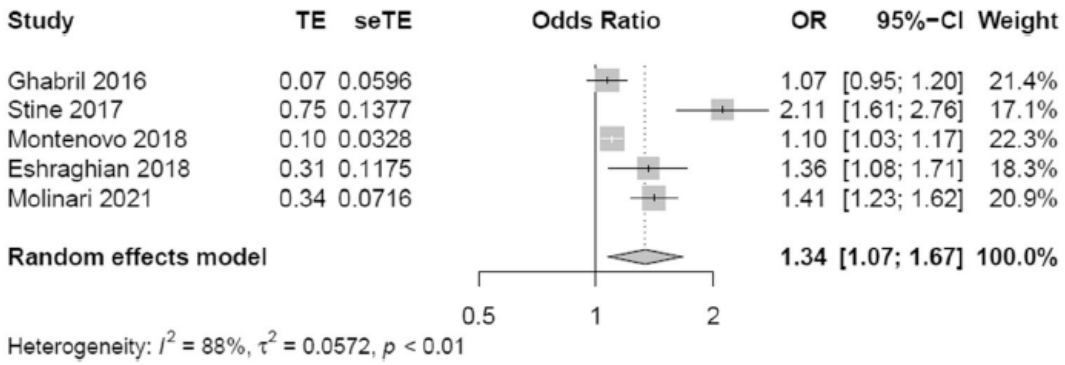


Fig. 1. Forest plot reporting the association between non-alcoholic fatty liver disease and the risk of prevalent portal vein thrombosis.[16]

TE : estimate of treatment effect; seTE : standard error of treatment estimate

To date, the most significant risk factor for PVT is the worsening severity of liver disease. This progression is marked by changes in coagulation, anatomical changes, and reduced blood flow through the portal vein, which together increase the likelihood of thrombosis. Other contributing risk factors include ethnicity, older age, and a higher model for end-stage liver disease (MELD) score. Recent research, including a systematic review and meta-analysis published in the *European Journal of Internal Medicine* in 2022,[17] indicates a clear association between the progression of liver cirrhosis, portal hypertension, and the risk of PVT. Furthermore, a prospective study on 1,243 patients with cirrhosis spanning 47 months found that the onset of PVT was more common in those with more advanced liver disease from the start.[1] Notably, among patients with a Child-Pugh A, who made up 67.5% of the study population, the incidence of liver decompensation associated with PVT was minimal. In the control group of the enoxaparin study,[2] patients with moderate to severe liver disease (Child-Pugh B and C), who lacked thrombophilic mutations and primarily had hepatitis C or alcohol-related conditions, experienced a 16% incidence of PVT.

Impact of PVT on course of cirrhosis

Data on the natural history of PVT are burdened by methodological deficiencies like almost all studies in this area. Among various factors, studies reporting outcome of partial or complete PVT are limited as usually patients with complete PVT receive anticoagulation.

However, despite the diversity in the original studies, meta-analyses examining the outcomes of patients with cirrhosis with PVT who did not receive anticoagulation have provided valuable insights (Fig. 2). These studies have consistently shown a 25% progression rate in PVT cases and have

informed our understanding of the impact of the condition on liver decompensation, patient survival, and liver transplantation outcomes.[17,18]

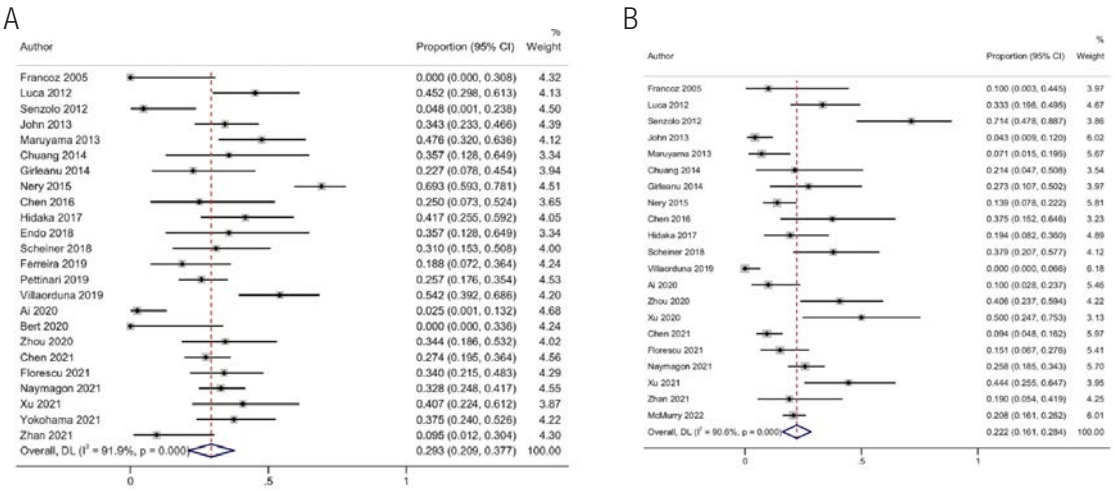


Fig. 2. Forest plot for pooled proportion of patients with cirrhosis with regression (A) or progression (B) of portal vein thrombosis (PVT).[18]

Data from 26 studies (24 observational and two RCTs, untreated arm) for a total number of 1,441 patients with cirrhosis were included in a meta-analysis aiming to evaluate the natural history of PVT in cirrhosis without anticoagulation. The pooled rate of PVT regression in patients with cirrhosis was 29.3% (95% CI, 20.9–37.7; I^2 = 91.9%). The pooled event rate of complete recanalisation was 10.4% (95% CI, 5.0–15.8; I^2 = 84.1%). The pooled event rate for PVT progression 22.2% (95% CI, 16.1–28.4; I^2 = 90.6%).

Decompensation

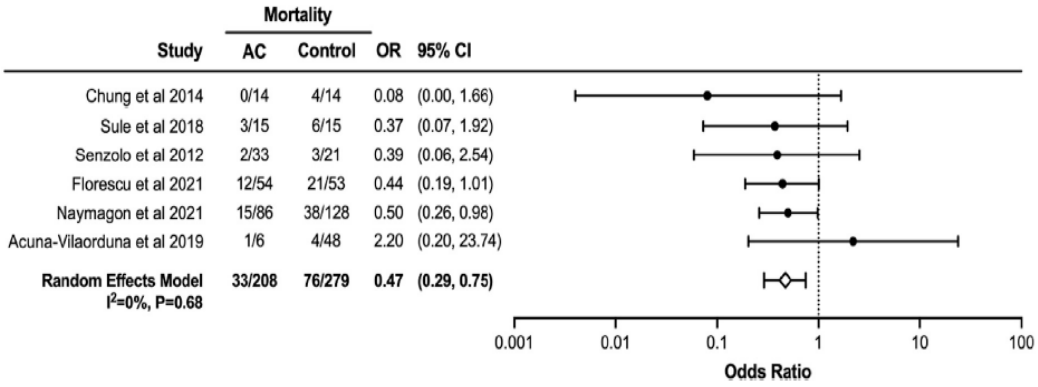
Few studies have addressed the relationship between PVT and occurrence of decompensation. One of the studies evaluating this relationship was the study by Luca *et al.*[19] in which the decompensation and need for liver transplant (LT) were not significantly different between with PVT regression and those with stable or increased PVT (59% *vs.* 51%, p = 0.549). In a small study on 27 patients followed up for 1 year, those with a progressive PVT showed an increase of MELD score.[20] It should be noted, however, that these studies do not clarify whether it is PVT progression that leads to decompensation or the more advanced hepatic condition that facilitates PVT occurrence.

Survival

Many studies have evaluated the impact of PVT occurrence on survival in absence of a therapeutic intervention. Two studies, one retrospective and the other prospective, found similar survival rates in patients with and without PVT.[3,19] These data were confirmed in a large prospective study.[1] A recent meta-analysis on a large number of patients with PVT[20] found that patients with cirrhosis presenting with PVT had a lower 1-year survival rate than patients without PVT (OR, 0.32; 95% CI, 0.14–0.75; p = 0.008). However, the cumulative survival rates were similar at 3 and 5 years. Patients with Child-Pugh class B and C disease or complete PVT had a higher risk of death.

In patients receiving anticoagulation, apart from the increased rate of recanalisation obtained by anticoagulation, two recent meta-analyses[21,22] have shown that anticoagulation is associated with a decrease of all-cause mortality independently of thrombosis severity and recanalisation (Fig. 3A–C).[22] This suggests that additional mechanisms, apart from anticoagulative effect, could be also involved.

A)



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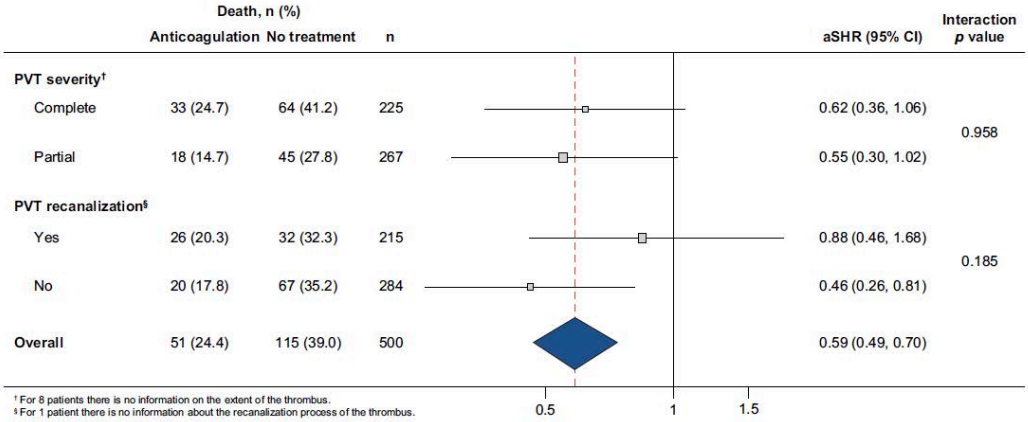

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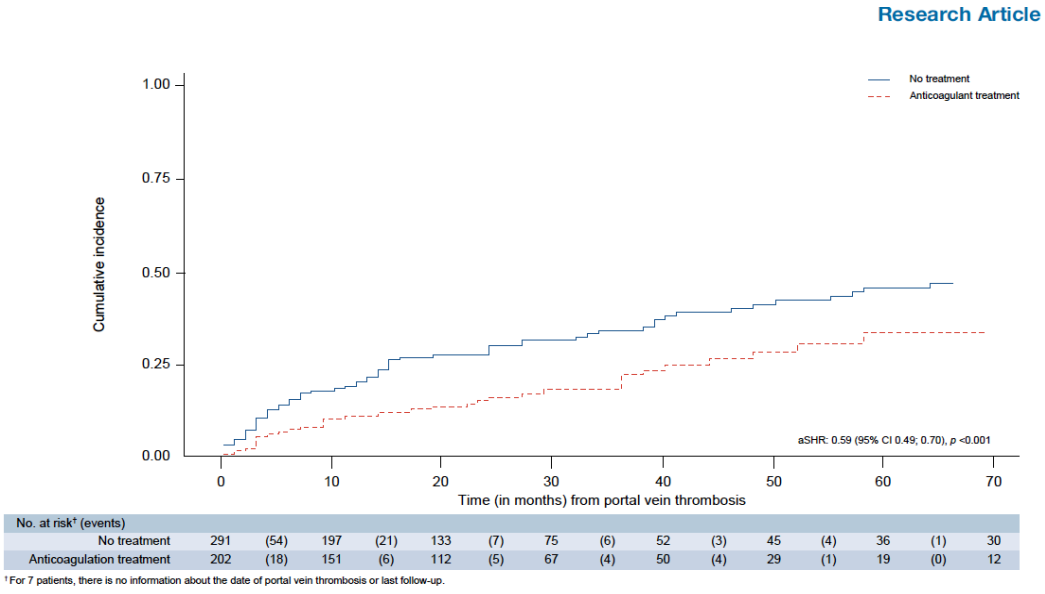

Fig. 3. (A): All-cause mortality following anticoagulation (AC) for portal vein thrombosis (PVT) in the setting of cirrhosis.[21] (B): Cumulative incidence of all-cause mortality estimated by the competing-risk analysis according to anticoagulation treatment.[22] (C): Subgroup analysis of the effect of anticoagulation on the competing risks of all-cause mortality according to PVT severity and recanalisation.[22]

Liver transplant

The development of non-occlusive PVT may not affect the progression of liver disease or increase the risk of mortality while on the waitlist for a LT. However, PVT is associated with increased early post-transplant mortality (Fig. 4). Importantly, anticoagulation therapy in patients awaiting LT does not negatively impact the transplant procedure. On the contrary, recanalisation of the portal vein before surgery can be advantageous. Notably, when PVT is complete and present during surgery, it significantly raises the risk of both early and late hepatic artery thrombosis after transplantation, which can negatively impact survival.[23]

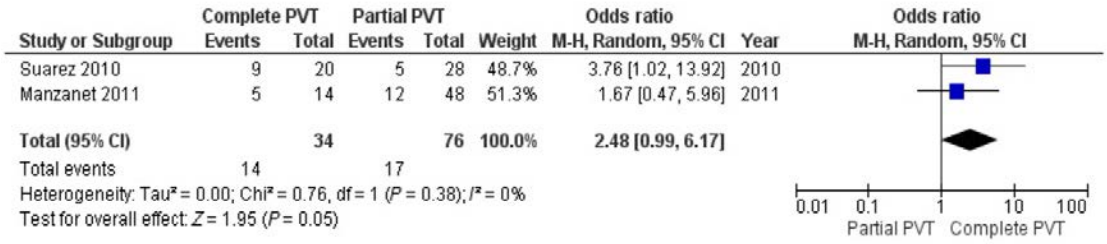

Fig. 4. One-year mortality in recipients with partial vs. complete portal vein thrombosis (PVT).[23]

The forest plot shows there was a significant increase in mortality in liver transplant recipients with complete PVT when compared with recipients with partial PVT, although it was at the inferior limit of statistical significance.

Indications for anticoagulation

The data presented above makes it evident that treating PVT involves considerations beyond the mere presence of a blood clot. Recognising that PVT is intertwined with the progression of liver disease, the approach to treatment should encompass this broader context.

Although there is indication from prophylactic studies that anticoagulation decreases occurrence of PVT and improves survival,[2] especially in patients who are Child B,[24] these studies were underpowered to allow a generalisation of PVT prophylaxis.

There is a consensus that treatment for acute symptomatic PVT should begin immediately. The European Association for the Study of the Liver (EASL) guidelines advocate for the prompt initiation of low-molecular-weight heparin (LMWH) in a dosage adjusted to the patient's weight for those with cirrhosis experiencing acute PVT.[25] The earlier the treatment starts, the better the prognosis. Data suggest that initiating anticoagulation therapy >6 months after PVT onset is unlikely to result in recanalisation. However, early and successful management of acute symptomatic PVT not only improves the disease trajectory, but also aids in the management of associated complications of portal hypertension, all with minimal adverse effects. Anticoagulation therapy should continue for 6 months. However, there is a lack of evidence-based data regarding the long-term use of anticoagulation. Only a handful of reports exist, drawn from small patient series. Although these reports confirm the safety of long-term anticoagulation, it remains unclear if there are definitive benefits compared with administering treatment again if the PVT recurs.

Data are less clear cut for PVT of unknown duration. The possible PVT impact on natural history of disease is feared especially in patients with more advanced CLD and possible transplant candidates. This has led to the performance of many interventional studies. Unfortunately, most of these studies present methodological problems. They are retrospective, observational, heterogenous in the choice of the drug or of the dosage and have enrolled small cohorts of patients. The meta-analyses that have elaborated the findings of the individual studies suffer from the same drawbacks, However, despite these limitations derived from the individual studies that cannot be mended by meta-analysis, they have reached some useful indications.

Data on different types of anticoagulants will be dealt with in another part of the syllabus. However, there is general agreement that treatment achieves higher rates of recanalisation than no treatment and lower rates of progression of thrombosis, independently from the drug used, with reasonable safety for the different categories of drugs (Table 1).

Overall, even in the absence of specific studies, anticoagulation merits consideration. This is especially true for potential LT candidates, patients with cirrhosis who are not candidates for LT but have PVT blocking >50% of the lumen – whether or not splanchnic veins are involved – and patients whose PVT obstructs <50% but shows signs of progression on follow up.[25] The most comprehensive meta-analysis to date[21,22] suggests that anticoagulation may positively influence both the recanalisation and overall patient survival. These promising insights necessitate confirmation through prospective research.

Table 1. Characteristics of meta-analysis studies on anticoagulation for portal vein thrombosis therapy in cirrhosis (from Rautou *et al.*[26], modified and updated).

AF, atrial fibrillation; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, vitamin K antagonist; PVT, portal vein thrombosis; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Reference	Study design	No. of studies evaluated	Population & no. involved	Drug	Performance	Complications
Yao *et al.*[21]	Meta-analysis	16 studies	Patients w/ cirrhosis w/ PVT: n = 1126		Improved recanalisation Decreased mortality	Bleeding risk: low and comparable among treatments
Li *et al.* 2023	Meta-analysis	3 studies (observational)	Patients w/ cirrhosis w/ PVT: n = 460	VKA, LMWH	Improved recanalisation	Bleeding risk: low and comparable among treatments
Guerrero *et al.*[22] 2023	Individual data meta-analysis	5 studies (observational)	Patients w/ cirrhosis w/ PVT: n = 500	VKA, LMWH	Improved survival in anticoagulation group No difference in recanalisation	Non-portal hypertension-related bleeding, greater in the anticoagulation group
Zhang *et al.* 2022	Meta-analysis	17 studies (14 observational and 3 RCT)	Patients w/ cirrhosis w/ PVT N = 1270	VKA, LMWH, and DOACs	Improved recanalisation	Bleeding risk: low and comparable among treatments
Koh *et al.* DLD 2022	Meta-analysis	11 studies (10 observational and 1 RCT)	Patients w/ cirrhosis w/ AF, VTE, PVT, or DVT N = 551	VKA; DOACs	PVT recanalisation and lower risk of PVT progression	Bleeding risk and mortality: similar between DOACs and VKA

Chen *et al.* CJGH 2021	Meta-analysis	36 studies 11 RCT 25 observational	Patients w/ cirrhosis w/ PVT N = 3,479	LMWH, VKA, DOACs, antithrombin III, aspirin	Recanalisation: DOACs > traditional anticoagulants	Bleeding risk and mortality: no differences in treatment groups Bleeding events increased in prophylactic group
Ng *et al.* Hepatology Int 2021	Network meta-analysis and single-arm meta-analysis	10 studies 3 RCT 7 observational	Patients w/ cirrhosis w/ PVT Network: n = 527 Single-arm: n = 200	LMWH, VKA, DOACs, antithrombin III	Recanalisation: DOACs > LMWH > VKA	Bleeding risk: low and comparable among treatments
Gao *et al.* CRHG 2021	Meta-analysis	8 studies	Patients w/ cirrhosis w/ PVT N = 225	VKA, LMWH, DOACs (n = 39)	Recanalisation: LMWH > VKA > no treatment	Bleeding risk: low and comparable among treatments
Wang *et al.* Adv Ther 2021	Meta-analysis	33 studies	Patients w/ cirrhosis w/ PVT: n = 1,696	VKA, LMWH	Recanalisation: DOACs > VKA > LMWH > no treatment	Bleeding risk and mortality: low and comparable among treatments
Mohan *et al.* Ann Gastr 2020	Meta-analysis	17 studies	Patients w/ cirrhosis w/ PVT: n = 648 AC; 96 Ctl	VKA, LMWH, DIAC	Recanalisation: DOACs > VKA > LMWH > no treatment	Bleeding risk: low and comparable among treatments

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Interventional radiology for chronic portal vein thrombosis

Hepatologist

Juan Carlos Garcia Pagan[1, 2, 3, 4]

[1]Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Institut de Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, *Spain*; [2]CIBEREHD (Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas), Madrid, *Spain*; [3]Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver), Hamburg, *Germany*; [4]Departament de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, *Spain*

E-mail address: jcgarcia@clinic.cat

Radiologist

Riad Salem[1]

[1]Department of Interventional Radiology, Northwestern University, Chicago. IL, *USA*

E-mail address: rsalem1@nm.org

Take-home messages

- In adult patients with chronic PVT, refractory portal hypertension-related bleeding is the main indication for portal vein recanalisation.
- Symptomatic portal cholangiopathy, refractory/recurrent ascites, before abdominal surgery and persistent severe abdominal pain are other potential indications for portal vein recanalisation.
- In adult patients with asymptomatic chronic PVT preventive portal vein recanalisation cannot be recommended.
- In patients with chronic PVT, recognising if there is or not an underlying chronic liver disease is essential because it can influence treatment decisions.
- The risk/benefit of indicating a portal vein recanalisation should be discussed by a multidisciplinary team in expert referral centres.

Case presentation

A 47-year-old man presented in the emergency room because of haematemesis. He has no relevant no relevant history of previous illness. No history of tobacco consumption or alcohol abuse. He was working and well until today. At admission: conscious, well perfused, well nourished. Mean arterial pressure: 70 mmHg; heart rate: 95 bpm. No signs of chronic liver disease. No hepatomegaly. Splenomegaly of 3 cm. Upper endoscopy: oesophageal varices with active bleeding. Via endoscopy, band ligation was performed. Somatostatin infusion was initiated. Bleeding was controlled and non-selective beta-blockers were initiated, and the patient was entered in a variceal eradication programme with endoscopic variceal ligation (EVL).[1]

Main results of blood test: aspartate aminotransferase (ASAT)/alanine aminotransferase (ALAT): 45/43 UI/L; gamma-glutamyltransferase 50. Normal alkaline phosphatase, Hb 10 g/L, platelet count 250,000.

At this point, there are three relevant issues:

1. Is there an underlying chronic liver disease?

2. Is it necessary to look for a potential thrombophilia cause of portal vein thrombosis (PVT)? Already discussed in the previous sections.

3. Definition of the extent of PVT.

Therefore, we are going to discuss points 1 and 3.

Point 1: It is important to discard the presence of an underlying chronic liver disease because it may influence management. If there is cirrhosis, hepatocellular cancer (HCC) screening is required. If there is underlying portosinusoidal vascular disorder (PSVD) with portal hypertension or cirrhosis in case of indicating portal vein recanalisation (PVR; discussed later) the probability of the need of ending the procedure with a TIPS is increased. This is because, in addition to PVT, there is an intraparenchymal increase in hepatic resistance to portal blood flow that may compromise the portal venous outflow and facilitate rethrombosis of a successful recanalisation procedure. Blood tests, imaging studies, and liver elastography may be of help to distinguish a normal from a pathological liver. However, in some instances: (a) persistent unexplained abnormal liver blood tests, (b) relevant alterations in the morphology of the liver, (c) elevated liver stiffness measurement values, or (d) before PVR a liver biopsy would be required.

A Doppler ultrasound was performed showing mild alteration in liver parenchyma structure and discrete atrophy of the left lobe. Other features were: occlusion of the main portal trunk with patent intrahepatic portal vein branches, doubtful mesenteric or splenic vein patency, splenomegaly of 15 cm. Liver elastography (FibroScan ECHOSENS®) was 7.5 kPa and spleen stiffness was 53 kPa. Abnormalities in liver enzymes were minimal and therefore at this time, liver biopsy was not considered necessary. The patient was supposed to have a 'healthy' liver before PVT.

From an interventional radiology perspective, the presence of cirrhosis will definitely alter the management approach. If the patient has cirrhosis, then transplantation will be the final destination, with PVR-transjugular intrahepatic portosystemic shunt (PVR-TIPS) will be the goal. From a technical side, approaches to this will be trans-splenic, transhepatic, and possibly transmesenteric. The success rates with this approach ranges from 80% to 95%, because often in such cases, the superior mesenteric vein (SMV) and splenic veins (SVs) are open and may be used for access to the occluded portal vein. It is critical to leave unstented the main portal vein, to permit an end-to-end anastomosis for transplantation. If the patient does not have cirrhosis, the transplantation, from a practical standpoint, is not a final therapeutic destination. In such settings, the SMV and SV are often diseased and represent technical challenges to recanalisation. Success rate in these settings will depend on centre experience. In a high-volume centre, success ranges from 75% to 90%. Stenting in patients without cirrhosis can be more liberal. Long-term management of patients without cirrhosis after PVR-TIPS will be heavily based on anticoagulation.

Point 3: In a patient with chronic PVT, defining the extent of PVT is essential for recognising potential future rethrombotic events of previously patent splanchnic vessels and, if a portal vein recanalisation is considered, defining the intervention strategy (see later by our IR colleague). Contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging are better than ultrasound with or without contrast agent to characterise the extension of PVT (vessels affected and degree of occlusion of the lumen).[2]

Contrast enhanced-CT was performed showing a complete occlusion of the portal vein trunk, patent right intrahepatic portal vein branch with partial occlusion of the left intrahepatic vein branch. The

splenoporto-mesenteric confluence was partially occluded. The distal superior mesenteric vein and proximal splenic vein were also patent. Splenomegaly was 15 cm; no ascites.

The thrombophilia study disclosed a mutation in the *JAK2* gene, and the haematologist confirmed the diagnosis of polycythaemia vera. The patient was initiated on specific haematologic treatment including anticoagulation.

The patient was discharged from hospital with treatment on an adequate dose of non-selective beta-blockers (NSBBs) and EVL sessions every 3–4 weeks. Despite that, 6 months later the patient had melena and a minor episode of variceal bleeding was confirmed by endoscopy. No transfusion was required and a new session of EVL was performed. The patient takes the NSBBs and follows the scheduled endoscopies and EVL sessions when required. However, again 6 months later a variceal bleed requiring admission and blood transfusion occurred, which was finally controlled with a new endoscopy session and the patient was referred for potential PV recanalisation. A new contrast-enhanced CT scan showed similar results to the previous one.

Now that the patient has progressed on standard of care and continues to bleed, definitive treatment with PVR-TIPS is warranted. The approach would first start with ultrasound-guided puncture of the intraparenchymal splenic vein. The occluded main PV would be recanalised and a snare placed in the liver for targeting. From the jugular side, the snare would be punctured. With the through-and-through access, persistent varices would be embolised followed by stenting. Not infrequently, stenting will include the entire main PV and often extend into the SV, thereby jailing the SMV. This is necessary to optimise outflow from the SV into the TIPS. The patient would be discharged after 1 day of observation, and would enter ultrasound surveillance at months 1 and 3, and CT scan at month 6 and 12. Non-invasive ultrasound monitoring would be used subsequently and the patient followed by hepatology.[6]

Taking into consideration the benefit/risk ratio, the current indications for PV recanalisation in adult patients with non-cirrhotic PVTs are portal hypertensive-related bleeding after failure of medical and endoscopic treatment. This is the most frequent indication in patients without cirrhosis (Fig. 1[3–8]). Failure to control bleeding or early rebleeding occurred in 17% of patients having a first variceal bleed and then being a potential candidate for PVR.[9] In this population, actuarial probability of rebleeding on secondary prophylaxis is ~50% at 5 years[9,10] making them also potential candidates for PVR.

	Qi *et al.*[3] (n = 21)	Klinger *et al.*[4] (n = 17)	Marot *et al.*[5] (n = 15)	Knight *et al.*[6] (n = 39)*	Artru *et al.*[7] (n = 31)	Deltenre *et al.*[8] (n = 85)
Indication						
Portal hypertensive bleeding	20	13	6	24	13	45
Abdominal pain	0	1	3	23	7	11
Before abdominal surgery	0	0	4	0	4	9
Portal cholangiopathy	0	1	2	1	3	11
Ascites	1	2		6	1	5
Other				Ischemia (1)	Severe gastropathy (2)	Prevent bleeding (1)
				Failure to anticoagulation (28)	Failure to anticoagulation (1)	Thrombopenia /portal hypertension (2)
						Failure to anticoagulation (1)
Associated TIPS	21	17	0	39	0	18

Fig. 1. Indications for portal vein recanalisation.
*Some patients had more than one indication.

Other indications (Fig. 1) for the use of PVR is to reduce portal hypertension and intra-abdominal collaterals in patients that require abdominal surgery and, less frequently, for recurrent/refractory ascites.[8]

Portal cholangiopathy, although observed in >80% of patients, is symptomatic in only ~20% of the cases in the form of cholecystitis, cholangitis, jaundice, and/or pruritus. Medical and endoscopic treatment is the first choice but in the case of non-response, PVR is considered as an alternative (Fig. 1). Interestingly, persistent and severe abdominal pain without an alternative cause, is also a frequent indication of PVR in patients with chronic PVT without cirrhosis. Indeed, in some cohorts this was the second most frequent indication (Fig. 1).

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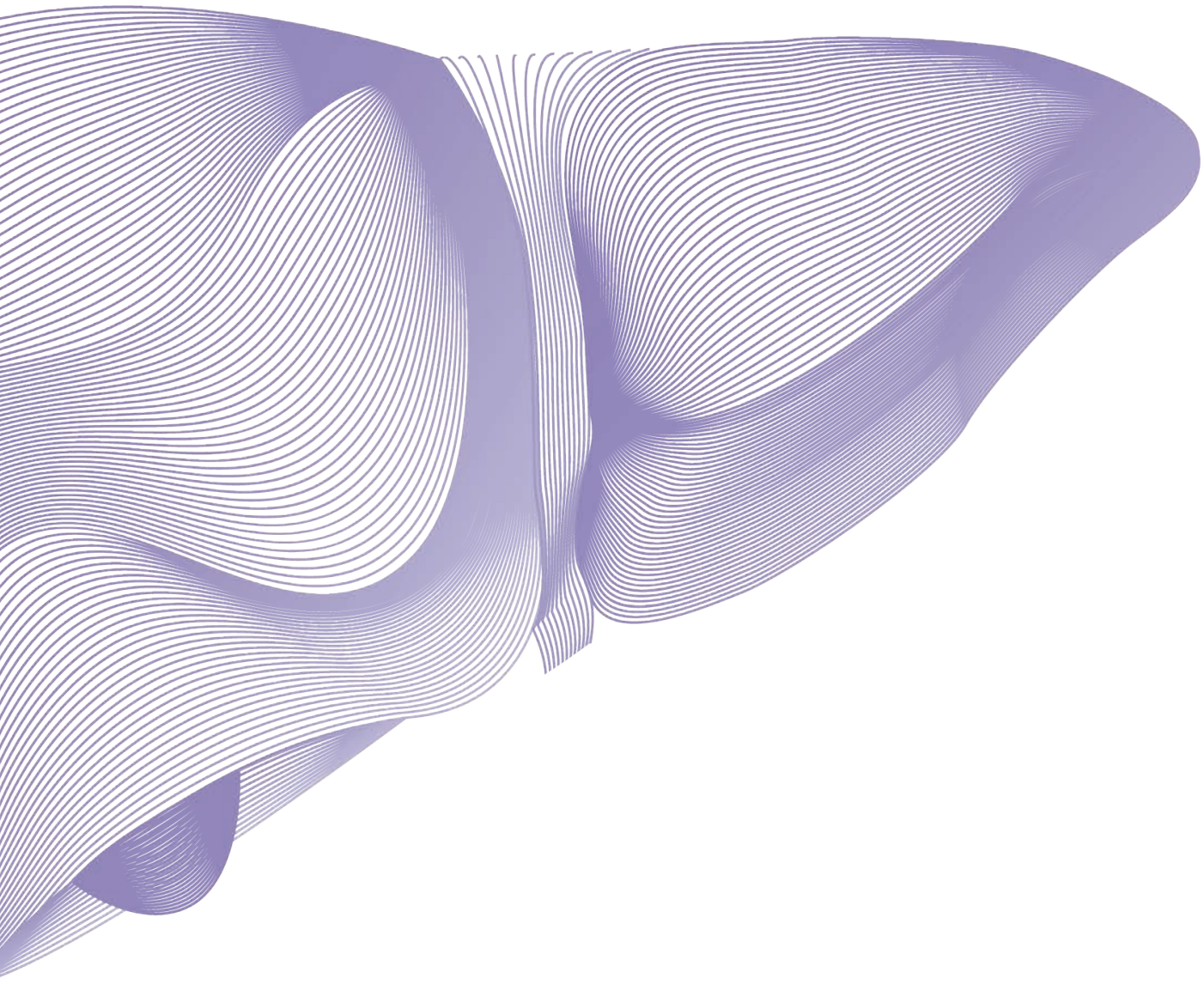
SESSION 2

MANAGEMENT OF PORTAL HYPERTENSION IN CIRRHOSIS: WHAT'S NEW?

WEDNESDAY 5 JUNE
11:45-13:15



Paradigm shifts in portal hypertension

Thomas Reiberger[1]

[1]Medical University of Vienna, Department of Medicine III, Division of Gastroenterology and Hepatology

E-mail address: thomas.reiberger@meduniwien.ac.at

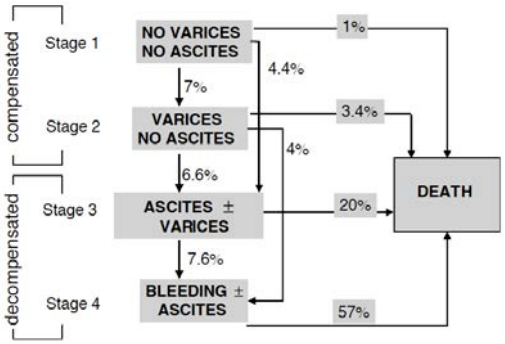
Take-home messages

- Primary prophylaxis of variceal bleeding in patients with clinically significant portal hypertension (CSPH) is best performed with Carvedilol, a non-selective betablocker (NSBB) with greater anti-portalhypertensive activity than conventional NSBBs.
- In patients with compensated cirrhosis and hepatic venous pressure gradient (HVPG) ≥10 mmHg Carvedilol/NSBB prevent decompensation (mainly ascites) and improve survival.
- The evidence for recommending Carvedilol/NSBB treatment for all patients with CSPH is derived from studies using HVPG to define CSPH and is strongest for patients with varices.
- It remains to be shown if Carvedilol treatment produces similar benefit in patients in whom compensated advanced chronic liver disease (cACLD) and CSPH is non-invasively diagnosed.
- Etiologic therapy improves hepatic function and may even induce cirrhosis recompensation. However, Carvedilol/NSBB should be continued as long as CSPH persists.

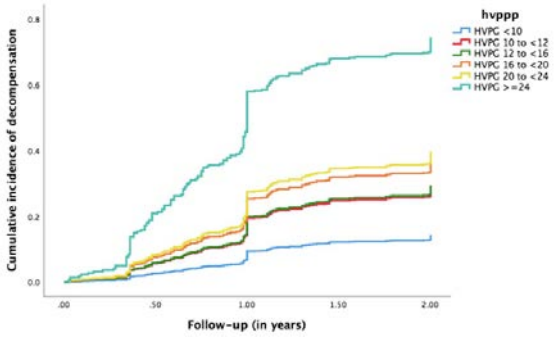
Introduction

The natural history of cirrhosis, nowadays better defined as advanced chronic liver disease (ACLD) has been described in traditional studies including mostly patients with viral hepatitis C and alcohol-related liver disease, who most often showed a progressive course with liver-related death – if not prevented by liver transplantation – as the ultimate outcome. Screening for gastroesophageal varices – that are a prognostic indicator of an increased risk of variceal bleeding – was a management priority in patients with cirrhosis, because primary prophylaxis by endoscopic or non-selective betablocker (NSBB) treatment was recommended to be an effective measure to prevent first variceal bleeding – in patients with high-risk varices[1].

Hepatic decompensation represents inarguably a watershed moment in the natural history of patients with cirrhosis/ACLD, however, ascites – and not variceal bleeding – is the most frequent first sign of hepatic decompensation[2]. And while effective strategies to control ascites are available and etiologic cure may even lead to hepatic recompensation[3] with regression of ascites, the concept of prevention of decompensation – as in other areas of medicine – has traditionally only been applied to variceal bleeding, despite the knowledge that the presence and severity of clinically significant portal hypertension (CSPH) represents the main driving force both for triggering variceal bleeding and for development of ascites[4].



D'Amico G (J Hepatol 2006)



Jindal A (Am J Gastroenterol 2020)

Fig. 1. From prevention of variceal bleeding to prevention of all-type decompensation. A) Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages. B) Cumulative incidence of decompensation.

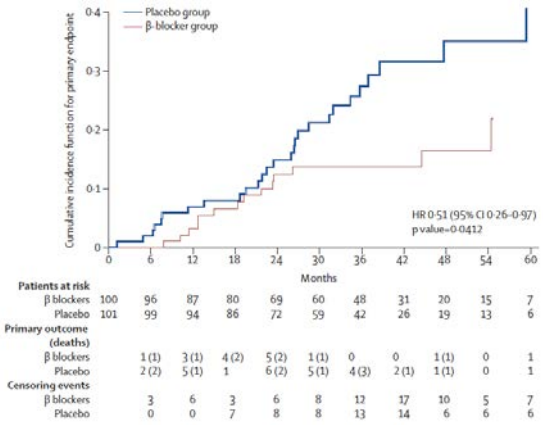
Back in 2015, the Baveno VI guidelines[5] stated that small varices without signs of increased risk of bleeding *"may"* be treated with non-selective betablockers (NSBBs) to prevent bleeding, but called for further studies to confirm their benefit. At that time endoscopic band ligation (EBL) and conventional NSBBs or carvedilol were recommended for the prevention of first variceal bleeding of medium or large varices.[5]

Now the Baveno VII guidelines[6] from 2021 have shifted the paradigm *"from prevention of first variceal bleeding (i.e. primary prophylaxis) to prevention of (all type) of decompensation, and treatment with NSBB, preferably carvedilol is recommended to prevent decompensation in patients with clinically significant portal hypertension (CSPH)"*. Since endoscopic therapies do neither prevent ascites nor hepatic encephalopathy, EBL is only recommended in patients with high-risk varices who have either contraindications or intolerance to NSBBs[6], and carvedilol should be used as first line treatment in all patients with CSPH.

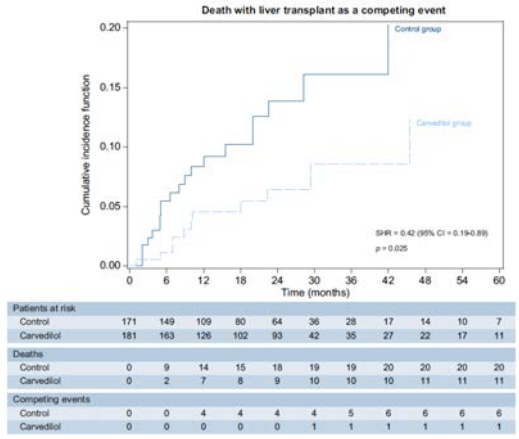
These changes in recommendation are largely based on the PREDESCI study[5] that randomized patients with compensated cirrhosis and hepatic venous pressure gradient (HVPG ≥10mmHg) but without high-risk varices to NSBB (either propranolol in responders to intravenous propranolol or carvedilol in non-responders to intravenous propranolol) or placebo and assessed the primary end-point of decompensation (i.e. ascites, bleeding, encephalopathy) or death. Decompensation/death occurred in 16/100 patients (16%) in the NSBB group and in 27/101 patients (27%) in the placebo group and thus, it was concluded that long-term NSBB treatment increases decompensation-free survival in patients with decompensated cirrhosis and CSPH.

Over a median duration of follow-up of 37 months in each group, the significantly reduced risk of decompensation was mainly due to prevention of ascites (placebo: 20% vs. NSBB: 9%), while the bleeding rate was interestingly similar (placebo: 3% vs. NSBB: 4%).

While a randomized controlled study from 2005 comparing timolol to placebo showed no difference in the primary endpoint of development of varices or variceal hemorrhage[7], there were already important positive signals towards an efficacy of NSBBs, since varices developed less frequently in patients with a HVPG decrease of >10% after one year. With the knowledge that NSBB only significantly decrease HVPG in patients with CSPH because the pharmaceutical *"target condition"* of hyperdynamic circulation is only present if HVPG rises to values ≥10 mmHg[8], and data on the superior anti-portalhypertensive efficacy of carvedilol over conventional NSBBs[9], a valid pathophysiologic explanation for the positive results in the PREDESCI study exists. A recent individual data meta-analysis also supports the use of Carvedilol in all compensated patients with CSPH, as it demonstrated not only a reduced risk of decompensation but also a survival benefit with carvedilol over no treatment or endoscopic treatment[10].



Villanueva C (Lancet 2019, PREDESCI study)



Villanueva C (J Hepatol 2022)

Fig. 2. A) Primary endpoint (decompensation or death) according to treatment group.[8] B) Cumulative incidence of the primary endpoints according to treatment group, considering LT as a competing event.[10]

Non-invasive identification of CSPH in cACLD patients

The term compensated advanced chronic liver disease (cACLD) has been first introduced at the Baveno VI(5) conference as a valuable alternative to compensated cirrhosis, based on the concept that liver biopsy is no longer used to stage fibrosis and elastography was widely adopted to stage fibrosis, back then mostly in patients with viral hepatitis to prioritize antiviral therapy. As cACLD was initially described as a condition for all-type etiologies of liver disease spanning advanced fibrosis and cirrhosis (i.e., F3/F4 on liver biopsy), many controversial discussion on different cut-offs for cACLD in different etiologies followed, however, in fact the pragmatically chosen liver stiffness measurement (LSM) cut-off at >10kpa for probable cACLD and >15kPa for confirmed cACLD was not primarily meant to identify patients with histological F3/F4 on liver biopsy but to indicate an increased risk for liver-related events (LREs). Now the risk of LRE in cACLD patients is strongly linked to the presence of CSPH, and since LSM not only rules-in cACLD but also strongly correlates with portal pressure (HVPG)[11], LSM – best in combination with platelet counts (PLT) can also be used to assess the risk of CSPH in cACLD patients. CSPH can be ruled-in by LSM >25kPa, however, the evidence is only strong in cACLD patients with viral hepatitis B/C, ArLD and non-obese MASLD.

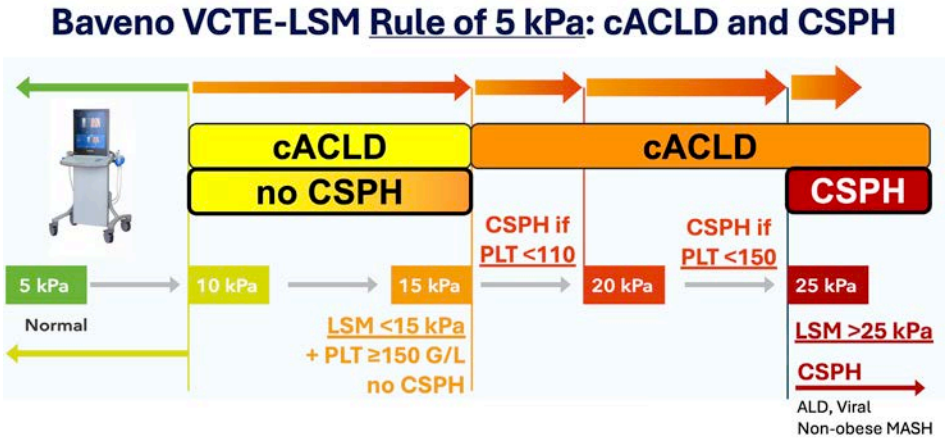


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Fig. 3. Algorithm for the non-invasive determination of cACLD and CSPH.[6]

Non-invasive CSPH-related risk stratification: sufficient to decide on NSBB/Carvedilol indication?

Since the diagnostic grey-zone to ruling-out CSPH with a combined LSM<15kPa and normal PLT (≥150 G/L) is significant, Baveno VII has suggested that CSPH can also be assumed in cACLD patients with LSM 15-20 kPa if PLT <110 G/L or with LSM 20-25 kPa if PLT <150 G/L.[6] These Baveno-VII non-invasive CSPH cut-offs have been elegantly validated in a large study showing that indeed the risk of LRE is significantly increased in cACLD patients meeting the CSPH rule-in criteria.[12] Still it remains unclear if the benefits of Carvedilol/NSBB reported for patients with CSPH identified by HVPG can be translated to a population with CSPH as identified by non-invasive LSM/PLT-based CSPH criteria.

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Non-invasive tools for assessment of risk in patients with compensated cirrhosis

Annalisa Berzigotti[1]

[1]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, *Switzerland*

E-mail address: annalisa.berzigotti@insel.ch

Take-home messages

- Non-invasive tools (NITs) used to assess the presence of clinically significant portal hypertension (CSPH) include laboratory tests, imaging tests, and assessment of liver and spleen stiffness.
- For liver stiffness, a pragmatic rule-of-five (vibration-controlled transient elastography) or rule-of-four (p shear wave elastography [SWE] or 2DSWE) can be used to assess the risk of CSPH at the bedside.
- The combination of liver stiffness and platelet count allows ruling-out and ruling-in CSPH with good accuracy in all aetiologies except obese MASLD, where body mass index should be used in the model as well.
- About 30–40% of patients with cACLD have an indeterminate risk of CSPH according to LSM and platelet count (*i.e.* belonging to a 'grey zone').
- Spleen stiffness and the VITRO score recently emerged as an additional tool to further stratify the risk of CSPH in patients with compensated cirrhosis, so refining the existing Baveno VII rules and reducing the number of patients in the grey zone.

Introduction

Clinically significant portal hypertension (CSPH) is a main driver of the transition from the compensated to the decompensated stage of cirrhosis. As portal pressure is susceptible to pharmacological and non-pharmacological treatments, CSPH should be identified as soon as possible in patients with compensated disease and treated to decrease the likelihood of clinical decompensation.[1] The gold standard to assess portal hypertension in cirrhosis is the measurement of the hepatic venous pressure gradient (HVPG) during hepatic veins catheterisation; a HVPG ≥10 mmHg defines CSPH. This method is safe, but it is invasive (even if minimally), relatively expensive, and requires expertise, factors that limit its widespread use.

Non-invasive tools (NITs) as potential alternative for HVPG have been thoroughly investigated, and the availability of elastography has represented a major advancement in this field.

How to identify the population of patients potentially at risk of CSPH

As CSPH is invariably present in the decompensated stage of chronic liver disease (CLD), patients with compensated advanced chronic liver disease (cACLD) should be seen as the target population to identify and treat portal hypertension. According to the Baveno VII Consensus Workshop,[1] a pragmatic rule-of-five (Fig. 1) can be used to interpret liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) to identify patients with CLD in this stage. Patients with LSM <10 kPa are excluded from this definition and do not require further assessment for CSPH.

Evidence regarding the use of point shear wave elastography and 2D shear wave elastography for risk stratification and for CSPH is less strong, but is concordant with that emerged by VCTE. However, as cut-offs are different using these technologies, a 'rule-of-four' (namely 5, 9, 13, and 17 kPa) has been suggested.[2]

How to rule in and rule out CSPH in patients with cACLD

A careful assessment of potential confounders increasing LSM irrespective of fibrosis is required in all cases of increased LSM, and repetition of the test should be considered before proceeding to further examinations.[3] As for the further steps to be taken in patients with confirmed LSM ≥10 kPa to estimate the risk of CSPH, platelet count plays a key role. Studies have shown that LSM <15 kPa combined with platelet count >150 G/L rules out CSPH with >90% accuracy, and that LSM ≥25 kPa rules in CSPH with >90% accuracy (Fig. 1). These values apply to patients with cACLD of different aetiologies, but are not accurate enough in patients with metabolic dysfunction-associated steatotic liver disease and obesity. In these patients the non-alcoholic steatohepatitis (NASH)-Anticipate model,[4] which includes body mass index (BMI) added to LSM and platelet count, helps to identify patients at high risk of carrying CSPH, and has been recently validated.[5]

In addition to LSM and platelet count, imaging (ultrasound initially) should be performed to obtain a more complete assessment of the liver and its vascular system. The presence of portosystemic collaterals on imaging should be taken into account and considered sufficient to diagnose CSPH and indicate a worse prognosis.[6]

In patients with LSM between 15 and 25 kPa, LSM and platelet count cannot provide a detailed assessment of the risk of CSPH, and these patients belong to the so-called 'grey zone' (indeterminate risk). The proportion of compensated patients in this category is 30–40% of current published series. Novel strategies have emerged after Baveno VII to further refine risk stratification for CSPH in this population.

Robust data regarding the use of spleen stiffness measurement (SSM) for this aim have been recently published. In a large individual patient meta-analysis,[7] the sequential use of the Baveno VII criteria and of a single SSM cut-off (SSM < or ≥40 kPa) was able to reduce the grey zone from 48% to 9%, so increasing the rate of patients correctly classified as having CSPH from 57% to 88%.

Another proposed strategy includes the quantification of von Willebrand factor in addition to platelet count to calculate the VITRO score.[8] The sequential use of the Baveno VII criteria and the VITRO score with two cut-offs (≤1.5 to rule out and ≥2.5 to rule in CSPH), allowed to reduce the grey zone from 45.7% to 9%, so increasing the rate of patients correctly classified as having CSPH from 57% to 88%.

Beyond these criteria, the Baveno VII Consensus proposed that changes in LSM and NITs ('dynamic' assessment) in the follow up could improve risk stratification. A recent study by Semmler *et al.*[9] validated the criteria, showing that a decrease in LSM ≥20% with a final LSM <20 kPa can be considered a clinically significant LSM decrease, as the risk of developing decompensation decreased by 50% in this group of patients. However, patients in whom LSM *increased* ≥20%, showed a 50% increase in risk of clinical decompensation.

The Baveno VII Consensus underlined that all patients with CSPH should be considered for treatment with carvedilol (a non-selective beta-blocker with anti-alpha-adrenergic activity), as treatment reduces the risk of clinical decompensation in this population. NITs could then be pragmatically used to select patients with an indication for treatment.[1]

In a very recent study including 412 patients with cACLD with various aetiologies,[10] HVPG and NITs (VITRO and ANTICIPATE ± NASH) showed similar time-dependent prognostic value (AUROCs 0.683–0.811 at 1 year and 0.699–0.801 at 2 years); any among the invasive reference standard and NITs remained independent predictors of decompensation when separately included in a model adjusted for model for end-stage liver disease score and albumin. This study strongly supports the utility of NITs for identifying patients who may benefit from medical therapies to prevent first hepatic decompensation.

Nonetheless, data to confirm the impact of NIT-based selection are still lacking and a pragmatic NIT-based approach to start therapy is not yet universally accepted.

How to rule in and rule out high-risk varices in patients with cACLD

High-risk varices (HRV; which include medium and large varices, and small varices with red signs) are an absolute indication to non-selective beta-blockers therapy, but their prevalence in cACLD is low.

Strategies based on NITs to better select patients requiring screening endoscopies are now available. The so-called Baveno VI criteria proposed the rule LSM <20 kPa by VCTE and PLT >150 G/L to rule out HRV and safely skip the screening endoscopy.[1] These criteria have been validated in all the common aetiologies of liver disease, and confirmed that patients within these criteria have a risk of HRV <3–5%. Because these criteria are very conservative, and lead to exclusion from endoscopy of only 10–35% of cases, research focused on novel strategies to avoid a larger proportion of unnecessary endoscopies. In this setting, sequential algorithms in which the Baveno VI criteria are applied first, and are followed by SSM (cut-off of 40–46 kPa) in those patients who would potentially need endoscopy, showed very good results with an increased rate of saved endoscopies ranging from 40% to 60%, and a low risk of missed HRV (2.5–4.3%).

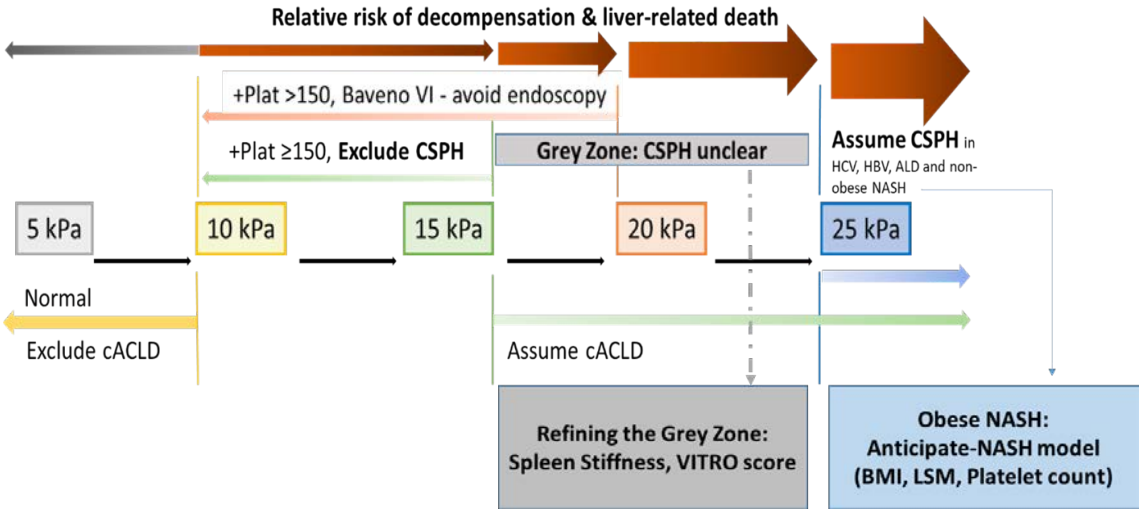

Fig. 1. The Baveno VII pragmatic 'rule-of-five' to assess the risk of clinically significant portal hypertension (CSPH), high-risk varices and clinical decompensation in patients with compensated liver disease. Notice the 'grey zone' for CSPH for patients with LSM between 15 and 25 kPa.

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Portal-hypertensive gastroenteropathy and GAVE syndrome: diagnosis and management

Patrick S. Kamath[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN, *USA*

E-mail address: kamath.patrick@mayo.edu

Take-home messages

- Portal-hypertensive gastropathy (PHG) and enteropathy, and gastric antral vascular ectasia (GAVE) are potential causes of chronic gastrointestinal blood loss, with PHG being more common than GAVE.
- PHG and GAVE are distinct lesions. PHG is secondary to portal hypertension, whereas GAVE is likely secondary to hypoxaemia-induced mucosal neovascularisation.
- Mild PHG is characterised by a mosaic pattern of the gastric mucosa whereas severe PHG is recognised as red spots that are superimposed on the mosaic pattern. GAVE lesions are seen as ectatic blood vessels in the gastric antrum without a background mosaic pattern.
- A mosaic pattern of the gastric mucosa is not specific for PHG, and may be seen in cardiac failure, *Helicobacter pylori* infections, amyloidosis, and gastric lymphoma.
- Severe PHG is treated with iron replacement and non-selective beta blockers, with red cell transfusions as required. Transjugular intrahepatic portosystemic shunt placement is effective in patients with refractory bleeding from PHG. GAVE lesions are usually treated using endoscopic ablation, and iron replacement with red cell transfusions as required. VEGF inhibitors such as bevacizumab and thalidomide may be tried in refractory GAVE. TIPS is ineffective, but GAVE lesions resolve following liver transplantation.

Introduction

Portal hypertensive gastropathy and gastric antral vascular ectasia

In addition to bleeding from oesophageal and gastric varices, patients with portal hypertension may have gastrointestinal bleeding secondary to portal hypertensive gastropathy (PHG), portal hypertensive enteropathy, and gastric and intestinal vascular ectasia (GAVE). PHG and GAVE are endoscopic diagnoses. At least mild PHG is invariable in patients with cirrhosis undergoing upper endoscopy. Severe PHG and GAVE are more likely present in patients with chronic gastrointestinal blood loss.

Pathophysiology

It is important to recognise that the pathophysiologies of PHG and GVE are distinct. PHG is likely related to elevated portal pressure, as patients on non-selective beta blockers have reduced frequency of bleeding. Prevalence of PHG parallels the severity of portal hypertension. Lesions may be stable, improve, or worsen on follow up depending on the progress of the underlying liver disease[1] In addition, bleeding from PHG usually resolves following placement of transjugular intrahepatic portosystemic shunts, supporting the importance of portal hypertension in the pathogenesis.

The pathophysiology of GAVE is less clear. Gastrointestinal vascular ectasia is believed to form secondary to hypoxaemia mediated via vascular endothelial growth factor (VEGF) neovascularisation.

Resolution of GAVE following liver transplantation strongly suggests that liver failure plays a major role in the formation of these lesions.

Diagnosis

Patients with PHG and GAVE may be asymptomatic and the diagnosis made incidentally during endoscopic surveillance for oesophageal varices. These lesions may also be recognised when patients are investigated for chronic gastrointestinal blood loss.

The hallmark for diagnosis of PHG is a mosaic or snakeskin pattern of the mucosa. Mild PHG is characterised by the mosaic pattern, whereas severe PHG has, in addition, superimposed red spots (Fig. 1). Chronic gastrointestinal blood loss is a feature of severe PHG. PHG may occasionally also be a cause of acute gastrointestinal bleeding.

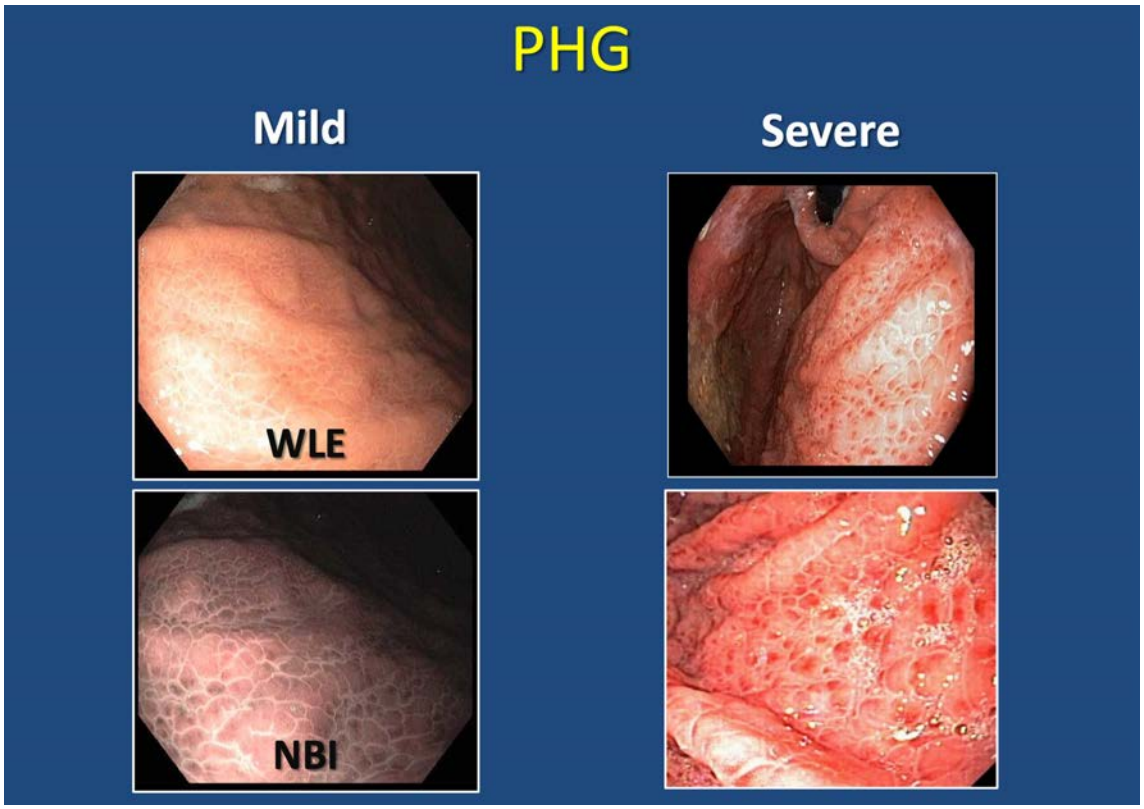

Fig. 1. Endoscopic appearance of portal hypertensive gastropathy (PHG) on white light endoscopy (WLE) and narrow band imaging (NBI).
In mild PHG there is a mosaic background and in severe PHG there are superimposed red spots on the mosaic pattern.

A mosaic gastric mucosal pattern is not specific for PHG. A similar mosaic pattern is seen in most patients with congestive heart failure,[2] and in patients with *H. pylori* infection, gastric amyloid, and gastric lymphoma.

Vascular ectasia may be seen in the stomach as well as in the small and large intestine. Although these ectasias may be seen more commonly in the gastric antrum, and in patients with cirrhosis with a diffuse distribution, vascular ectasia may also be seen in the proximal stomach, typically in the area the gastric cardia. Thus, the term gastric vascular ectasia (GVE) is preferred to gastric antral vascular ectasia. Vascular ectasias are recognised as ectatic red mucosal spots in the absence of a background mosaic pattern (Fig. 2). A nodular form of vascular ectasia is also identified.

Severe PHG may sometimes be difficult to differentiate from GVE. PHG is certainly more common, and a proximal distribution with a background mosaic pattern favours PHG. Both lesions may be present in the same patient. There are insufficient data available to determine whether occult bleeding from PHG can be considered as hepatic decompensation.[3]

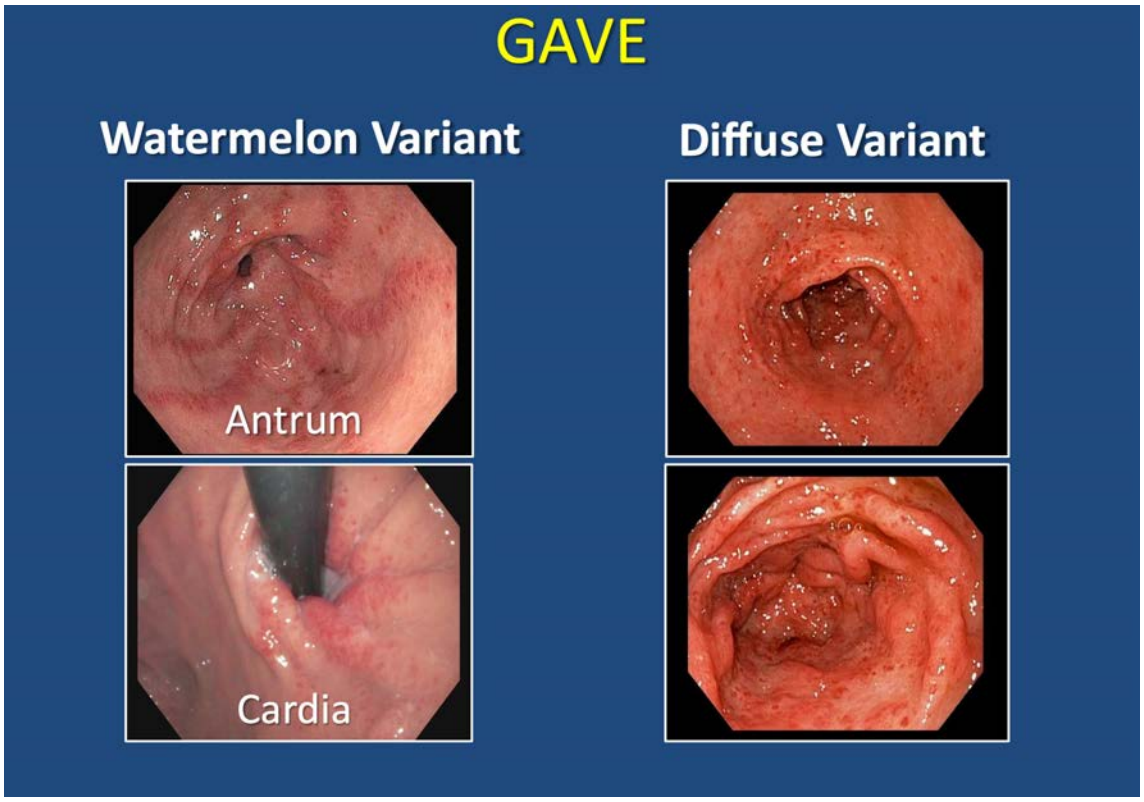

Fig. 2. Endoscopic appearance of gastric vascular ectasia.
Note the aggregates of red spots without a background mosaic pattern.

Gastric vascular ectasia is not specific for cirrhosis. Identical vascular lesions are seen in patients with connective tissue disease such as scleroderma, cardiovascular diseases, respiratory failure, and chronic kidney disease (CKD). In patients with scleroderma, connective tissue diseases, and in CKD there may be linear aggregates of vascular ectasia in the gastric antrum and the term 'watermelon stomach' is sometimes used to describe these lesions.

Management

General measures

Initial management of patients with chronic blood loss from PHG or GVE is iron supplementation, either oral or via infusions, with red cell transfusions administered on an as-required basis to keep the haemoglobin above 7 g/dl in patients without cardiovascular disease. Because GVE lesions are more common in older patients who might also have underlying cardiovascular disease, a haemoglobin target of 9 g/dl may be required in selected individuals.

Specific measures

Bleeding from portal hypertensive gastropathy

The initial specific treatment for chronic bleeding from PHG is with non-selective beta blockers (Fig. 3). In a small study, the actuarial percentages of patients free of rebleeding from PHG were significantly higher in the propranolol-treated patients than in the untreated controls at 12 months (65% *vs.* 38%; $p < 0.05$) and at 30 months of follow up (52% *vs.* 7%; $p < 0.05$).[4]

Approximately 75% of the patients with severe PHG refractory to beta-blocker therapy respond to transjugular intrahepatic portosystemic shunt (TIPS) with improvement in endoscopic findings and by a decrease in transfusion requirements; 89% of patients with mild PHG have endoscopic resolution.[5]

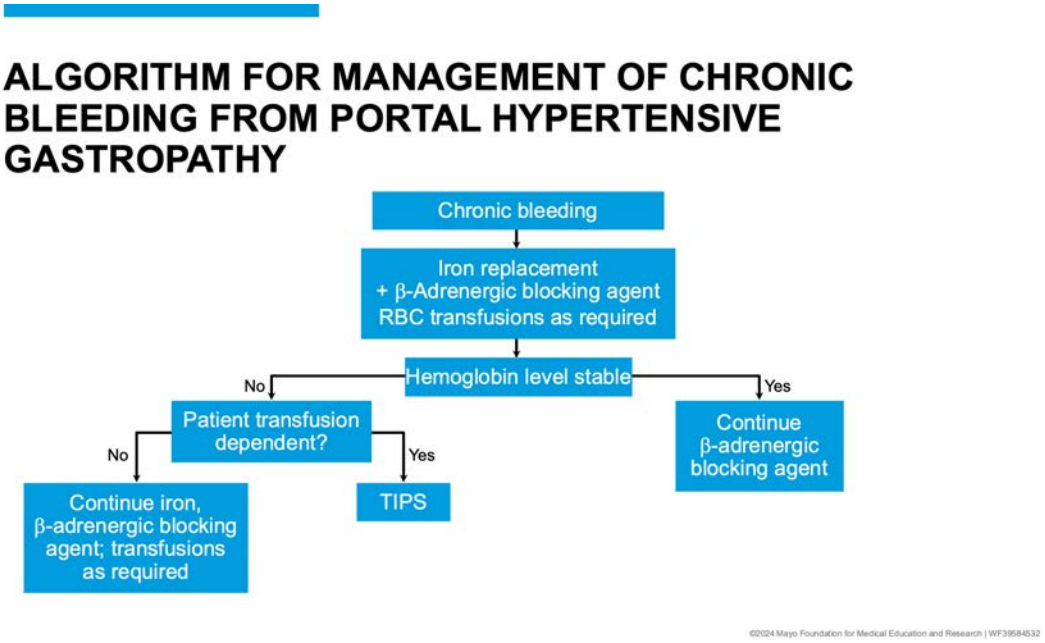

Fig. 3. Algorithm for treatment of bleeding from portal hypertensive gastropathy.

Bleeding from gastric vascular ectasia

Initial management of GVE is with argon plasma coagulation (APC) with suggested settings 45 W (range 20–80 W) and flow rate of 1 L/min (range 0.5–2 L) with an interval of 4–6 weeks between procedures. One downside of aggressive APC therapy is the formation of hyperplastic polyps which may then themselves be a source of bleeding. Cryotherapy may be used for more diffuse lesions. CO_2 gas at a temperature of -78°C is delivered at a rate of 6–8 L/min and a pressure of 450–750 psi. Because of the large volume of gas used a gastric venting tube is essential.[6] Results with cryotherapy have not been very encouraging. Band ligation is carried out for nodular gastric vascular ectasia.

When thermal ablation or cryotherapy are ineffective, pharmacological agents such as oestrogen/progesterone are tried, but agents that inhibit VEGF such as thalidomide and bevacizumab may be more beneficial (Fig. 4).[7,8] The response to bevacizumab in patients with GVE secondary to cirrhosis is lower than in patients without cirrhosis. Adverse effects that are described in patients with cancer treated with bevacizumab are uncommon in patients with cirrhosis and GVE treated with bevacizumab, likely because additional anticancer chemotherapy is not used in these patients with cirrhosis.

Patients with GVE have neither endoscopic resolution nor a decrease in transfusion requirements after TIPS.[5] The vascular ectasia resolve following liver transplantation.

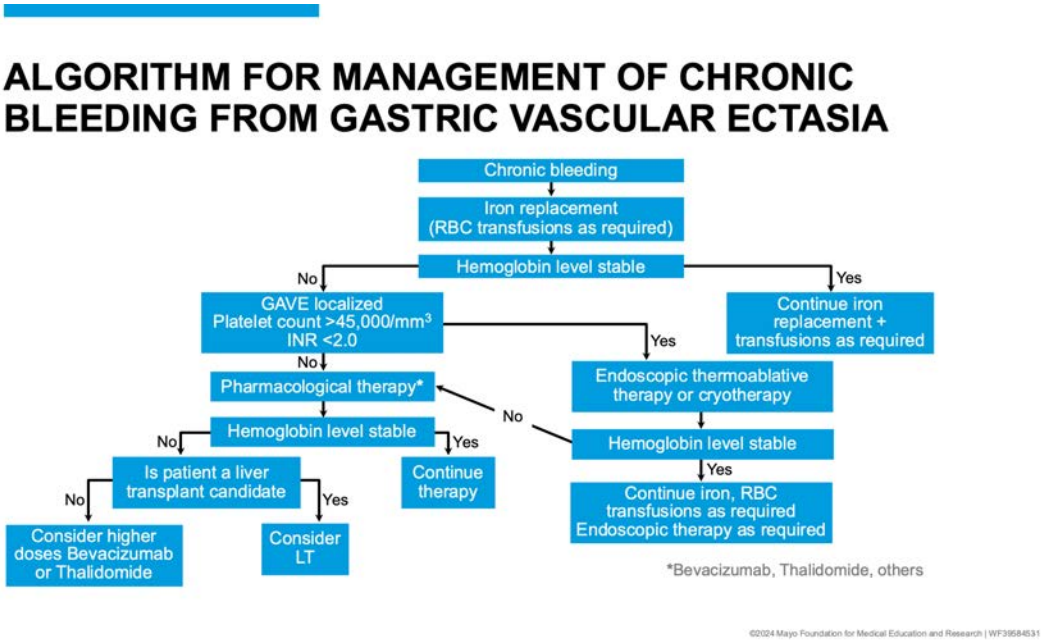

Fig. 4. Algorithm for treatment of bleeding from gastric vascular ectasia.

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TIPS: where do the limits lie?

Hélène Larrue[1], Christophe Bureau[1]

[1]Service d'Hépatologie Hôpital Rangueil CHU Toulouse et Université Paul Sabatier, Toulouse, *France*

E-mail address: bureau.c@chu-toulouse.fr

Take home messages

- The selection of patients for the TIPS procedure varies depending on whether the indication is urgent or not.
- In cases of salvage TIPS, futility criteria should be considered only for patients ineligible for liver transplantation.
- In cases of preemptive TIPS, once the indication criteria are met, no established futility criteria exist at present.
- For non-urgent TIPS procedures, it is crucial to conduct all necessary examinations to assess procedural risk and best evaluate the benefit-risk ratio.
- For non-urgent TIPS procedures, the main selection examinations focus on assessing hepatic and cardiac function, along with risk factors for hepatic encephalopathy development.
- It is worth noting that predicting the individual prognosis for a given patient remains challenging, and no absolute threshold for parameters used (score, age, etc.) can be universally applied.

Introduction

In this brief review, we will discuss the limits of TIPS and the role of **biological tests** and **scoring systems** in the patient selection process. Firstly, it is crucial to distinguish between two scenarios: the use of transjugular intrahepatic portosystemic shunt (TIPS) as an urgent procedure, during portal hypertension (PH)-related bleeding, and TIPS as an elective intervention for managing difficult-to-treat ascites or for secondary prevention of bleeding. In urgent situations, liver function assessment parameters are influenced by both the bleeding itself and the potential acute exacerbation of hepatitis, such as acute alcoholic hepatitis. As a result, traditional liver function scoring systems may not accurately reflect true hepatic reserves. The evaluation of the balance between the expected benefits and risks of the TIPS procedure is more critical in an emergency TIPS scenario compared with a planned one. However, in the context of a planned TIPS, prognostic scores are more reliable because of the stability of the patient's condition. This elucidates why a Child-Pugh class C status is considered a relative contraindication for elective TIPS procedures, whereas it serves as an indication for pre-emptive TIPS during a bleeding episode, given the high risk of potentially lethal recurrence in the latter situation.

The main risks associated with the creation of the shunt include liver failure (LF), hepatic encephalopathy (HE), and heart failure (HF). As a result, the patient selection process aims to thoroughly assess these risks and avoid the procedure for patients deemed unsuitable. This careful selection is crucial for minimising post-procedure complications and optimising patient outcomes.

TIPS in acute variceal bleeding

Salvage/rescue TIPS

The American Association for the Study of Liver Diseases (AASLD) guidelines use the term 'salvage TIPS' for patients treated with TIPS who experience uncontrolled bleeding, despite vasoactive and endoscopic treatments, whereas 'rescue TIPS' is used for patients with early (<5 days) recurrence of bleeding after an initial control.[1] Uncontrolled or early recurrent bleeding occurs in 10–20% of patients.[2] All studies in the field are observational, and the results are consistent across reports, showing an immediate haemostasis rate close to 90% after TIPS and a 30-day mortality ranging from 7% to 60%. Patients succumb to complications such as LF, infection, or renal failure. Therefore, the indications for salvage/rescue TIPS should be carefully considered against potential futility. Factors significantly associated with higher mortality include infection, **renal failure**, the need for vasopressors, high model for end-stage liver disease (**MELD**), **APACHE II**, and **Child-Pugh** scores. The 1-year mortality for patients with a Child-Pugh score >13 may approach 100%. A multicentre retrospective study revealed that high lactate levels (>12 mmol/L) and/or MELD scores >30 were significantly associated with a 6-week mortality exceeding 90%.[3] However, it remains to be determined whether a dynamic evaluation of lactate is a better predictor of outcomes. Generally, the indications for rescue TIPS should consider whether the patient is a potential candidate for transplant. A small series showed that rescue TIPS could successfully serve as a bridge to liver transplantation, even in patients with severe liver disease (Child-Pugh score >13). Futility criteria may be useful only in patients clearly ineligible for future liver transplantation. Applying futility criteria in patients with potential liver transplant plans seems inappropriate. The decision to perform TIPS in such patients must be collaborative and made on a case-by-case basis.

Pre-emptive TIPS

Pre-emptive TIPS is defined as the placement of a TIPS within 72 h following variceal bleeding, which has initially been controlled by optimal care.[2] The primary goal is to prevent a recurrence of bleeding in patients at high risk of treatment failure. High-risk patients are identified based on clinical and biological parameters, utilising the **Child-Pugh score**. In a randomised controlled trial conducted by Garcia Pagan, pre-emptive TIPS increased survival compared with standard therapy.[4] This result was confirmed by all but one study. Subsequently, an individual patient data meta-analysis showed that patients with Child-Pugh scores of 10–13 and those with Child-Turcotte-Pugh (CTP) scores >7 with active bleeding at the initial endoscopy were deemed at high risk and derived significant benefits from pre-emptive TIPS.[5] The survival advantage is not observed in patients without severe liver dysfunction (Child-Pugh Class A and B with Child-Pugh score 7). To date, there is no defined set of futility criteria to identify the most severe patients who may not benefit from pre-emptive TIPS. The study by Lv *et al.*[6] study showed that pre-emptive TIPS reduced the absolute risk of 1-year mortality by -33% for patients with a **MELD score ≥19.** Similarly, a subgroup analysis in the meta-analysis by Nicoara-Farcau *et al.*[5], focusing on 84 patients with **bilirubin levels >10 mg/dl**, indicated that pre-emptive TIPS remained beneficial with significantly higher survival in the TIPS group. Observational studies suggest that HE, jaundice, or acute-on-chronic liver failure (ACLF) at the time of bleeding do not significantly impact these results.[7–9] However, these studies likely involved highly selected patients, necessitating further research for confirmation.

Most studies exclude patients over 75 years old, those with severe liver dysfunction (Child-Pugh score >13), hepatocellular carcinoma (HCC) beyond Milan criteria, bleeding from isolated gastric or ectopic varices, total portal vein thrombosis (PVT), severe renal failure, HF, and recurrent HE. Consequently, limited data are available for these patients.

In conclusion, it appears that futility scores are lacking in the context of pre-emptive TIPS. The assessment of the risk of HE and LF may not be as crucial in this context compared with a planned TIPS, given the anticipated benefits.

Planned TIPS

Assessing the risk of liver failure

Hepatic function remains the primary determinant of morbidity and mortality following TIPS. Consequently, several prognostic scoring systems have been developed to aid in patient selection for TIPS placement in patients with cirrhosis. It is noteworthy that:

- Most of these scoring systems are non-specific to patients with cirrhosis treated with TIPS but also serve as reliable indicators of outcomes in patients with cirrhosis.
- Studies aiming to predict factors influencing mortality after TIPS often lack consistent categorisation of liver-related mortality, particularly that linked to post-TIPS LF.
- These studies often exclude patients with severe LF (*e.g.* MELD >15 or >18, Child-Pugh C, or total bilirubin >50 µmol/L).

Numerous studies have compared different models, yielding results that are not always consistent possibly owing to the heterogeneity of the characteristics of the patients included.[10] It should also be acknowledged that the prognosis of patients depends not only on the pre-TIPS assessment, but also on the quality of follow up and the management of the underlying aetiology of the liver disease. The prognostic value of international normalised ratio (**INR**), **serum bilirubin**, and **serum creatinine** is well documented, and these parameters are often included in scoring systems. Recently, **albumin** has gained interest and was incorporated into the Freiburg Index of Post-TIPS Survival (**FIPS**)[11] whereas **serum sodium** was included in a model with serum creatinine for older patients.[12]

Selecting an optimal scoring system and establishing a strict threshold for definitively contraindicating a TIPS procedure poses challenges. For instance, although the MELD score has been extensively evaluated for predicting post-TIPS mortality, no absolute threshold has been established to definitively contraindicate the procedure. In a recent study comparing MELD and MELD-Na, MELD was found to be superior for both 30-day (0.762 *vs.* 0.709) and 90-day (0.780 *vs.* 0.730) mortality after TIPS.[13] The optimal cut-off score for 90-day mortality was 16 (95% CI, 0.705–0.855) for MELD. Notably, there were 24 patients with a high MELD-Na ≥17, but a low MELD <15, and the 90-day mortality in this group was 8.3%. Another study by Xiong *et al.*[14] assessed whether sarcopenia may provide added value to existing scores. Among 386 patients, five existing scores were compared (Child-Pugh, MELD, MELD-Na, MELD 3.0, and FIPS) with FIPS identified as the most powerful. Interestingly, FIPS significantly correlated with the presence and severity of sarcopenia before TIPS and with its reversal after TIPS. Moreover, the addition of sarcopenia to this score improved survival prediction and risk stratification.

Although it is quite easy to categorise patients without LF (MELD <12, Child-Pugh class B) and those with severe LF (MELD >18, Child-Pugh score >11), the grey zone requires careful consideration of other factors such as age and comorbidities. The more risks accumulate, the less the patient is considered an appropriate candidate.

Considering the risk of exacerbating LF in patients with impaired hepatic function (Child-Pugh class C, MELD >18, bilirubin >50 µmol/L), most experts suggest that TIPS may be considered on a case-by-case basis. In such patients, collaboration with a transplant centre is critical during the pre-TIPS evaluation to anticipate the potential need for liver transplantation. It is likely more comfortable to consider a TIPS procedure for a high-risk patient when liver transplantation can be done as a rescue.

One of the limitations of current scores is that they do not account for mortality related to other competitive risks and comorbidities such as HCC, HF, sarcopenia and others. This limitation might explain why, by combining traditional parameters of liver function assessment, their performance reaches a glass ceiling, and their AUC rarely exceeds 0.8. There is high hope for new scores that will incorporate additional biological parameters (inflammatory/immune, haemodynamic), physical (CT scan) or electrical (ECG) measurements.

Assessing the risk of hepatic encephalopathy

The most common complication following TIPS is HE, occurring in approximately 35–50% of cases. Although the majority of cases are episodic, 5–10% of patients experience debilitating HE, either recurrent or persistent. The main risk factors for post TIPS HE are[15]:

- *Previous episodes of overt HE (OHE)*: are a well-established predictor of post-TIPS HE.[16] Recurrent and persistent HE remains an absolute contraindication to TIPS (except in the rescue procedure). Minimal HE (MHE) has also been reported to be associated with the risk of post-TIPS OHE, although evidence is weaker.[17] An abnormal test result for MHE alone cannot be considered a contraindication. Therefore, systematic screening of MHE in clinical routine is not recommended.
- *Severe liver dysfunction*: is closely associated with the risk of post-TIPS HE.[18,19] Regarding the prediction of post TIPS LF, no absolute MELD value exists to contraindicate TIPS.[1]
- *Older age*: particularly age >70[20] is a risk factor but high age alone should not exclude patients from TIPS, but requires particular attention.
- *Sarcopenia*: many studies have observed an association between sarcopenia and HE.[21] In a recent systematic review with meta-analysis, the authors concluded that sarcopenia was associated with HE with an OR of 2.74 (95% CI, 1.87–4.01).[22] Whether nutritional approaches associated with physical activity will decrease the incidence of HE in patients undergoing TIPS placement remains to be shown. TIPS placement was found to have a positive impact on muscle alterations with a reversal of sarcopenia. In patients treated with TIPS, Artru *et al.*[23] observed a significant increase in transversal right psoas muscle thickness and total psoas muscle area (TPMA) after the intervention. Similar observations were reported with the measurement of SMI.[24–26]
- *Large spontaneous portosystemic shunts (LSPSS)*: are associated with the risk of HE after TIPS.[27] A recent RCT comparing TIPS alone *vs.* TIPS with embolisation of LSPSS showed that that the latter group had fewer HE episodes (22% *vs.* 51% at 1 year).[28] Conversely, a smaller retrospective study of 33 patients found that embolisation of SPSS before TIPS did not lower the post-TIPS HE incidence compared with a control group without SPSS.[29]
- *Hyponatremia,*[30] *type 2 diabetes and obesity,*[31] *renal impairment*[32] 24–34: also found to be associated with post TIPS HE.

Awareness of these associations allows better patient selection, anticipation of preventive interventions, and closer monitoring of high-risk patients. However, the individual prediction remains challenging. Predictive models based on a combination of risk factors have been developed for predicting post-TIPS HE,[35] but none so far have gained sufficient validation. An ideal candidate remains a young patient without previous HE with preserved liver and renal functions.

Assessing the risk of heart failure

Currently, there is an increasing recognition of the need for accurate cardiac assessments, given that the shunting of blood flow following TIPS placement leads to a marked rise in right atrial pressure and cardiac output. However, predictive studies of HF are still limited and yield conflicting results. In addition to standard cardiac contraindications requiring assessment such as severe left ventricular dysfunction or severe pulmonary hypertension, aortic stenosis, other parameters, notably those indicating diastolic dysfunction, have been explored.

A recent retrospective analysis involving 234 patients with cirrhosis revealed that pre-existing diastolic dysfunction was linked to an increased risk of HF following TIPS placement.[36] Notably, 18% of patients experienced cardiac decompensation within 1 year following shunt creation. This incidence aligns with the findings of a prospective study by Billey *et al.*,[37] which documented that 20% of patients encountered cardiac decompensation after undergoing TIPS. In this latter study, the measurement of brain natriuretic peptides was also useful to stratify risk levels. Interestingly, both studies observed a higher mortality rate among patients who developed HF post-TIPS. However, other studies were unable to replicate these results.[38] Recent guidelines advocate for a thorough evaluation of cardiac function in TIPS candidates to detect any underlying cardiomyopathies, although the most suitable diagnostic method and marker remain to be defined. Other haemodynamic parameters or fluid challenge tests warrant further explorations to more accurately stratify the risk of HF in these patients. This ongoing research is crucial for improving patient selection and management strategies, ultimately enhancing outcomes for those undergoing TIPS.

Conclusions

Today, the efficacy TIPS for specific indications is widely accepted. We are currently in a period dedicated to advancing our knowledge of the optimal candidate selection, which will, in turn, delineate its limitations more precisely. Such progress is contingent upon the analysis of extensive, well-designed prospective multicentre cohorts and the application of appropriate statistical methods to improve prognostic evaluations on an individual level.

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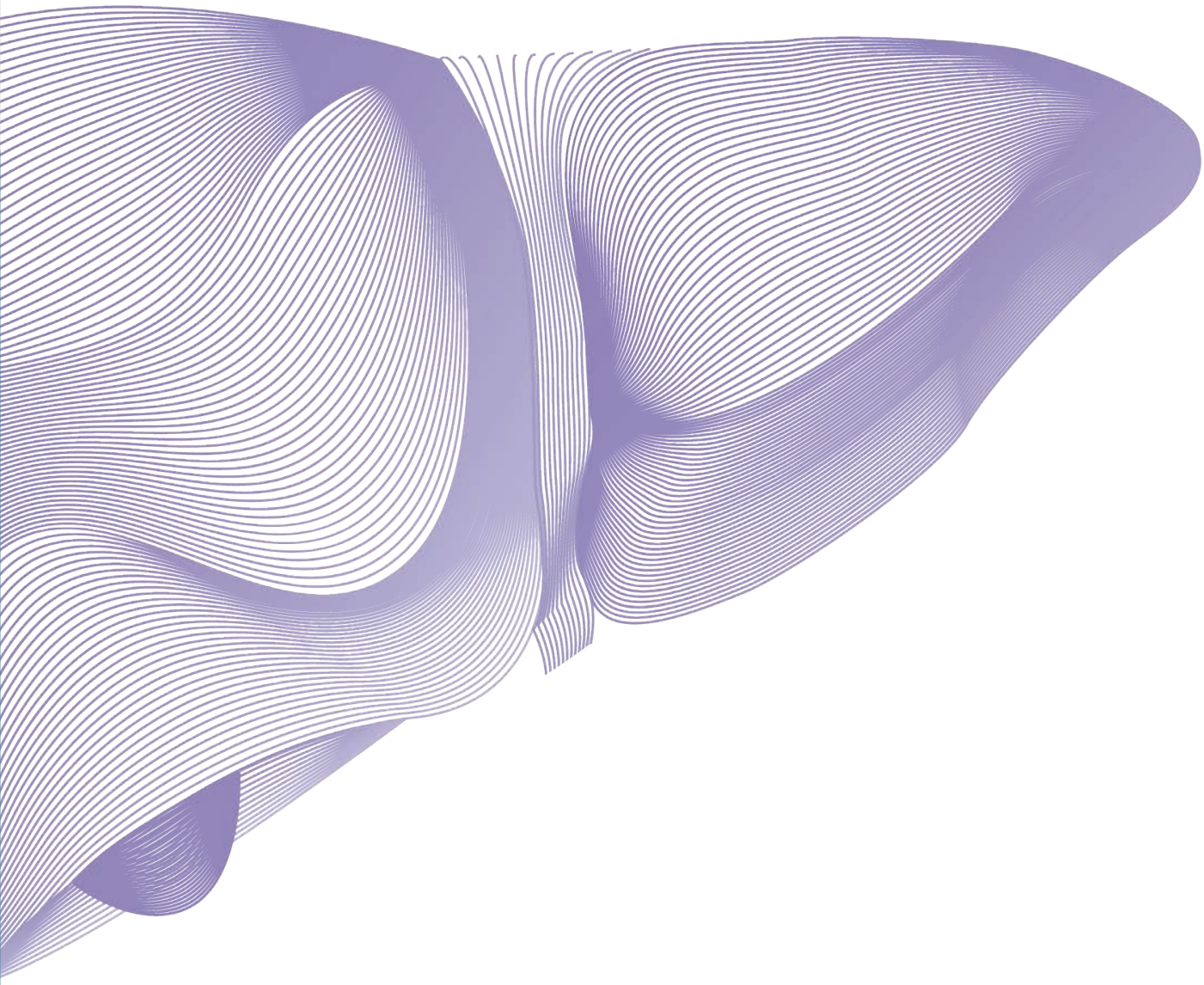
SESSION 3

COAGULATION CHANGES IN PATIENTS WITH CIRRHOSIS: FROM CONCEPTS TO PRACTICE

WEDNESDAY 5 JUNE
14:45-16:00



Haemostasis in cirrhosis: what the clinician needs to know

Ton Lisman[1, 2, 3]

[1]Surgical Research Laboratory, and Section of Hepatobiliary Surgery and Liver Transplantation, Groningen, *The The Netherlands*; [2]Department of Surgery, University of Groningen, Groningen, *The The Netherlands*; [3]University Medical Center Groningen, Groningen, *The The Netherlands*

E-mail address: j.a.lisman@umcg.nl

Take-home messages

- Cirrhosis is associated with simultaneous changes in both pro- and antihaemostatic pathways.
- The net effect of these haemostatic changes is one of 'haemostatic rebalance'.
- The new haemostatic balance in patients with cirrhosis has distinct hypo- and hypercoagulable features.
- Bleeding complications in patients with cirrhosis are frequently unrelated to haemostatic failure, but rather to portal hypertension or mechanical injury.
- Prevention or treatment of bleeding in patients with cirrhosis is not primarily accomplished by prohaemostatic treatment such as infusion of blood products.

Introduction

The liver plays a central role in the haemostatic system as it is the site of synthesis of many proteins involved in haemostasis. As a consequence, patients with chronic and acute liver failure frequently acquire complex changes in their haemostatic system. These changes include a low platelet count, low circulating levels of coagulation factors and inhibitors of coagulation, and low levels of proteins involved in clot breakdown. In routine diagnostic testing, these haemostatic changes may result in abnormal test results such as a low platelet count, prolongations in clotting tests such as the prothrombin time (PT) and activated partial thromboplastin time (APTT), and in patients with very advanced disease decreased levels of fibrinogen. The combination of these test results is suggestive of a bleeding tendency. Clinical observations and laboratory studies performed during the past two decades have convincingly shown that abnormal diagnostic haemostasis test results do not indicate a bleeding tendency. Rather, a simultaneous decline in pro- and antihaemostatic factors result in a reset of the haemostatic balance.[1] In this article the evidence for the concept of rebalanced haemostasis and the clinical consequences of this new concept is discussed.

Rebalanced haemostasis in cirrhosis

Although it has long been recognised that patients with cirrhosis may have a prolonged PT, the relevance of this finding historically has been misinterpreted. The PT is a test that is only sensitive for the level and functionality of five procoagulant proteins (factors VII, X, V, II, and fibrinogen). A prolonged PT thus indicates a defect in one or more of these factors. Whereas an isolated defect in one of these coagulation factors may be associated with a bleeding tendency, the situation is different in patients with cirrhosis who acquire simultaneous changes in both pro- and anticoagulant proteins. The net effects of these simultaneous changes in pro- and anticoagulant factors only became apparent when Tripodi *et al.*[2] used a research-type coagulation assay that is sensitive for the balance between pro- and anticoagulant proteins.because they do not allow full activation of the main

anticoagulant factor, protein C, whose levels are considerably reduced in cirrhosis. We used a thrombin generation test to investigate the coagulation function in patients with cirrhosis. Thrombin generation measured without thrombomodulin was impaired, which is consistent with the reduced levels of procoagulant factors typically found in cirrhosis. However, when the test was modified by adding thrombomodulin (i.e., the protein C activator operating in vivo Using this thrombomodulin-modified thrombin generation test, it was demonstrated that the capacity to generate thrombin, the ultimate enzyme in the coagulation cascade, was identical to, or even enhanced in patients with cirrhosis as compared with healthy individuals. In other words, the PT gives diametrically opposite information from the thrombin generation test. As the latter test likely much better represents physiology, the role of changes in the coagulation system in clinical bleeding began to be questioned, and the lack of a true haemostatic bleeding tendency in patients with cirrhosis will be discussed below. This simple thrombin generation experiment thus showed that the defects in procoagulant pathways was balanced by the defect in anticoagulant mechanisms in cirrhosis patients. Additional work demonstrated that the thrombocytopenia in cirrhosis is, at least in part, compensated for by highly elevated levels of the plasma protein von Willebrand factor, that plays a crucial role in adhesion of platelet to the damaged vasculature in flowing blood.[3] Also, it was shown that the fibrinolytic system was rebalanced by simultaneous changes in pro- and antifibrinolytic factors.[4] Fig. 1 demonstrates the various changes in pro- and antihaemostatic pathways that may occur in patients with cirrhosis.

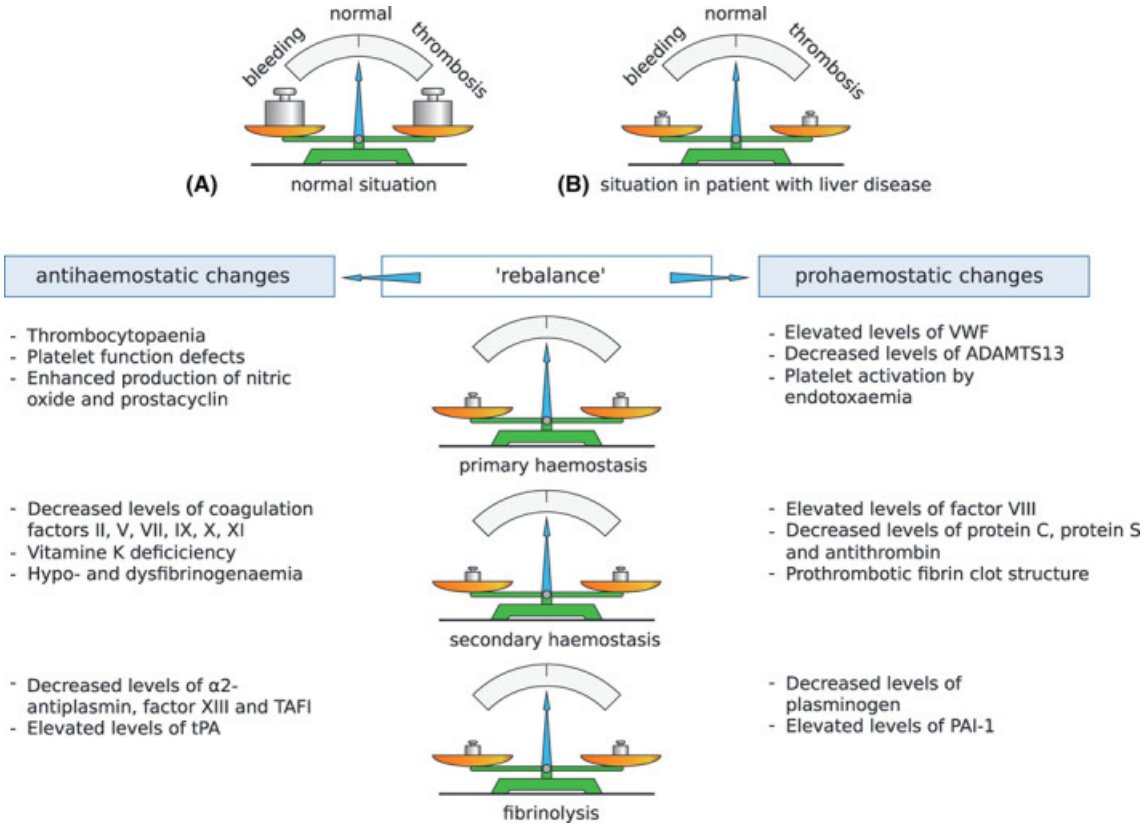


Fig. 1. Haemostatic changes promoting bleeding (left) or thrombosis (right) in patients with cirrhosis.

Remarkably, haemostatic balance appears maintained in critically ill patients with cirrhosis, although individual patients may show specific hypo- or hypercoagulable features, which in part relate to comorbidities such as infection and renal failure.[5] Of note, even in critically ill patients, bleeding complications are relatively uncommon, and most often related to portal hypertension.[6]

It becomes more and more accepted that the platelet count and PT are inadequate tests of haemostasis in patients with cirrhosis.[7] Many clinicians revert to alternative tests, most notably thromboelastography (TEG) and rotational thromboelastometry (ROTEM). Although these whole blood, bedside tests better represent physiology as compared with the platelet count and PT, there are notable limitations to these tests. First, TEG and ROTEM are insensitive to von Willebrand factor (that compensates for the low platelet count), and for the anticoagulant protein C system (that is defective in cirrhosis patients). Both TEG and ROTEM likely thus underestimate true haemostatic capacity.[8] Second, TEG and ROTEM do not provide the same information in patients with cirrhosis. Whereas TEG tracings are often normal in cirrhosis patients, ROTEM often indicates a hypercoagulable state.[7] This difference likely reflects differences in reagents used in these tests. Although TEG and ROTEM may be useful to guide transfusion management in a bleeding patient, these tests are likely unsuitable to predict bleeding risk.

Causes of bleeding in cirrhosis

Patients with cirrhosis frequently bleed. Two dramatic bleeding complications specific to patients with cirrhosis are variceal bleeding and bleeding during liver transplantation. Variceal bleeding is a frequent event in patients with cirrhosis, but is a consequence of portal hypertension and local vascular abnormalities. Importantly, variceal bleeding should not be treated by prohaemostatic treatment, which is not only ineffective, but may do harm. Specifically, fresh frozen plasma (FFP) and platelet concentrates may result in fluid overload and increases in portal pressure, which may aggravate rather than treat the bleed.[9] The antifibrinolytic drug tranexamic acid was ineffective in a large randomised trial on gastrointestinal bleeding with a signal for harm.[10] Patients that use anticoagulant drugs at the time of a variceal bleed did not have a worse outcome compared with patients who did not use anticoagulants, reinforcing the notion that variceal bleeding is unrelated to haemostatic failure.[11] Historically, liver transplant surgery was associated with massive bleeding.[12] However, improvements in surgical and anaesthesiological management have led to a marked reduction in blood loss, and nowadays many patients can undergo liver transplant surgery without the need for any blood products.[13] Many surgical teams accept preoperative abnormalities in platelet count and PT, and do not require blood product infusion with the aim to normalise these laboratory values before surgery. These observations reinforce the notion that patients with cirrhosis have adequate haemostatic capacity despite a low platelet count and prolonged PT.

Three major causes of bleeding in patients with cirrhosis can be distinguished (Fig. 2). First, and perhaps most importantly, bleeds may be related to portal hypertension. Second, bleeds related to mechanical injury to blood vessels may occur inadvertently during invasive procedures. Finally, bleeds that are likely a direct consequence of haemostatic failure may occur. Haemostatic bleeds in patients with cirrhosis include nosebleeds, gum bleeds, bleeding after dental extraction, and bleeding following venepuncture. Importantly, these bleeding complications are usually mild and do not require specific haemostatic interventions. Management of bleeding complications in patients with cirrhosis thus mainly concerns management of non-haemostatic bleeds.

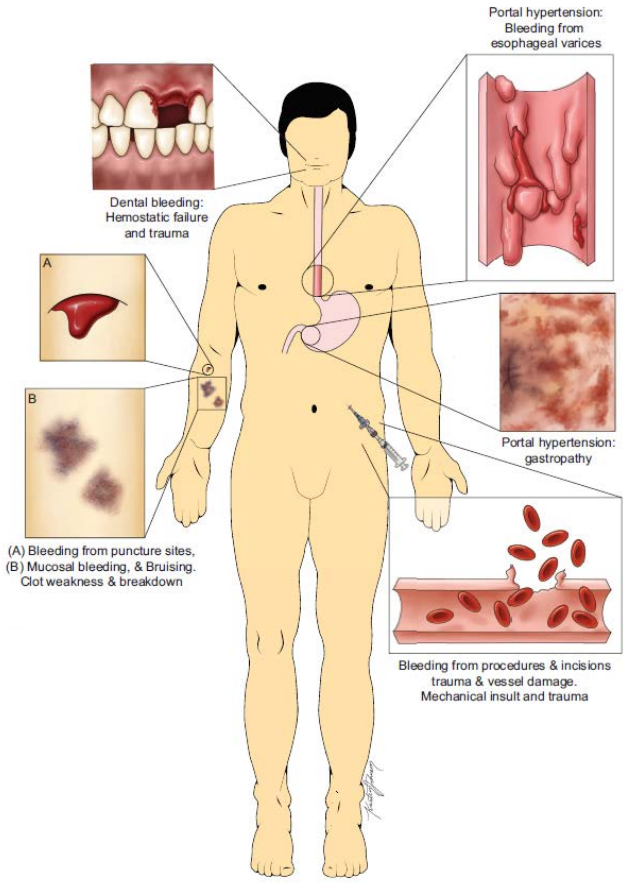


Fig. 2. Causes of bleeding in patients with cirrhosis.
Reprinted from Northup *et al.*[14]

Prevention and treatment of bleeding in patients with cirrhosis

Strategies to prevent or treat bleeding complications in patients with cirrhosis depend on the cause of the bleed. Management of portal hypertensive bleeds relies on strategies to reduce portal pressure and on endoscopic interventions. Infusion of FFP and platelet concentrates is not indicated, and red cell transfusion should be given restrictively to avoid fluid overload and increases in portal pressure. Prevention of mechanical bleeds is accomplished by image guidance during invasive procedures where appropriate and by meticulous surgical techniques, for example during liver transplantation. Treatment of a mechanical bleed relies on local treatment of the injury. To avoid haemostatic bleeds, antithrombotic drugs should be stopped where appropriate (*e.g.* before dental extraction), and when possible, comorbidities such as infection and renal failure should be treated. When a haemostatic bleed occurs, this can often be managed by local measures. Prohaemostatic treatment should be restricted to those patients with intractable bleeding. Strategies to prevent or treat bleeding in patients with cirrhosis are summarised in Fig. 3.

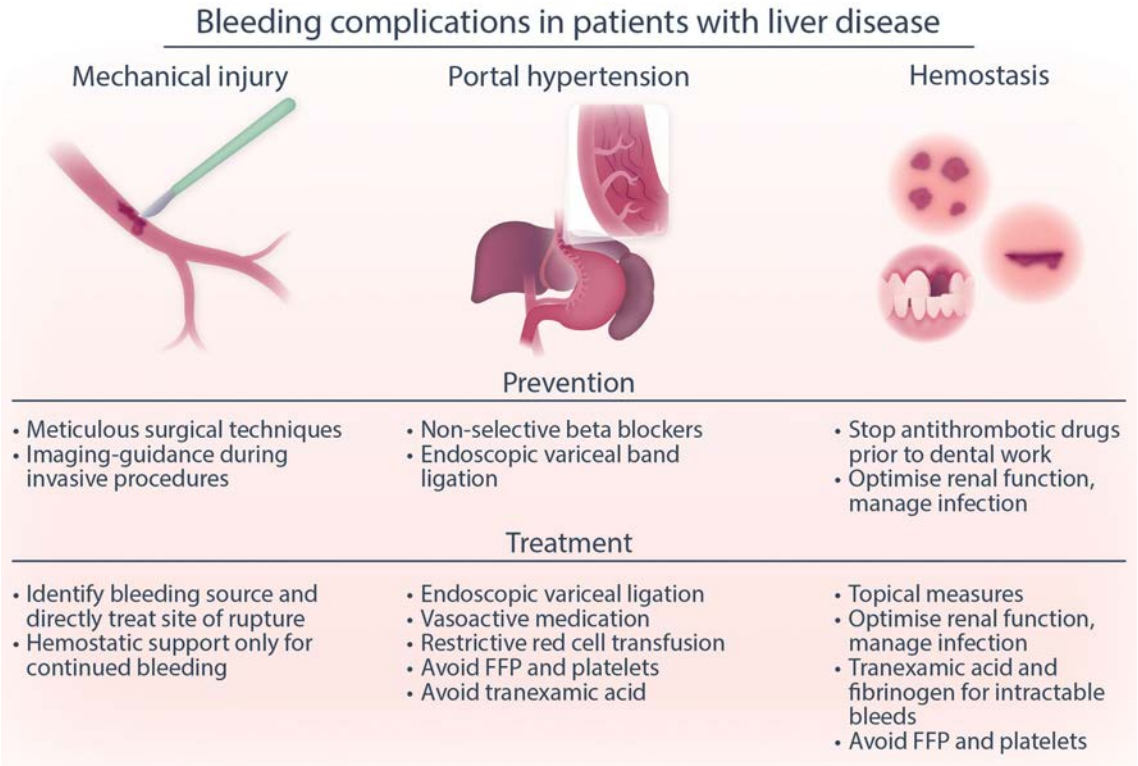


Fig. 3. Strategies for prevention and treatment of bleeding complications in patients with cirrhosis.
FFP, fresh frozen plasma.

Why prohaemostatic treatment is seldomly indicated

Patients with cirrhosis are in a rebalanced haemostatic state, and seldomly have major bleeding complications as a result of defective haemostasis. Attempts to correct abnormal tests of haemostasis such as the platelet count or PT with infusion of blood products is generally not required as discussed by clinical guidance documents issued by various international societies.[14-17] Unfortunately, adherence to these guidance documents appears poor. Infusion of generous amounts of blood products to patients with cirrhosis are associated with costs, side effects including fluid overload, and transfusion-associated acute lung injury. Studies have even suggested that infusion of blood products are associated with decreased survival.[18]

In addition, studies have shown that infusion of platelets or FFP may improve the platelet count and PT, but this does not translate into a meaningful increase in haemostatic capacity as assessed by more advanced haemostasis tests.[19-21] Indeed, it has never been demonstrated that (prophylactic) platelet or FFP infusion improves clinical haemostatic outcome. The take-home message of this presentation thus is that one should not rely on haemostatic testing to predict bleeding, and that prophylactic measures to avoid bleeding are seldomly required. Finally, even in the bleeding patient, prohaemostatic therapy is not the first-line therapy. First do no harm in managing haemostasis in patients with liver disease thus means: do not treat abnormal laboratory values, and treat the real underlying cause of the bleed.

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Prevention of bleeding related to invasive procedures in patients with cirrhosis

Nicolas M. Intagliata[1]

[1]Department of Medicine, Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, VA, *USA*

E-mail address: nmi4d@uvahealth.org

Take-home messages

- Procedural related bleeding in hospitalised patients with decompensated cirrhosis is rare and major bleeding is very rare.
- Conventional haemostatic parameters do not predict bleeding and correction of these factors does not protect against bleeding. Clinicians should focus on rescue strategies and supportive care plans in the event bleeding occurs, rather than prophylactic strategies.
- Factors such as MELD and the risk of procedure may better predict bleeding.
- Other factors including ACLF, AKI, and infection may also contribute to bleeding risk. Research is currently limited by the rarity of bleeding events and limitations in multivariate modelling posed by predictor covariance and multicollinearity.
- Hepatologists and gastroenterologists should now work to educate colleagues regarding this now well-established paradigm shift with the goal of improving and standardising patient care.

Introduction

Patients with decompensated cirrhosis frequently require management and invasive procedures from multiple different specialty providers. Although well-established within hepatology, the modern understanding of a rebalanced haemostatic system in cirrhosis is not universally recognised amongst all clinicians. As such, there is significant practice variation in periprocedural bleeding risk management.[1]

As a result of persistent variation in practice patterns, the European Association for the Study of the Liver (EASL)[2] and other medical societies[3–7] have adopted recommendations for practice standards related to procedural-related bleeding in patients with cirrhosis. However, the authors of the EASL Clinical Practice Guidelines (CPGs) note several research challenges: (1) lack of prospective and sufficiently powered studies, (2) inclusion of a wide array of procedures with varying levels of bleeding risk, (3) bias in current studies based on accepted routine practice of providing blood product transfusion prior to procedures, (4) coexistent alterations in haemostatic factors making isolating contribution of specific factors challenging, and (5) the dynamic nature of cirrhosis (stable, decompensated, to acute-on-chronic liver failure [ACLF]) contributes to bleeding risk which can change rapidly.

Procedural risk level

Patients with cirrhosis undergo a wide variety of procedures which vary considerably in overall risk of bleeding. Guidelines from EASL and the American Association for the Study of Liver Diseases (AASLD) have adopted a procedure risk classification based on prior expert consensus where procedures are designated low or high risk based on predicted rates of bleeding.[2,3] Low-risk procedures have rates of major bleeding <1.5%, whereas high-risk procedures have estimated major bleeding rates of >1.5% or where haemorrhage would be difficult to control or have catastrophic consequences (*e.g.* central

nervous system). A recent survey of experts in the field highlights some challenges in this dichotomy and aims to improve consensus on procedure risk stratification for future studies.[8]

Strategies to reduce inappropriate prophylaxis

There is now a strong consensus among experts that conventional parameters **do not predict bleeding risk before procedures** and **should not be used as a guide for prophylaxis**. Considering these limitations, global coagulation assays, such as viscoelastic tests (VETs), have attracted interest. Although VETs (thromboelastography [TEG] and rotational thromboelastometry [ROTEM]) do not predict bleeding before procedures, they may have a role in periprocedural management of bleeding. A seminal early study randomised patients with cirrhosis undergoing both low- and high-risk procedures to TEG-guided approach to prophylaxis *vs.* standard conventional parameters.[9] There was a statistically significant reduction in use of plasma and platelet transfusions in patients randomised to the TEG-guided approach with a low rate of bleeding complications. A systematic review combined three prospective studies using VET before procedures in patients with cirrhosis and demonstrated clear reduction in use of prophylaxis, but because of the rarity of bleeding events did not demonstrate a reduction in bleeding events.[9–12] There remains a knowledge gap regarding the use of VET in the periprocedural management of haemostasis in patients with cirrhosis and further study in this field is warranted.[7]

Use of pre-procedural prophylaxis

Despite the growing acceptance in the hepatology community of a rebalanced haemostatic system in cirrhosis, inappropriate use of pre-procedure prophylaxis unfortunately remains common practice. Many proceduralists rely on conventional parameters with specific preprocedure 'thresholds' (*e.g.* international normalised ratio [INR] <1.5, platelet count >50x10^9/L), even for low-risk procedures. Correction of INR with plasma transfusion before procedures is not recommended (EASL CPG LoE 2, strong recommendation). Similarly, the use of prothrombin complex concentrates (PCCs), fibrinogen concentrates, and cryoprecipitate before procedures to correct coagulation deficiency or prevent bleeding is not recommended (EASL CPG: LoE 3, weak recommendation, LoE 4 strong recommendation).

For patients with thrombocytopenia, no prospective studies have effectively evaluated the effect of platelet transfusion or thrombopoietin receptor (TPO-R) agonists on procedure bleeding incidence. Avoiding routine platelet transfusion or use of TPO-R agonists for thrombocytopenia in most clinical situations is recommended. However, individualised approaches for management in patients with more severe thrombocytopenia (*e.g.* 20x10^9/L – 50x10^9/L and <20x10^9/L) undergoing high-risk procedures is recommended (LoE 3/4, strong recommendation). Guidance published from the International Society of Thrombosis and Haemostasis (ISTH) suggests a similar individualised approach to be reserved for very high-risk procedures or surgery (*e.g.* neurosurgery or intraocular surgery).[6]

Risk and prediction of periprocedural bleeding

Most of the clinical research in this field has been limited to single-centre retrospective cohort studies focusing on specific procedures (such as risk of bleeding with paracentesis or liver biopsy) or cohorts undergoing multiple types of procedures to determine overall bleeding rate. As major procedural bleeding is rare, the conclusions are generally limited without reliable multivariate models to control for confounding predictor relationships. For example, as liver disease progresses in cirrhosis,

INR increases, fibrinogen decreases, and thrombocytopenia worsens. These changes reflect consequences of disease progression and severity related to a myriad of factors. An early study examined a group of patients with decompensated cirrhosis undergoing a variety of procedures and found bleeding events to be associated with thrombocytopenia.[13] However, a similar subsequent retrospective cohort study found overall bleeding rates to be very low with no association with thrombocytopenia.[14] Multiple other studies have examined specific procedures and have found no clear correlation with conventional coagulation parameters and bleeding.[15] For example, an early study in outpatients with cirrhosis undergoing large volume paracentesis for refractory ascites found no occurrences of bleeding despite high prevalence of thrombocytopenia and elevated INR.[16] More recently, a cohort of hospitalised patients with ACLF undergoing large volume paracentesis found higher rates of bleeding events (~3% bleeding rate).[17] These studies highlight the importance of adequate sample size and cohort selection when investigating procedural-related bleeding in cirrhosis.

Several randomised controlled trials conducted in patients with cirrhosis undergoing procedures have enhanced our understanding of procedural-related bleeding prevalence. As previously mentioned, studies have examined the role of VETs compared with standard coagulation testing for prophylaxis before procedures. Overall, these studies demonstrate very low rates of bleeding and argue strongly against the routine use of prophylaxis before most procedures. However, only one of the three studies included a restrictive comparison arm where prophylaxis was not administered.[12] Future studies should consider large cohorts randomised **without use of prophylaxis** to determine if VETs can improve outcomes of clinical bleeding and mortality. The other main group of randomised controlled trials in this field include studies examining TPO-R agonists. Large trials examining avatrombopag[18] and lusutrombopag[19] enrolled patients with cirrhosis and thrombocytopenia undergoing procedures and randomised them to receive TPO-R agonist *vs.* placebo. These studies included both low- and high-risk procedures and demonstrated that TPO-R agonists significantly increase platelet level in patients and reduce the need for platelet transfusions. However, without a restrictive arm not receiving any correction of platelets, it is not clear if TPO-agonists prevent bleeding or, more importantly, if thrombocytopenia needs correction in the first place. A multivariate analysis including six studies found that TPO-agonists are effective at raising platelets, thereby avoiding need for platelet transfusions, but have not demonstrated reduction in procedural-related bleeding (OR, 0.73; 95% CI 0.34, 1.55).[20] Although TPO-R agonists appear safe and effectively raise platelets, their role in the prevention of bleeding in patients with severe thrombocytopenia remains to be defined. Future studies focused on high-risk procedures with restrictive control arms may be valuable in this regard.

If available tests of coagulation and haemostasis are not clearly predictive of bleeding, then what predictors are associated with bleeding risk? A recent review discusses factors that may contribute to destabilisation of the haemostatic system in acutely decompensated cirrhosis.[21] One important case control study examined the risk of haemoperitoneum with large volume paracentesis and determined in multivariate analysis that the presence of AKI was independently associated with bleeding risk.[22] Bleeding risk was not predicted by MELD, thrombocytopenia, or INR in this study. Infection is common in decompensated cirrhosis and has multiple effects on the haemostatic system which may contribute to bleeding risk.[21] Patients with ACLF may be particularly vulnerable to bleeding complications. Studies have demonstrated alterations in haemostatic tests in ACLF arguing for a unique haemostatic risk profile.[23–25] One study in patients with cirrhosis admitted to the intensive care unit found low fibrinogen and low platelets to be predictive of bleeding.[26] However, this study did not differentiate types of bleeding (portal hypertension *vs.* procedural) in analysis which highlights the risk of confounding relationships with haemostatic markers and liver disease severity. A recent prospective study followed patients with acutely decompensated cirrhosis and measured multiple tests of haemostasis to determine predictors of bleeding events and development of ACLF.[27] There were no

significant differences in tests of haemostasis, rather severity of inflammation and the development of ACLF were associated with bleeding.

As noted by the authors of the EASL CPGs, the rarity of bleeding makes randomised controlled trials challenging to design and implement. A prospective multicentre cohort study was designed to determine the incidence of procedural related bleeding in hospitalised patients with cirrhosis and to define predictive factors associated with bleeding. Twenty centres prospectively enrolled 1,187 hospitalised patients with decompensated cirrhosis undergoing 3,006 non-surgical procedures.[28] A total of 93 procedural-related bleeding events occurred (involving 6.9% of admissions [3% procedures]; major bleeding in 2.3% of admissions [0.9% procedures]). In multivariate analysis (1) high-risk procedures, (2) elevated BMI, and (3) model for end-stage liver disease (MELD) at admission were independently predictive of bleeding. Notably, the number of procedures performed, preprocedural platelet count, and preprocedural INR were not predictive of bleeding. Use of prophylaxis before procedures was significantly more common in patients with bleeding compared with patients without bleeding in univariate analysis.

Conclusions

Although there remain significant knowledge gaps in this field, the most critical finding to emerge across all studies is that **bleeding related to procedures is rare in cirrhosis**. Reassuringly, most procedures in patients with decompensated cirrhosis can be performed safely without prophylaxis or deviation from standard procedure. Because of the interdependent relationship of factors linked to bleeding, the rapidly dynamic changes in physiology of advanced cirrhosis, and complexity of *ex vivo* measurement of the haemostatic system, it is unlikely that one isolated 'haemostatic test' will ever accurately predict bleeding from procedures. However, many clinicians remain attached to old dogma which relies on stringent thresholds and a tendency toward pre-emptive action based on misleading tests. This practice is largely ineffective, wasteful, and not without risk. Now consensus society expert-based guidance offers a clear and pragmatic outline for clinicians caring for this population. These guidelines merge the established foundation of rebalanced haemostasis from translation studies into a widely heterogenous collection of clinical studies to produce a very practical approach to periprocedural management in patients with cirrhosis. Future collaborative multicentre clinical research will bridge remaining knowledge gaps. In the meanwhile, hepatologists should work to promote guideline recommendations broadly among clinicians to improve and standardise care of patients with cirrhosis.

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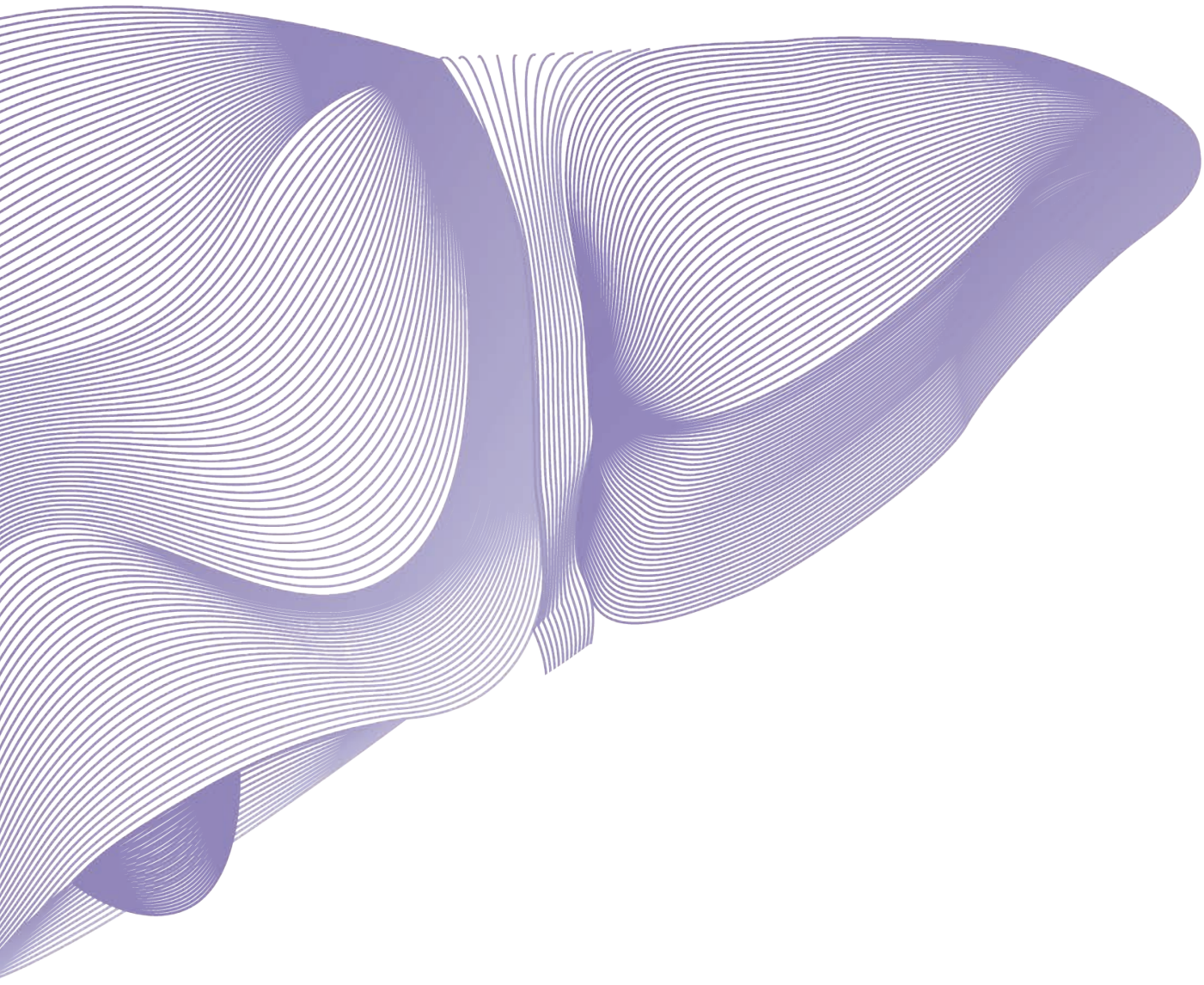
SESSION 4

VASCULAR CONSEQUENCES OF CIRRHOSIS OUTSIDE THE LIVER

WEDNESDAY 5 JUNE
17:45-19:15



Portopulmonary hypertension: diagnosis and management

Laurent Savale[1, 2, 3]

[1]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, *France*; [2]Université Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, *France*; [3]Assistance Publique – Hôpitaux de Paris (AP-HP), Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, *France*

E-mail address: laurent.savale@aphp.fr

Take-home messages

- Echocardiographic screening of portopulmonary hypertension (PoPH) is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation or transjugular intrahepatic portosystemic shunt, even in the absence of symptoms. Right catheterisation is mandatory to confirm the diagnosis.
- The current management approach to PoPH is based on a multidisciplinary approach and combines early detection of the disease and use of pulmonary arterial hypertension (PAH) therapies.
- In candidates for liver transplantation (LT), the use of PAH therapies allows, in the majority of cases, acceptable haemodynamic criteria to be achieved for a safe LT.
- The combination of PAH therapies and LT confers good long-term survival in selected patients.
- Pulmonary haemodynamic normalisation or near-normalisation is an achievable goal in some patients after LT, but predictive factors of reversibility need to be identified.

Introduction

Portopulmonary hypertension (PoPH) is characterised by the combination of portal hypertension and pulmonary arterial hypertension (PAH) defined by mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary artery wedge pressure (PAP) ≤15 mmHg and partial virological response (PVR) >2 Wood units.[1,2] The prevalence of PAH in patients with liver disease is estimated to be between 2% and 6% and can be observed in various forms of liver diseases including portosystemic shunt, extrahepatic portal hypertension, or intrahepatic portal hypertension with cirrhosis regardless of severity.[3,4] PoPH, as with all forms of PAH, is characterised by a progressive structural and functional remodelling of the small-calibre pulmonary arteries responsible for a progressive increase in pulmonary vascular resistance (PVR). As elevation of right ventricular afterload can lead to right heart failure, PoPH is a serious complication of portal hypertension, which affects both the functional status and prognosis of patients.

Diagnosis of portopulmonary hypertension

The diagnosis of PoPH is based on the presence of otherwise unexplained precapillary pulmonary hypertension in patients with portal hypertension or a portosystemic shunt. The diagnostic approach is the same as in other patients with suspected or newly detected PH. Transthoracic echocardiography (TTE) remains the best screening tool for pulmonary hypertension in patients with chronic liver disease. The last guidelines from the European Society of Cardiology/European Respiratory Society (ESC/ERS) stipulate that echocardiographic screening is recommended in symptomatic patients with liver disease or portal hypertension and in all candidates for liver transplantation (LT) or transjugular intrahepatic

portosystemic shunt (TIPS), even in the absence of symptoms.[1] By using echocardiography, systolic PAP can be measured in ~80% of patients with portal hypertension, which aids decisions to perform right heart catheterisation (RHC). The echocardiographic probability of pulmonary hypertension is based on the level of peak tricuspid regurgitation velocity (TRV) and/or the presence of other echocardiographic signs of pulmonary hypertension. An intermediate probability of pulmonary hypertension is defined by a peak TRV <2.8 m/s with indirect signs of pulmonary hypertension or a peak TRV between 2.9 and 3.4 m/s without evidence of indirect signs of pulmonary hypertension. A high probability of pulmonary hypertension is defined by a peak TRV between 2.9 and 3.4 m/s with indirect signs of pulmonary hypertension or a peak TRV >3.4 m/s. As patients with portal hypertension are at risk of developing PAH, an RHC should be performed in an expert centre if an intermediate or high probability of pulmonary hypertension is found on the TTE.

RHC is mandatory to confirm the diagnosis of PoPH, to exclude other mechanisms of pulmonary pressure elevation in cirrhosis, and to assess severity of PoPH (Fig. 1).

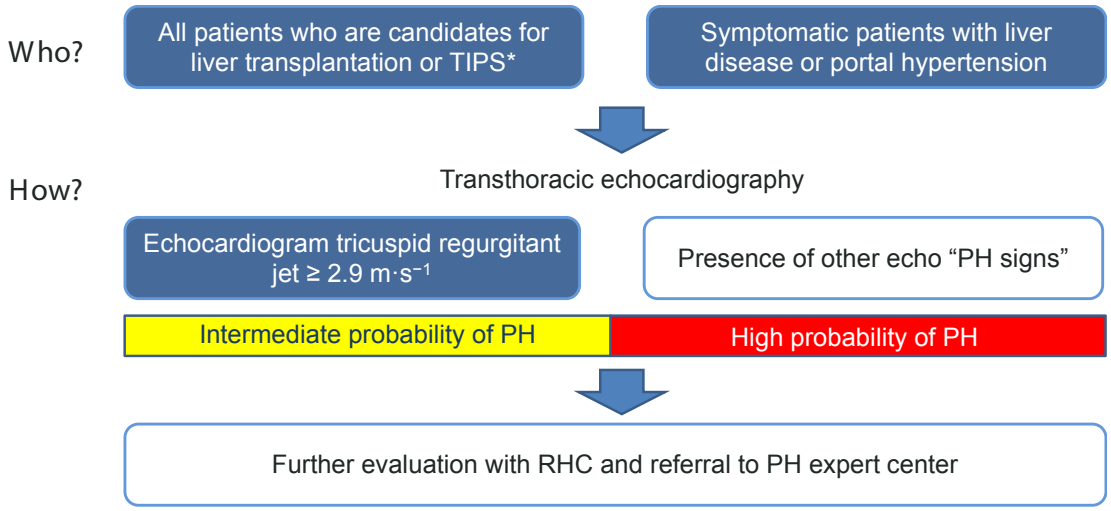


Fig. 1. Diagnostic approach in portopulmonary hypertension.
PH, portal hypertension; RHC, right heart catheterisation.

Management of portopulmonary hypertension

The current management approach to PoPH combines early detection of the disease and use of PAH-targeted therapies, considering the severity of both pulmonary haemodynamic and the underlying liver disease. For patients who are candidates for LT, PoPH may have a serious impact on outcomes and perioperative management, requiring a multidisciplinary approach (Fig. 2).

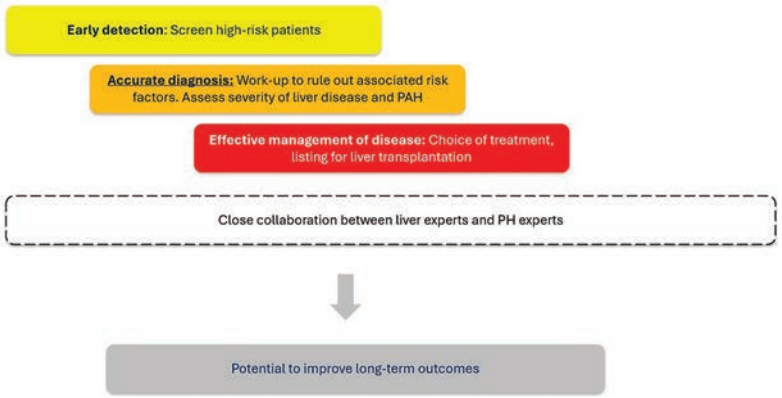


Fig. 2. Principles of portopulmonary hypertension management.
PAH, pulmonary arterial hypertension; PH, portal hypertension.

Non-specific medical therapies

As fluid overload is often observed in PoPH owing to the combination of right heart failure and liver dysfunction, diuretics are required in most patients. As in idiopathic PAH, continuous long-term oxygen therapy is recommended in patients when arterial oxygen partial pressure is consistently <8 kPa (60 mmHg). The use of β-blockers in the prophylactic treatment of oesophageal varices may be associated with a significant worsening in exercise capacity and haemodynamics of patients with PoPH because of the negative effects of β-blockade on the right ventricle (decreased CO and increased PVR).[5] It is, therefore, recommended to avoid or withdraw β-blocker therapy whenever possible in patients with PoPH and to attempt ligation of oesophageal varices if needed. TIPS has no place in the management of PoPH. This procedure can increase right ventricular preload and potentially precipitate right heart failure. Therefore, it is contraindicated in patients with confirmed PoPH.

Use of PAH therapies in PoPH

The use of PAH-targeted therapies in the management of PoPH is based on clinical and pharmacological experience acquired in the treatment of idiopathic PAH. All drugs approved for PAH can principally be used to treat patients with PoPH, keeping in mind that these patients are usually excluded from registration studies. Nevertheless, retrospective and observational data with PAH-targeted drugs in PoPH are encouraging in terms of safety and efficacy. Clinicians must take into account the severity of the underlying liver disease in treatment decision and during follow-up. The three classes of drugs used are prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE-5) inhibitors (Fig. 3). The largest series published so far reported on 574 patients with PoPH treated with various PAH drugs, mostly PDE5is or ERAs, alone and in combination.[6] Most patients (56.8%) were in Child-Pugh class A at the time of PAH diagnosis. At the first follow up, improvements were seen in haemodynamics, WHO-FC, 6MWD, and BNP/NT-proBNP. The only randomised controlled trial (RCT) dedicated to PoPH treatment (PORTICO), was a 12-week study that randomised 85 patients to receive either macitentan (n = 43) or placebo (n = 42). PORTICO successfully achieved its primary endpoint, showing a significant reduction in pulmonary vascular resistance (PVR) from baseline.[7]

There has been speculation regarding the impact of PAH-targeted therapies on portal hypertension, attributed to their potential vasodilatory effects on the splanchnic circulation. However, evidence supporting this possibility varies across studies and is occasionally conflicting. Hence, initiating PAH-specific treatments necessitates vigilant monitoring for signs of decompensated portal hypertension, particularly in patients with advanced liver disease.

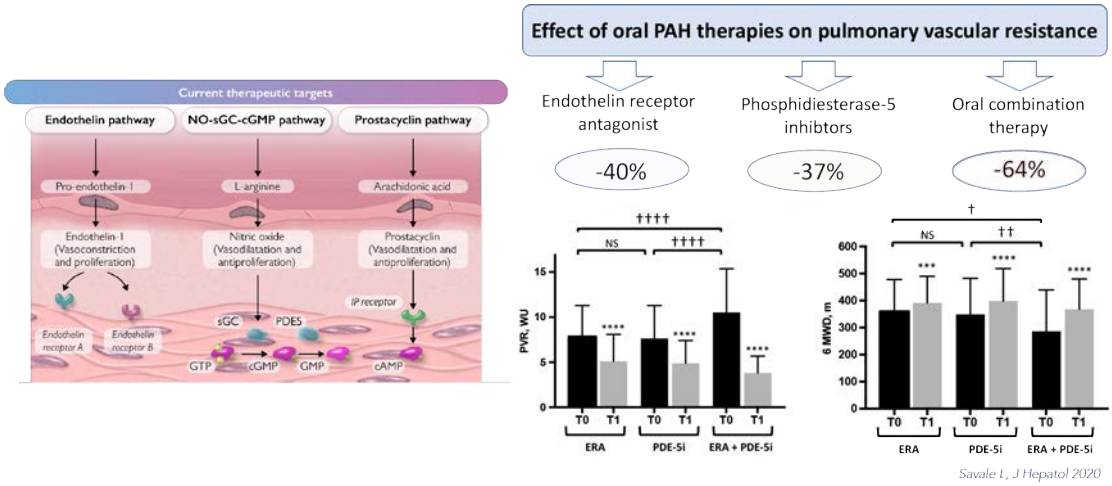


Fig. 3. Use of pulmonary arterial hypertension (PAH) therapies in portopulmonary hypertension.

Portopulmonary hypertension and liver transplantation

The impact of LT on PoPH and *vice versa* is a complex problem. As outcomes of PoPH after LT remains difficult to predict, transplant evaluation is pursued only in patients with controlled PAH and with liver disease meeting transplantation criteria. However, recent evidence backing the effectiveness of PAH-targeted therapy as a bridge to LT and its potential positive impact on long-term outcomes may eventually expand the indications for LT.

In PoPH patients with severe haemodynamic impairment, there is an unacceptably high perioperative risk of death. As a consequence, severe or uncontrolled pulmonary hypertension is a contraindication for LT.[2] Patients with advanced PoPH can develop severe right heart failure during or just after the surgical procedure as a result of haemodynamic changes imposed by both vena cava clamping and graft reperfusion. At the time of liver graft reperfusion, sudden increase in CO is unpredictable and may precipitate right heart failure in a patient with a right ventricle that is already overloaded. Cases of PoPH worsening were also observed later, within 4–6 months after LT, and may require escalation of PAH therapy.[8]

Once the diagnosis of PoPH is established, operative risk should be estimated according to the haemodynamic severity and patient comorbidities. The last International Liver Transplantation Society practice guidelines stipulated that all patients with a mPAP >35 mmHg must be treated with PAH-targeted medications to decrease mPAP and PVR and improve right ventricular function before transplantation.[2] Some studies, often limited by the small number of patients, reported a favourable effect of PAH-targeted therapies, either in monotherapy or in combination therapy, as a bridge to LT.[8] The optimal post-treatment haemodynamic values that could permit LT are not clearly established. Nevertheless, the risk of LT can be considered acceptable if the PAPm is <35 mmHg and the PVR <5 Wood units or if the PAPm is between 35 and 45 mmHg with good right ventricular function and a PVR <3–4 Wood units. A persistent mPAP >50 mmHg despite PAH-specific treatment should be considered as an absolute contraindication to LT. The mortality while on the LT waitlist is higher for patients with PoPH. Both the severity of liver disease (as assessed by the model for end-stage liver disease [MELD] score) and severity of PoPH (as assessed by PVR) were significantly associated with waitlist mortality in the current Organ Procurement Transplantation Network.[9] Accordingly, PoPH should be considered as an indication for MELD exception to reduce the waiting time and to reduce the risk of haemodynamic worsening during this period.

Interestingly, several observations have shown that stabilisation, improvement, or normalisation of pulmonary haemodynamics after the critical period following LT, is an achievable goal. In the era of modern PAH therapies, we observed that survival of selected patients with PoPH who underwent LT was better than for non-transplanted patients, including those with mild cirrhosis.[6,10] This observation likely results from a more aggressive management of the PoPH with PAH-targeted therapies as a bridge to LT to improve cardiopulmonary haemodynamics and reduce the risk of perioperative right heart failure. The survival benefit of LT in patients with PoPH raises the question of whether LT should be considered in selected patients with PoPH who do not have an LT indication because of mild liver disease. Further research is needed to identify predictive factors of PoPH resolution after LT.

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Hepatopulmonary syndrome

Sarah Raevens[1, 2]

[1]Department of Gastroenterology and Hepatology, Ghent University Hospital, Ghent, *Belgium*; [2]Liver Research Center Ghent, Ghent University, Ghent, *Belgium*

E-mail address: sarah.raevens@ugent.be

Take-home messages

- HPS most commonly occurs in patients with liver cirrhosis and portal hypertension but can also occur in patients with vascular liver disease.
- HPS affects 10–30% of patients evaluated for liver transplantation and significantly affects prognosis.
- Patients with HPS are frequently asymptomatic, resulting in under-recognition of the disease and a delay in diagnosis.
- Workup consists of arterial blood gas and contrast echocardiography.
- Effective pharmacological therapies are still not available.
- Liver transplantation is the only effective therapeutic option and results in resolution of the syndrome in most cases.
- Long-term survival in HPS has drastically changed since MELD exception implementation.

For a detailed review on the topic, we refer to Raevens *et al.*[1]

Definition and clinical presentation

Hepatopulmonary syndrome (HPS) is characterised by impaired gas exchange owing to intrapulmonary vascular dilatation (IPVD) and right-to-left shunts. Diagnostic criteria are represented in Fig. 1.[2]

HPS most commonly occurs in patients with liver cirrhosis and portal hypertension, but can also occur in patients with vascular liver disease or vascular abnormalities characterised by altered blood flow between the liver and lung, for example Abernethy malformation.[2]

The presence or severity of HPS does not closely parallel the severity of the underlying liver disease.

HPS is frequently asymptomatic, indicating the need for active screening in patients on the waitlist for liver transplantation (LT). Clinical signs are digital clubbing, cyanosis, and diffuse telangiectasias. Classically described in HPS, but less frequently observed are platypnoea (dyspnoea worsening when moving from supine to upright position) and orthodeoxia (>5% or >4 mmHg decrease in partial pressure of arterial oxygen (PaO_2) after changing from supine to upright position), which are present in a minority, 18–20%, of patients.

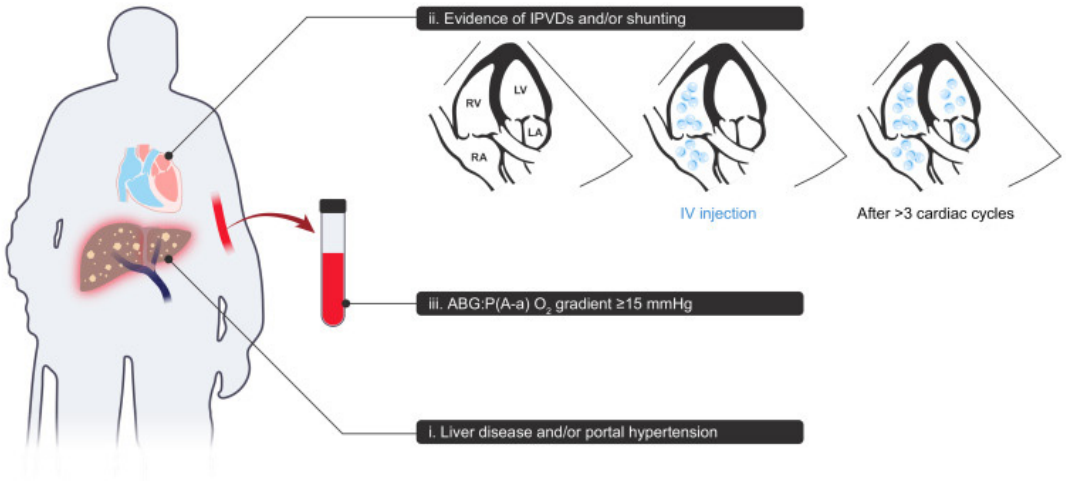

Fig. 1. Diagnostic criteria for hepatopulmonary syndrome the following.
(1) Liver disease and/or portal hypertension. (2) Evidence of IPVDs and/or shunting. Gold standard is contrast-enhanced echocardiography. 'Delayed' presence of microbubbles in the left heart after intravenous injection (three or more cardiac cycles after seen in the right heart) indicates IPVDs or shunts. (3) P(A-a)O_2 gradient ≥15 mmHg (or >20 in case of ≥65 years of age), as determined on arterial blood gas (ABG).[1]

Screening and diagnosis

HPS is frequently underdiagnosed or inaccurately diagnosed. The diagnosis of HPS relies on documenting IPVDs and/or shunts and impaired gas exchange in the absence of another cause for gas exchange abnormalities. IPVDs are detected using contrast-enhanced transthoracic echography. During this examination, saline is agitated, creating microbubbles (>10 µm diameter), which are injected into a peripheral vein. Under normal circumstances these do not pass through the pulmonary capillary bed (<8–15 µm diameter) and are therefore only visualised in the right heart. 'Delayed' presence of microbubbles in the left heart after peripheral injection (three or more cardiac cycles after seen in the right heart) indicates the presence of IPVDs or shunts. Echocardiography can distinguish intrapulmonary from intracardiac right-to-left shunts, in which microbubbles appear in the left atrium as soon as within three cardiac cycles. An alternative method to document IPVDs is a ^{99m}Technetium-labeled macroaggregated albumin (Tc-MAA) lung perfusion scan. In contrast to echocardiography, Tc-MAA scan cannot differentiate between intracardiac and intrapulmonary shunting.

Impaired gas exchange is documented by arterial blood gas (ABG) analysis with measurement of the alveolar–arterial oxygenation gradient (P(A–a)O_2) as a measure of ventilation–perfusion (V/Q) mismatch. ABG should be obtained while the patient is sitting in upright position, breathing room air. The P(A-a) O_2 gradient is calculated as: [(Patm – PH_2O)x0.21 – $PaCO_2$/0.8] – PaO_2. The severity of HPS is classified based on PaO_2 levels: mild >80 mmHg, moderate 60–79 mmHg, severe 50–59 mmHg, very severe <50 mmHg.

Chest radiographs are most often normal, although as with high-resolution computed tomography (CT), may demonstrate increased lower lobe interstitial or vascular markings as signs of IPVDs. Pulmonary angiography may be indicated in cases of severe hypoxaemia (PaO_2 <60 mmHg), when large arteriovenous (AV) malformations, amenable to embolisation, are detected on high-resolution CT.

Pulmonary function tests typically show decreased diffusing capacity for carbon monoxide, which is, however, frequently seen in cirrhotic patients, and thus non-specific for HPS. In addition, subtle abnormalities, lower forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) with preserved FEV1/FVC ratio, have been demonstrated in patients with liver disease and HPS compared to those without HPS.

Oxygen saturation (SaO_2) measurements by pulse oximetry have been used as a simple and non-invasive screening strategy to detect hypoxaemia in HPS, using a cutoff of 94–96% for further diagnostic testing. However, small changes in SaO_2 may be associated with large changes in PaO_2 because of the shape of the oxyhaemoglobin dissociation curve, limiting the sensitivity and specificity of this technique to detect any form of HPS.[3] Forde *et al.*[4] reported that pulse oximetry represents a poor screening test for HPS in LT candidates, and showed that a SaO_2 of 94% provides poor sensitivity (22.1%) and specificity (89.8%) to detect severe HPS. As such, ABG analysis is mandatory to detect increased $P(A–a)O_2$.

Pathophysiology and pathogenesis

The development of impaired gas exchange in HPS has been attributed to three mechanisms resulting from the alterations in the alveolar microcirculation: V/Q mismatch, diffusion limitation, and the presence of direct AV communications.

The pathogenesis of alterations in the microcirculation in HPS has been the focus of study over the last 20 years. This work has been facilitated by the recognition that experimental common bile duct ligation (CBDL) recapitulates many features of human HPS.[5,6] Work in the CBDL model has identified underlying pathophysiologic triggers for three mechanisms that contribute to the development of hypoxaemia in the disease: relaxation of blood vessels leading to vasodilation, angiogenesis leading to shunt formation, and alveolar dysfunction.[7] The underlying processes responsible for these three mechanisms are summarised in Fig. 2.[1,7]

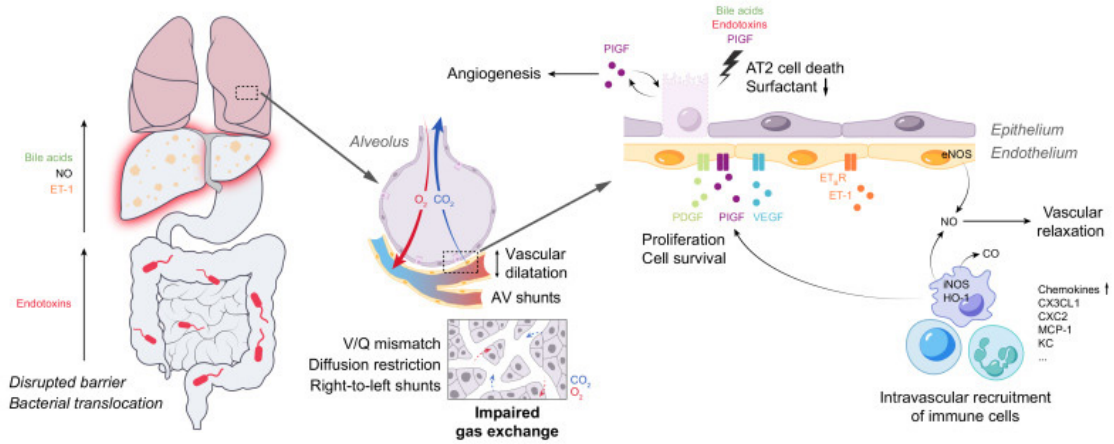

Fig. 2. Pathophysiology and pathogenesis of HPS.
A complex interaction between the liver, the gut and the lungs, predominately impacting pulmonary endothelial cells, immune cells and respiratory epithelial cells, is responsible for the development of IPVDs and intrapulmonary shunting in HPS. These phenomena result in V/Q mismatch, diffusion restriction and right-to-left shunting, responsible for impaired gas exchange and hypoxaemia. Bacterial translocation with pulmonary intravascular recruitment of immune cells, pulmonary endothelial dysfunction, angiogenesis, and AT2 cell dysfunction represent the most important underlying

mechanisms and are considered potential therapeutic targets. AT2, alveolar type II; AV, arteriovenous; CO, carbon monoxide; HPS, hepatopulmonary syndrome; IPVDs, intrapulmonary vascular dilatations; NO, nitric oxide; V/Q, ventilation–perfusion.[1]

Natural history and prognosis

HPS significantly increases mortality and worsens quality of life.[8] If left untreated, patients with HPS have a median survival of 24 months and a 5-year survival rate of 23%.[9] The prospective Pulmonary Vascular Complications of Liver Disease study demonstrated that mortality is doubled in patients with cirrhosis with HPS being evaluated for LT compared with patients without HPS.[8] Mortality is the highest in patients with severe HPS.[9–11] The PaO_2 decreases in 85% of patients over time, with an average decline of approximately 5 mmHg/year.[9] Long-term survival in HPS drastically changed with the recognition of LT as a cure for the disease, and after model for end-stage liver disease (MELD) exception implementation. The natural history of HPS is illustrated in Fig. 3.

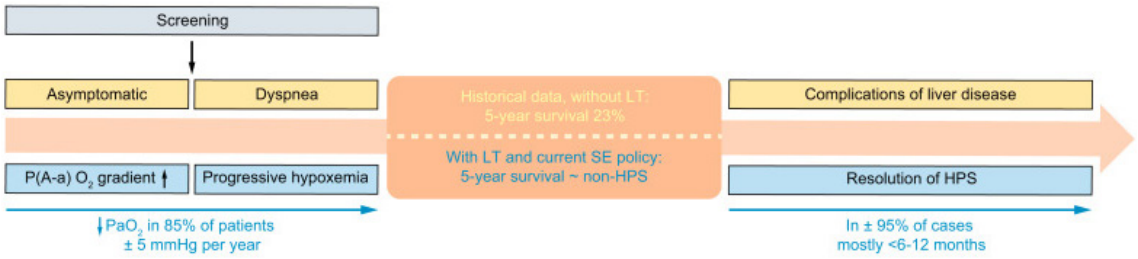

Fig. 3. Natural history of HPS.

HPS is frequently detected by screening; most patients are asymptomatic or only experience dyspnoea on exertion. ABG reveals a widened $P(A–a)O_2$ gradient. Hypoxaemia is usually progressive over years. Untreated HPS carries poor prognosis. LT represents the only curable treatment option, and significantly improved survival of these patients over the past years.[1] ABG, arterial blood gas; HPS, hepatopulmonary syndrome; LT, liver transplantation; $P(A–a)O_2$, alveolar–arterial oxygenation gradient.

Management and treatment options

Medical treatment

Despite significant progress in HPS research, effective pharmacological therapies are not available. Novel treatments are needed, that either resolve and cure HPS or slow down its progression to facilitate successful LT.

The identification of angiogenesis as an essential driver of HPS development stimulated interest in the use of angiogenesis inhibitors. In a first randomised controlled pilot trial in HPS, 28 Child-Pugh A/B patients were treated with low dose sorafenib (400 mg/day) or placebo for 12 weeks based on findings in experimental HPS. Sorafenib did not improve gas exchange or functional status at the dose used and was associated with recognised side effects.[12]

Supportive and palliative therapy

Continuous long-term low-flow oxygen is the only effective supportive therapy for HPS, and should be started in case of severe hypoxaemia at rest.[8] For patients with HPS who are not candidates for LT, coil embolisation of AV malformations is a potential palliative treatment.

Liver transplantation

The role of LT in HPS has significantly evolved over the years. LT has been shown to successfully improve HPS in the vast majority of patients (complete resolution in ±95% of cases, mostly within 6–12 months) with good overall survival.[10] A MELD standard exception (SE) has been created for those with severe HPS (PaO_2 <60 mmHg) as hypoxaemia in HPS is generally progressive, post-LT mortality is highest as severity worsens, and HPS severity does not correlate with the severity of the underlying liver.

Data from large studies in the USA and Europe indicated that since the implementation of the MELD SE policy the outcome in patients with HPS has significantly improved compared with the pre-MELD era.[11,13] There has been discussion on the determination of the degree of hypoxaemia at which patients with HPS benefit from LT without compromising their post-LT outcomes. Some studies associated very severe HPS with increased risk for complications and mortality after LT. In any case, patients with severe HPS should be referred to specialised high-volume LT centres, experienced with post-LT interventions to treat severe post-LT hypoxaemia.

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Heart involvement in cirrhosis: where are we now?

Lisa B. VanWagner[1]

[1]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX, *USA*

E-mail address: Lisa.VanWagner@utsouthwestern.edu

Take-home messages

- Cirrhosis-related systemic inflammation and oxidative stress drive cardiac functional and structural changes which over time result in a unique cardiac phenotype termed *cirrhotic cardiomyopathy.*
- Cirrhotic cardiomyopathy affects up to 47% of patients with cirrhosis, including children, and is associated with adverse clinical outcomes in select patients on non-selective beta-blockers, hepatorenal syndrome, acute-on-chronic liver failure, transjugular intrahepatic portosystemic shunt creation and liver transplantation.
- Cirrhotic cardiomyopathy is diagnosed using comprehensive transthoracic echocardiography according to the 2020 Cirrhotic Cardiomyopathy Consortia Criteria and includes both systolic and diastolic dysfunction.
- Cirrhotic cardiomyopathy may not be reversible.
- Surveillance of cirrhotic cardiomyopathy may be of clinical benefit in select patients.

Cardiovascular physiology in cirrhosis

The long-recognised characteristic cardiovascular finding in cirrhosis is the hyperdynamic circulation characterised by a low systemic vascular resistance and high cardiac output state (Fig. 1).[1] In cirrhosis and portal hypertension, there is increased vascular response to vasodilators and decreased responsiveness to vasoconstrictors in the systemic and splanchnic circulation but not in the hepatic microcirculation. Vasodilation and associated hypotension lead to activation of vasoconstrictor systems including the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system resulting in renal vasoconstriction and sodium and fluid retention. This in turn expands circulating volume further exacerbating the hyperdynamic circulation.

Although patients with cirrhosis often exhibit total body volume overload, increased arterial compliance leads to a functional hypovolemia and therefore a decrease in cardiac pre-load. Over time, the heart fails to increase cardiac output in response to the decrease in effective circulating volume which may in part be attributed to high peripheral arterial vasodilation. This cardiac insufficiency may also be masked by splanchnic arterial vasodilation which further unloads the ventricle by increasing splanchnic blood flow. Other contributors to the blunted cardiac response (*e.g.* chronotropic incompetence) in cirrhosis include autonomic dysfunction and impaired volume and baroreceptor reflexes. In animal models, the cardiac alterations that characterise cardiomyopathy in cirrhosis have been attributed to a variety of molecular causes including biophysical changes in the cardiomyocyte-membrane through altered K^+ channels, altered L-type Ca^{2+} channels, and altered Na^+/Ca^{2+} exchanger, attenuation of the stimulatory β-adrenergic system, and overactivity of negative inotropic systems mediated via increases in cyclic GMP (guanosine monophosphate).[2]

In recent years this 'hyperdynamic hypothesis' of circulatory dysfunction in cirrhosis has been expanded to include advanced understanding of the role of systemic inflammation, oxidative and nitrative stress, vasoactive mediator imbalance, dysregulated endocannabinoid and autonomic nervous systems, endothelial dysfunction and the gut microbiome in mediating the complex interplay between the liver

and the heart (Fig. 1).[3,4] With progressive damage to the liver, several vasoactive, pro-inflammatory and pro-oxidative mediators, as well as damage-associated molecular patterns (DAMPs), are produced and released. In addition, tissue injury in the splanchnic region can increase the translocation of pathogen-associated molecular patterns (PAMPs) from the gut. Together, these mediators promote systemic inflammation and oxidative and nitrative stress, inducing tissue damage in the liver and other organs, including the heart. Collectively, this results in structural and functional changes in the heart in the absence of any other heart disease, a condition known as **cirrhotic cardiomyopathy (CCM).** CCM is characterised by systolic dysfunction (latent or at rest), diastolic dysfunction, chronotropic incompetence, and often electrophysiological abnormalities.[5]

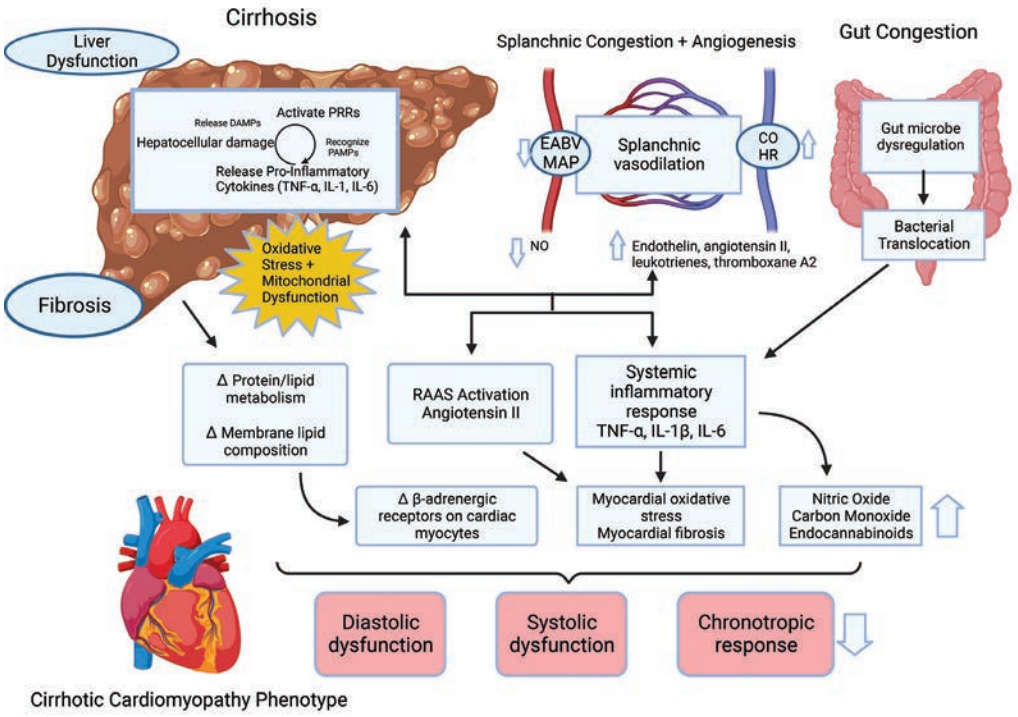

Fig. 1. Schematic of the complex interplay between the liver and heart in the development of cirrhotic cardiomyopathy.

CO, cardiac output; DAMPs, damage-associated molecular pattern molecules; EABV, estimated arterial blood volume; HR, heart rate; MAP, mean arterial pressure; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; RAAS, renin–angiotensin–aldosterone system.

Cirrhotic cardiomyopathy: epidemiology

Because of the latent nature of the disease, the actual prevalence, incidence, and natural history of CCM is largely unknown. Typically, the syndrome is not recognised until clinical decompensation occurs in which patients often present with features of high-output heart failure or diastolic heart failure. With regard to heart failure, there are four stages for its development; stage A: the presence of risk factors (*e.g.* hypertension diabetes mellitus), stage B: presence of structural changes (*e.g.* remodelling) without clinical features; stage C: clinical presentation; and stage D: refractory clinical presentation (Table 1).[6] Patients with CCM where there is LV remodelling will fall under stage B and it is conceivable that patients with cirrhosis at risk of CCM fall under stage A.

Table 1. Cirrhotic cardiomyopathy in the spectrum of heart failure[5]

CCM, cirrhotic cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; LV, left ventricle.

	HF stage[6]	CCM correlate	Therapeutic target
Early Stage	Stage A	At risk of HF = Patients with cirrhosis or metabolic syndrome and its components without structural heart disease and without symptoms	Risk factor modification (*e.g.* control blood pressure, weight loss as needed)
	Stage B	LV remodelling and/or systolic or diastolic dysfunction on imaging *without* HF symptoms	Treat structural heart disease to prevent progression to symptomatic HF (Stage C)
Late Stage	Stage C	LV remodelling and/or systolic or diastolic dysfunction + prior or current HF symptoms	GDMT to prevent progression to Stage D HF
	Stage D	Refractory HF requiring specialised interventions	GDMT to reduce mortality

Attempts have been made to extrapolate the prevalence of CCM by looking at the prevalence of QT interval prolongation in patients with cirrhosis, which previously was touted as the most common manifestation of CCM (see *Diagnosis)*.[5] The prevalence of QT interval prolongation increases with severity of portal hypertension from 25% in Child A cirrhosis to up to 60% in Child C cirrhosis.[7] However, QT can be prolonged owing to a variety of causes (*e.g.* obesity, medications), which limits its use as an accurate surrogate for CCM. Based on transthoracic echocardiography, CCM is present in 20–47% of patients with cirrhosis, including children, with prevalence dependent on cirrhosis aetiology (*e.g.* metabolic dysfunction associated steatohepatitis [MASH] 47%, alcohol-associated liver disease 33%, other aetiologies 20%), comorbidity, and diagnostic criteria used.[8,9]

Cirrhotic cardiomyopathy: diagnosis

Diagnostic criteria for CCM have evolved in line with our understanding of the pathophysiology of cirrhosis. Kowalski and Abelman[1] first described hyperdynamic changes in patients with cirrhosis in 1953. In 1969, Gould[10] first described chronotropic incompetence. Yet, it was not until 1996 that the term 'cirrhotic cardiomyopathy' was coined by Ma and Lee[11] and nearly 10 years later at the World Congress of Gastroenterology in 2005 initial diagnostic criteria for CCM were proposed.[5] The 2005 CCM criteria described the systolic component of CCM (*i.e.* systolic dysfunction) as having reduced left ventricular ejection fraction (LVEF) <55% or having suboptimal contractile response to pharmacologically or physiologically induced stress. The 2005 CCM criteria described the diastolic component of CCM (*i.e.* diastolic dysfunction) as low early to late diastolic transmitral flow velocity (E/A) <1, isovolumetric relaxation time >200 ms, or deceleration time >80 ms.[12] Finally, the 2005 criteria included a set of cardiac surrogates to support the diagnosis of CCM such as prolonged QT interval.

Although the 2005 attempt to characterise CCM was an important first step in the right direction, applying 2005 CCM criteria to clinical practice is challenging for multiple reasons. First, because of a decrease in systemic vascular resistance (afterload), LVEF is frequently inflated and may not identify the true cardiac dysfunction that can manifest once a normal afterload is restored. By American and European cardiology guidelines, >50% represents preserved LVEF and LVEF <50% is reduced; LVEF >60% is hyperdynamic.[6] Second, applying depressed contractile response to stress to daily practice is limited by lack of unanimous definition or characterisation of what depressed contractile response to stress entails. In addition, widespread use of non-selective beta blockers (NSBBs) in patients with cirrhosis lowers cardiac output by reducing heart rate and thus, impairs cardiac responsiveness. Third, the 2005 diastolic dysfunction criteria exhibit U-shape phenomenon in cirrhosis where measurements on both ends of the spectrum (*i.e.* normal diastolic dysfunction and advanced diastolic dysfunction) often look alike.[5] Additionally, volume overload and its effect on preload impedes the utility of the E/A ratio since it is relatively preload-dependent.[5] Finally, as mentioned above supportive criterion, such as QT prolongation, has limited diagnostic utility owing to multiple causes of this finding.

The challenges in applying 2005 criteria to clinical practice triggered interest in revising them and the evolution in echocardiography technology paved the path for the revision. In 2020, the Cirrhotic Cardiomyopathy Consortium (CCMC), an international multidisciplinary consortium, published revised CCM criteria (Fig. 2).[5] Systolic dysfunction was defined as either (1) LVEF ≤50% or (2) an *absolute* value of global longitudinal strain (GLS) <18%.[2] Of note, in echocardiography reports, GLS, which is an index of cardiac mechanics that correlates with clinical outcomes in may cardiovascular disease states including small studies of CCM, is reported as a negative value. The CCMC recommended that changes in GLS be described as changes in the absolute value.[2] The diastolic component was defined by having at least three of the following: early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e′) ≥15, left atrial volume index > 34 ml/m^2, septal e′ <7 cm/s, or tricuspid regurgitation maximum velocity >2.8 m/s in the absence of pulmonary hypertension. When diastolic dysfunction is diagnosed, the severity can be determined using the E/A ratio (0.8–2 = grade II and >2 = grade III). Patients with only two out of the four criteria need further echocardiographic evaluation to define diastolic dysfunction and its grade. This additional evaluation entails assessing E/A ratio change during Valsalva, pulmonary vein velocity, GLS, left atrial strain, and isovolumetric relaxation time (IVRT). While 2020 CCM criteria do not include supportive criteria like those of 2005, the CCMC suggested studying the diagnostic utility of a group of variables (*e.g.* abnormal chronotropic or inotropic response, myocardial mass change, and serum biomarkers) that may have future potential in the management of CCM.[5]

Although echocardiography is used clinically to identify CCM it is limited by operator expertise and a restricted acoustic window. Cardiac magnetic resonance (CMR) imaging identifies myocardial abnormalities earlier than echo and may better inform risk and interventions.[5] For example, CMR T1 and T2 tissue mapping can detect myocardial fibrosis and subendocardial oedema, which are markers of myocardial remodelling described in early CCM.[5,13] The potential clinical utility of CMR in CCM requires further study.

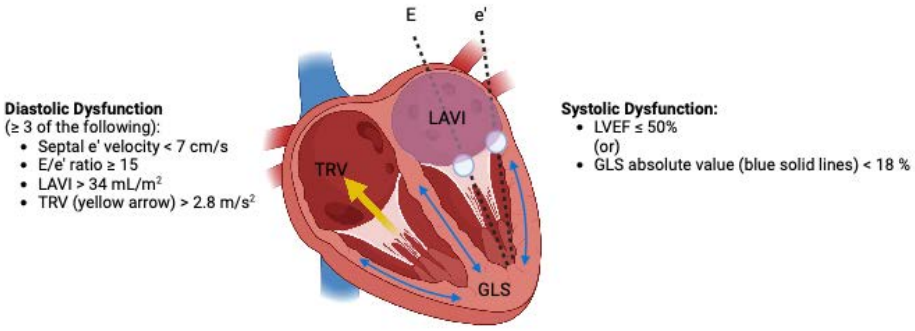

Fig. 2. The 2020 Cirrhotic Cardiomyopathy Consortium Criteria.
Note: a higher E/e′ ratio is indicative of abnormal left-sided ventricular pressures. e′, septal mitral annular early diastolic velocity; E, mitral inflow early diastolic velocity; GLS, global longitudinal strain; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TRV, tricuspid regurgitant velocity.

Cirrhotic cardiomyopathy: implications for clinical practice

Use of non-selective beta-blockers

Beta blockers, as anti-remodelling agents, have been the core of guideline-directed medical standard of care for various cardiomyopathies with reduced ejection fraction.[6] They tend to improve left ventricular contractility (i.e. systolic function) and filling pressures (i.e. diastolic function) except in restrictive cardiomyopathies. NSBBs are standard of care in patients with cirrhosis for primary and secondary prevention of variceal bleeding,[14] and recently, carvedilol, a unique NSBB with beta1-, beta2- and alpha1-adrenergic properties, is guideline-recommended for prevention of decompensation in patients with compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH).[15] However, it remains unclear if CCM responds favourably or adversely to beta-blockade given the unique haemodynamics in cirrhosis.

Alvarado-Tapias *et al.*[16] recently demonstrated that patients with decompensated cirrhosis and greater decline in cardiac output while on NSBBs (cardiac output <5 L/min *vs.* cardiac output <5 L/min) had worse survival. Notably, patients with more remarkable decline in cardiac output (<5 L/min) also had impaired GLS compared with those with higher cardiac output on NSBBs (absolute GLS value 18% ± 2 *vs.* 21% ± 2) suggesting that perhaps CCM may be an explanation for the study's findings; albeit CCM prevalence was not reported and indeed very few patients underwent echocardiography assessment. In another study, Giannelli *et al.*[17] demonstrated among 584 patients with cirrhosis evaluated for liver transplantation, 50% of whom received NSBBs, that among those with subclinical LV dysfunction (assessed invasively with right heart catheterisation by the left ventricular stroke work index), treatment with NSBBs was significantly associated with waitlist mortality independent of model for end-stage liver disease with sodium (MELD-Na) score (subdistribution hazard ratio 1.96; 95% CI 1.32–2.90; $p = 0.0009$). Of note, presence of LV dysfunction was most prevalent in those with refractory ascites. Collectively, these data support *careful consideration* of NSBB, particularly in patients with LV systolic dysfunction.

Hepatorenal syndrome and terlipressin

Small cohort studies have suggested that relative reduction of cardiac output in cirrhosis, such as that observed in CCM, results in renal hypoperfusion and might predict the development of hepatorenal syndrome–acute kidney injury (HRS–AKI).[18] Use of NSBBs to prevent variceal bleeding has been associated with a greater risk of developing HRS–AKI and shown to increase mortality in selected patients with refractory ascites and documented low cardiac output.[17] However, two recent studies demonstrated significantly higher cardiac output in patients with HRS–AKI compared with those without.[19,20] Consequently, the predominant pathophysiological mechanism behind HRS–AKI may not be directly related to reduced cardiac output but rather driven by an inability to increase cardiac output in response to stress, a hallmark of CCM.[20] Collectively, these seemingly disparate findings suggest that perhaps there is a 'window' beyond which in the development of HRS–AKI that impaired cardiac response to stress 'gives way' to CO decline. Interventions which worsen this trajectory (*e.g.* NSBBs, unguided volume expansion) may in fact worsen renal recovery. However, whether interventions that protect or improve cardiac output result in improved renal function is currently unknown.[21]

Treatment of HRS–AKI with terlipressin and albumin provides survival benefit in HRS–AKI and is guideline-recommended for select patients, however terlipressin may decrease cardiac output.[21] The cardiosuppressive effect of terlipressin on cardiac output may explain why HRS is irreversible in some patients, particularly those with CCM. Accordingly, Premkumar *et al.*[22] recently assessed 140 patients with HRS–AKI with point-of-care (POC) echocardiography and demonstrated that CCM defined using the 2020 CCM criteria and its features (E/e''>12.5 [indicating increased left filling pressures, C-statistic-0.774], e' velocity <7 cm/s [indicating impaired relaxation; C-statistic-0.791], >20.5% reduction in cardiac index at 72 h [C-statistic-0.885]; p <0.001) were predictors of terlipressin non-response. In addition, presence of CCM was independently associated with poor survival in patients with HRS–AKI (adjusted hazard ratio 1.9, 95% CI 1.8–4.5, p = 0.009). Thus, CCM may provide important prognostication in patients with HRS–AKI and predict terlipressin non-response.

Acute-on-chronic liver failure

Patients with acute-on-chronic liver failure (ACLF) have splanchnic and systemic vasodilation, which is associated with reduced systemic vascular resistance (and increased cardiac output) resulting in a hyperdynamic state. This imbalance between the splanchnic and systemic circulation causes a state of relative hypovolemia which becomes more pronounced in sepsis. POC echocardiography is a well-established tool for identifying haemodynamic instability in critically ill patients with sepsis with aetiology other than cirrhosis and can guide physicians in titrating appropriate therapeutic interventions (*e.g.* fluids, vasopressors, inotropes) to optimise tissue perfusion and organ support in septic shock. Kajal *et al.*[23] recently used POC-echocardiography to assess CCM (according to the 2020 CCM criteria) in 120 patients with ACLF, of whom 57% had circulatory failure. CCM prevalence was 53%. They demonstrated that markers of CCM (E/e' and e' velocity) and change in cardiac index reliably predicted circulatory failure and mortality in ACLF with severe sepsis and even suggest that CCM markers may enhance the predictive performance of the CLIF-Consortium (CLIF-C) ACLF and MELD-Na scores.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) creation directs blood away from the portal system into the systemic circulation. Although TIPS is a highly effective treatment for portal hypertension, it is associated with a 20% risk of heart failure caused by, in part, increased blood return to the right heart.[24] Biley *et al.*[24] evaluated cardiac decompensation within 1 year after TIPS in 100 patients and showed that elevated E/e' (11 in the cardiac decompensation group *vs.* 7 in others) or left atrial volume index (LAVI, 40 *vs.* 29 mL/m^2) pre-TIPS were associated with higher risk of cardiac decompensation post-TIPS. Jansen *et al.*[25] retrospectively reviewed the 2-year clinical course of 114 patients who underwent TIPS and found that decreased LV contractility detected as depressed GLS absolute value <16.6% was associated with development of ACLF and impaired survival. Recently, among 883 patients from North America enrolled in the retrospective Advancing Liver Therapeutic Approaches (ALTA) TIPS study, elevated pre-TIPS right atrial pressure was significantly associated with greater odds of post-TIPS complications, including HF-related hospitalisations and TIPS dysfunction.[26] Moreover, the authors found that the mortality risk associated with right arterial pressure (RAP) begins at levels above 8 mmHg and rises thereafter but is not confined to those with marked elevations. Elevated pre-TIPS RAP levels (particularly low-level increases) could be a marker for the presence of subclinical cardiopulmonary abnormalities (*e.g.* CCM) that are unmasked after TIPS; higher RAP levels may also reduce TIPS effectiveness by limiting the reduction in portal pressure.

Liver transplantation

As improvements in liver transplantation (LT) survival and quality of life have been achieved, LT recipients continue to be older and have inherently more comorbidities. Among these, cardiac disease is one of the three main causes of morbidity and mortality after LT with cumulative incidence as high as 30.3% within 8 years post-LT.[27] Several reasons exist including the high prevalence of associated risk factors, which can also be attributed to the rise in the proportion of patients undergoing LT for MASH.

Overt heart failure is rare in LT candidates, as severe cardiac dysfunction (*e.g.* LVEF <40%) is an absolute contraindication to LT without combined heart transplantation.[27] However, subclinical cardiac dysfunction is highly prevalent occurring in 20–47% of LT candidates.[9] Subclinical cardiac dysfunction impacts post-LT outcomes with pre-LT diastolic dysfunction predicting post-LT cardiovascular disease and post-LT overt heart failure being associated with increased mortality.[9] Whether CCM is 'reversible' after LT is not clear, as longstanding CCM physiologic changes can lead to myocardial fibrosis which may be irreversible.[9,12] Additionally, the hyperdynamic physiology of portal hypertension may take up to 12 months to recover after LT.[28] Data in LT recipients has suggested an LVEF <60% to be associated with increased post-LT MACE and worse post-transplant survival, likely reflecting hyperdynamic measures of true cardiac dysfunction.[29] Thus, one could argue that post-transplant echocardiographic follow up be considered in individuals with pre-LT LVEF <60% to optimise post-transplant cardiac function.[30] Guidance documents suggest an LVEF 41–49% is a relative contraindication to LT that requires routine follow-up transthoracic echocardiography (TTE) while listed every 6 months.[5] An LVEF <50% that does not increase with stress may also identify a subset of high-risk patients within this category that could be considered a contraindication to LT.[30] Thus, although cardiac stress testing has fallen out of favour for detection of coronary artery disease, stress testing may have benefit to assess cardiac reserve in select LT candidates.[30] In summary, careful cardiac follow up in selected patients while listed and after LT among those with identified CCM is recommended.

Future directions

Although our knowledge of CCM has advanced over the past decade, multiple unanswered questions remain with multiple opportunities for future investigations (Fig. 3). The true prevalence of CCM in all comers with decompensated cirrhosis remains unknown as studies have focused predominantly on LT candidates. CCM has been historically associated with HRS; however, this association needs to be re-evaluated according to the new criteria. The evolution of CCM after LT and factors predicting reversal versus persistence of CCM need to be explored to potentially identify patients who can benefit from early intervention.

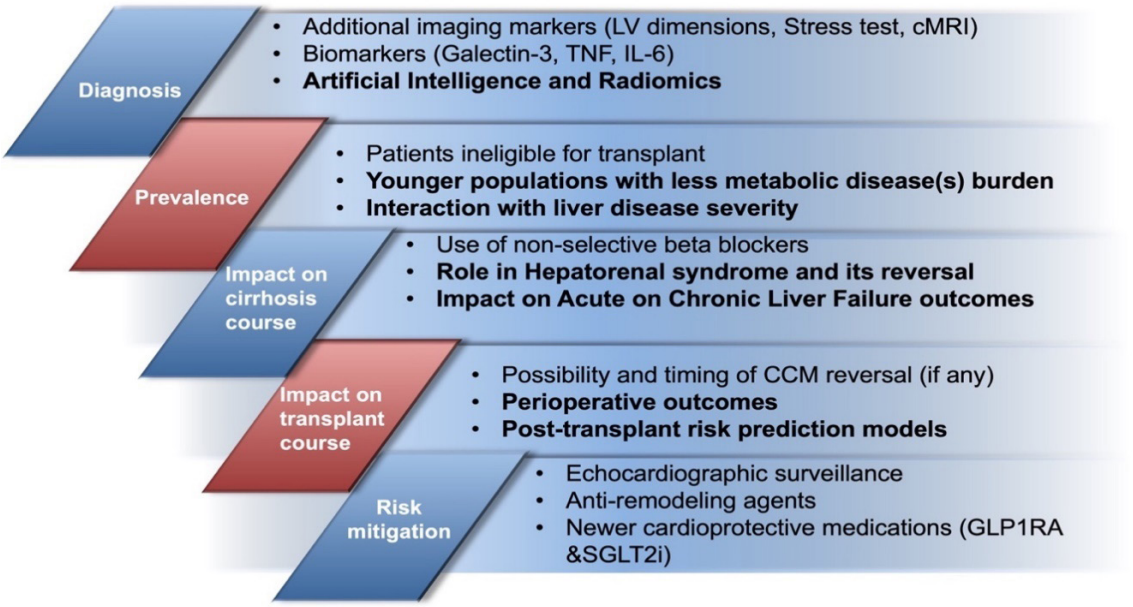

Fig. 3. Unanswered questions in cirrhotic cardiomyopathy.
Image Courtesy of M. Izzy (unpublished).

Conclusions

There are new criteria for CCM for which assessment needs to be incorporated in the standard echocardiographic exams performed in patients with ESLD. CCM and its components appear to negatively impact outcomes in patients while awaiting LT, after TIPS, or after LT. Therefore, close follow up is warranted in these patients. Prospective studies are critically needed to further evaluate pre- and post-transplant outcomes in CCM patients.

Acknowledgments

I would like to thank Dr Manhal Izzy, Associate Professor Hepatology, Vanderbilt University, and Dr Gonzalo Crespo from the Liver Unit, Hospital Clinic, University of Barcelona for their critical review of the syllabus material. I would also like to acknowledge Dr Elena Gavrila, Resident Physician University of Texas Southwestern Medical Center, for her assistance with Figs 1 and 2.

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Diagnosis and management of AKI–hepatorenal syndrome

Valeria Calvino[1], Salvatore Piano[2]

[1]Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine (DIMED), University and Hospital of Padova, Padua, *Italy*; [2]Unit of Internal Medicine and Hepatology, Department of Medicine, University and Hospital of Padova, Padua, *Italy*

E-mail address: salvatorepiano@gmail.com

Take-home messages

- Hepatorenal syndrome–acute kidney injury (HRS–AKI) is a life-threatening complication of decompensated cirrhosis.
- HRS–AKI occurs in the context of severe splanchnic arterial vasodilation, systemic inflammation, maximal activation of endogenous vasoconstrictors systems, and kidney hypoperfusion.
- In the current epidemiological scenario, the differential diagnosis between HRS–AKI and acute tubular necrosis is tricky, and the implementation of urinary biomarkers for clinical practice is warranted.
- The combination of vasoconstrictors and albumin represents the first line treatment of HRS–AKI, but it should be handled with caution because of risk of adverse events.
- Liver transplantation is the best treatment of HRS–AKI.

Introduction

Acute kidney injury (AKI) is a common complication of cirrhosis, occurring in 35–50% of patients hospitalised for an acute decompensation of the disease.[1] The high susceptibility to AKI in patients decompensated cirrhosis is caused by a reduction of effective circulating volume in the context of splanchnic arterial vasodilation and systemic inflammation (Fig. 1). To preserve kidney perfusion and glomerular filtration rate, there is a compensatory increase in the systemic activation of endogenous vasoconstrictors systems (renin–angiotensin–aldosterone system, systemic nervous system, and non-osmotic secretion of vasopressin) and intrarenal production of prostaglandin (to vasodilate afferent arteriole). The hyperactivation of endogenous vasoconstrictors system leads to an increase in cardiac output which contributes to increase renal perfusion, however, in patients with long-lasting disease and cirrhotic cardiomyopathy, the relative reduction of cardiac output predisposes to the development of AKI. In this context, any acute events causing a sudden reduction of effective circulating volume (*e.g.* gastrointestinal bleeding, diarrhoea, diuretic overdose, large volume paracentesis without albumin) a worsening of systemic inflammation (*e.g.* bacterial infections) and/or affecting intrarenal regulation (*e.g.* use of non-steroidal anti-inflammatory drugs [NSAIDs]) can cause an acute reduction in glomerular filtration rate, causing AKI.[1] Other factors that can contribute to kidney injury are direct kidney damage mediated by local and systemic inflammation, increase in circulating bile acids (causing bile cast nephropathy) and tense ascites, causing compartment syndrome. The occurrence of AKI is associated with a fourfold increase in mortality rate.

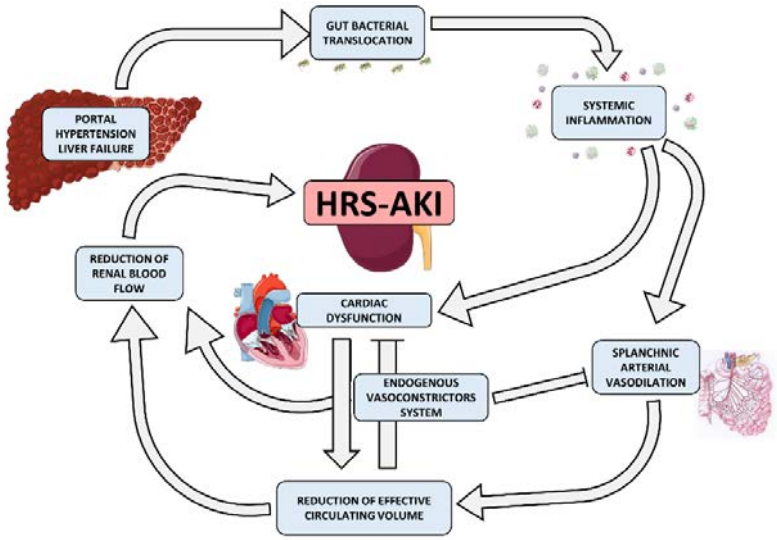

Fig. 1. Pathophysiology of hepatorenal syndrome–acute kidney injury (HRS–AKI).

Definition of AKI and HRS–AKI

AKI is characterised by a sudden decline in renal function, which can be measured by an increase in serum creatinine (sCr) levels and/or reduced urinary output (UO). AKI is defined by (Table 1) an increase in sCr by ≥0.3 mg/dl (≥26.5 µmol/L) within 48 h, or an increase to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days and/or a UO <0.5 ml/kg/h for 6 h.[2]

Baseline SCr should be the closest, stable value of SCr. Ideally, baseline SCr should be available within the previous 3 months,[1] but a time range of 12 months can be used for those without a value in the previous 3 months. In patients without a baseline SCr value within 12 months, the International Club of Ascites (ICA) and Acute Disease Quality Initiative (ADQI) suggested to use the lowest value between SCr at admission and a SCr value back calculated from an estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73 m^2.[2]

UO criteria can be very useful in critically ill patients, but in patients admitted in regular ward the measurement of UO is frequently inaccurate. Moreover, UO should be interpreted with caution in patients with refractory ascites which may be oliguric as a result of severe sodium and water retention.

According to the percentage increase in serum creatinine, three stages of AKI can be identified: stage 1, sCr increase less than twofold of baseline value; stage 2, sCr increase to more than twofold to threefold of baseline value; stage 3, sCr increase to more than threefold of baseline value or SCr increase to ≥4.0 mg/dl (≥353.6 µmol/L) or need for renal replacement therapy.

At least four studies including >5,000 patients with AKI, suggested that patients with AKI stage 1 can be subclassified in two groups according to the value of sCr: stage 1A, AKI and serum creatinine <1.5 mg/dl; stage 1B, AKI and serum creatinine >1.5 mg/dl.[3]

These two groups have different phenotypes of AKI (predominantly hypovolemic in AKI 1A, higher rate of HRS–AKI in AKI 1B), different probability of resolution of AKI (lower for stage 1B) and different risk of mortality (lower for stage 1A). AKI staging is useful for the initial management of AKI.

AKI has different clinical phenotypes that have a distinct prognosis and treatment. About 40–60% have a hypovolemic AKI, which is often precipitated by diuretic overdose, gastrointestinal bleeding, diarrhoea or infections, and improves with diuretic withdrawal and fluid administration.

About 15–25% of patients with cirrhosis and AKI develop hepatorenal syndrome–acute kidney injury (HRS–AKI), a predominantly functional type of AKI (*i.e.* there is a lack of or minimal tubular and glomerular injury), characterised by a severe reduction of effective circulating volume, maximal activation of endogenous vasoconstrictors systems, intrarenal vasoconstriction, reduced renal perfusion, and lack of improvement after plasma volume expansion.About 15–30% of AKI episodes are attributable to acute tubular necrosis, whereas <10% are a result of other causes (*e.g.* glomerulonephritis, IgA nephropathy, obstructive nephropathy).

The ICA defined HRS–AKI according to the following criteria (Table 1)[1]:

- Cirrhosis with ascites.
- AKI.
- No sustained improvement of sCr after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg body weight).
- Absence of shock.
- No current or recent use of nephrotoxic drugs (*e.g.* NSAIDs, aminoglycosides, iodinated contrast media).
- No macroscopic signs of structural kidney injury defined by absence of proteinuria (>500 mg/day), absence of microhaematuria (>50 red blood cells per high-power field) and normal findings on renal ultrasonography.

Table 1. Diagnostic criteria and staging of AKI and HRS–AKI.

*No specific type/dose of fluids established. †Strong evidence for an alternative explanation includes: septic shock, acute glomerular injury, obstruction and nephrotoxin-induced AKI. †No threshold for urinary sediment and damage markers of acute glomerular and/or tubular damage was determined. ADQI, Acute Disease Quality Initiative; AKI, acute kidney injury; HRS, hepatorenal syndrome; ICA, International Club of Ascites; RBCs, red blood cells; sCr, serum creatinine.

Diagnostic criteria of AKI	
Increase in sCr by ≥0.3 mg/dl (26.5 µmol/L) within 8 h; or Increase in sCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; and/or Urinary output <0.5 L/kg/h for 6 h.	
Staging of AKI	
Stage 1	sCr increase 1.5- to 1.9-fold of baseline; or Cr increase ≥0.3 mg/dl (26.5 µmol/L); or urinary output <0.5 ml/kg/h for 6–12 h.
Stage 2	sCr increase 2.0- to 2.9-fold of baseline; or urinary output <0.5 ml/kg/h for ≥12 h
Stage 3	sCr increase >3.0-fold baseline; or sCr increase to ≥4.0 mg/dl (353.6 µmol/L); or initiation of renal replacement therapy; or urinary output <0.3 ml/kg/h for ≥24 h; or anuria for ≥12 h.

Diagnostic criteria of HRS–AKI
ICA criteria (2015)
Cirrhosis with ascites.
AKI.
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight)
Absence of shock.
No current or recent use of nephrotoxic drugs (*e.g.* NSAIDs, aminoglycosides, iodinated contrast media, etc.)
No macroscopic signs of structural kidney injury defined as: absence of proteinuria (>500 mg/day), absence of microhaematuria (>50 RBCs per high-power field) and normal findings on renal ultrasonography.
ICA–ADQI criteria (2024)
Cirrhosis with ascites.
AKI.
Absence of improvement in sCr and/or UO within 24 h following adequate volume resuscitation.*
Absence of strong evidence for an alternative explanation as the primary cause of AKI.†

However, these criteria have potential limitations. Firstly, the need of 2 days of plasma volume expansion could cause a delay in the administration of vasoconstrictors and albumin, the treatment of choice for HRS–AKI. Moreover, in the current epidemiological scenario of cirrhosis, with a raise of cirrhosis caused by metabolic-associated steatotic liver disease (MASLD), there is high burden of comorbidities, including diabetes and chronic kidney disease (CKD). Patients with CKD have frequently a mild proteinuria and/or an abnormal urine sediment. Therefore, although HRS–AKI can occur in patients with cirrhosis and CKD, the current criteria do not allow a proper diagnosis in these patients.

To overcome these limitations, the ICA and ADQI recently suggested that the diagnosis of HRS–AKI can be secured earlier, in patients showing a lack of improvement in sCr after diuretic withdrawal and adequate volume resuscitation within 24 h.[2] The implications and impact of this approach is yet to be determined.

In addition, ICA and ADQI downgraded the role of proteinuria, stating that the diagnosis of HRS–AKI can be done in patients that have no strong evidence of an alternative cause of AKI (no septic shock, no urinary tract obstruction, no nephrotoxin-induced AKI). However, the role of urinary sediment and urinary biomarkers was not clearly established.

Initial management of AKI in cirrhosis

The first step in the management of patients with cirrhosis and AKI is to identify and treat potential triggers of AKI (workup and treatment for infections, restore volume if dehydration/bleeding, tapering/discontinuation of diuretics, discontinuation of nephrotoxic medications)[1,5] (Fig. 2). These measures are effective in treating AKI in >80% of patients with AKI stage 1A. For patients with AKI stage 1B, 2, and 3, the European Association for the Study of the Liver (EASL) guidelines and ICA recommend withdrawal of diuretics and plasma volume expansion with albumin 1 g/kg of body weight to rule out

hypovolemia.[1,5] For those not responding to plasma volume expansion, the differential diagnosis is frequently between HRS–AKI and acute tubular necrosis (ATN)–AKI. Although the treatment of these two entities is extremely different, the differential diagnosis is not easy. Moreover, a long-lasting HRS–AKI could evolve into ischemic ATN–AKI. Clinical scenarios and medical history can help in discriminating between the two entities (*e.g.* shock and recent use of nephrotoxic drugs are suggestive of ATN–AKI) as well as urinary sediment (epithelial tubular cells and casts are suggestive of ATN–AKI), fractional excretion of sodium (usually <1% in HRS–AKI and >2% in ATN–AKI) or fractional excretion urea.[4]

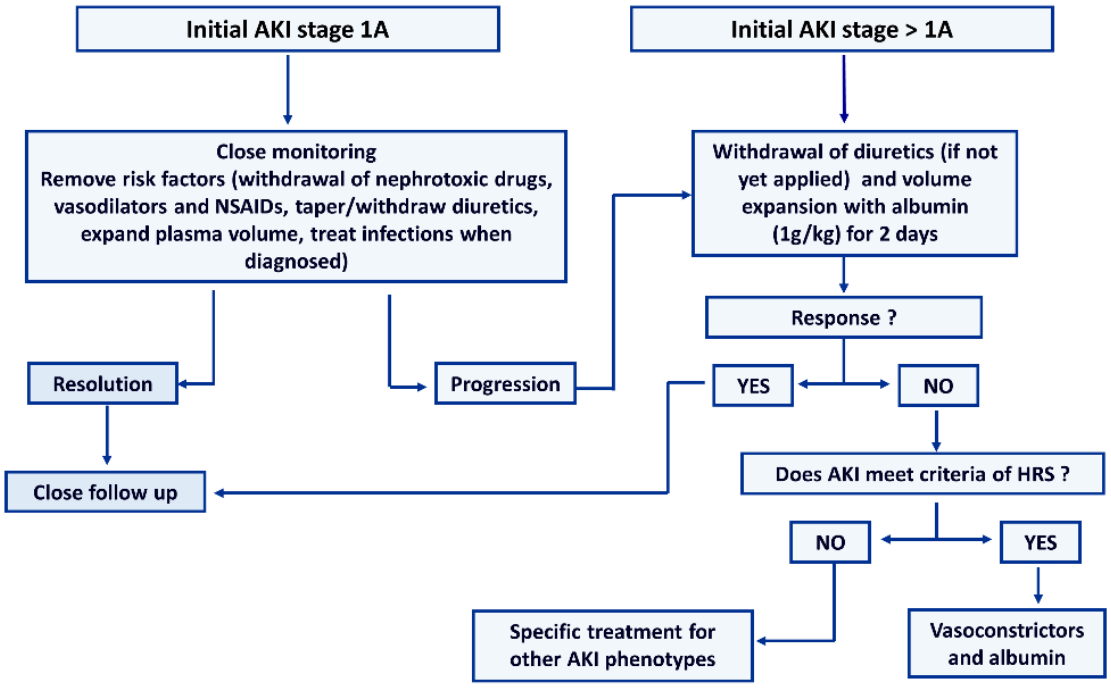

Fig. 2. EASL guidelines algorithm for the management of acute kidney injury in patients with cirrhosis (modified from Angeli et al.[5]).

Novel urinary biomarkers of tubular damage may improve the differential diagnosis of AKI. Indeed, urinary neutrophil gelatinase-associated lipocalin (NGAL) has been found to be increased in patients with cirrhosis and ATN compared with patients with HRS, with an area under the curve >0.85.[6,7] The best urinary NGAL thresholds to discriminate between ATN–AKI and other types of AKI is 220–300 µg/g creatinine or 220–300 ng/ml.[6,7] Interestingly, patients achieving a reversal of HRS–AKI after treatment with vasoconstrictors and albumin had significantly lower values of urinary NGAL than those who did not.[7] These findings suggested that: (i) some patients with HRS–AKI have subclinical tubular damage that cannot be improved with vasoconstrictors and albumin; (ii) urinary NGAL can be useful in predicting response to treatment. Future studies should confirm these findings and identify optimal NGAL thresholds to be used in clinical practice.

Other urinary biomarkers, such as liver fatty acid binding protein, kidney injury molecule-1, and interleukin-18, were also found to be increased in patients with ATN–AKI; however, their discrimination ability is lower than that of NGAL. In the future these biomarkers may be used in the differential diagnosis of AKI.

Treatment of HRS–AKI

Vasoconstrictors and albumin

The pharmacological treatment of HRS–AKI includes the combination of vasoconstrictors plus albumin.[4] Vasoconstrictors counteract the splanchnic arterial vasodilation and increase mean arterial pressure, whereas albumin counteracts the reduction of effective circulating volume, and increases cardiac contractility and stroke volume. Albumin is poorly effective alone, but it seems to enhance the efficacy of vasoconstrictors.

Among vasoconstrictors, terlipressin has the most solid evidence in the treatment of HRS–AKI. Four randomised controlled trials (RCTs) comparing terlipressin (1 mg every 4–6 h) plus albumin (20–40 g/day) *vs.* albumin alone, demonstrated that resolution of HRS–AKI is more common in patients treated with terlipressin.[4] The dose of terlipressin is increased every 48–72 h in case of no significant reduction of sCr (<25–30% decrease) up to a maximum of 12 mg/day. Terlipressin and albumin is effective in reversing HRS–AKI in 30–50% of patients and the efficacy is higher in patients with lower baseline serum creatinine, lower bilirubin, lower acute-on-chronic liver failure (ACLF) grade a and higher increase in mean arterial pressure.[8] The treatment should be continued up to reversal of HRS–AKI (return of sCr within 0.3 mg of the baseline value or <1.5 mg/dl for patients without baseline value), occurrence of severe adverse events or lack of response after 14 days of treatment. HRS–AKI can recur in ~20% of cases after withdrawal of terlipressin and retreatment is often effective. The combination of terlipressin and albumin is associated with adverse events such as diarrhoea, abdominal pain, peripheral ischemia, arrhythmias, myocardial infarction, and circulatory overload. The CONFIRM trial found a higher rate of respiratory failure in patients with HRS–AKI receiving terlipressin plus albumin, therefore, peripheral oxygen saturation should be monitored frequently in these patients.[9] Risk factors for respiratory failure were ACLF grade 3 and low baseline oxygen saturation. As the terlipressin half-life of elimination is 50–70 min, continuous intravenous infusion has been explored as an alternative to intravenous boluses in a RCT. Continuous infusion has similar efficacy to intravenous boluses, but the rate of adverse events was significantly lower in patients treated with continuous infusion.[10] These findings led the European Medicine Agency and Food and Drug Administration to suggest caution about treatment with terlipressin in patients with ACLF grade 3 and to recommend continuous infusion as the preferred administration route. Suggestions about the use of terlipressin and albumin in HRS–AKI are reported in Table 2.

Table 2. Practical tips about the use of terlipressin and albumin in patients with HRS–AKI. ACLF, acute on chronic liver failure; HRS–AKI, hepatorenal syndrome–acute kidney injury; POCUS, point of care ultrasound; sCr, serum creatinine.

Topic	Suggestion
Avoid use of terlipressin if clear contraindications	Avoid use of terlipressin in patients with: history of ischemic heart disease, peripheral artery disease (without revascularisation) peripheral oxygen saturation <90%
Optimise the treatment response	Do not delay the administration of terlipressin and albumin as soon as the diagnosis of HRS–AKI has been secured
Administration route of terlipressin	Prefer continuous intravenous infusion

Titration of treatment with terlipressin	Starting dose (2 mg/24 h as continuous intravenous infusion or 1 mg every 6 h); increase the dose every 48 h if no reduction of sCr of at least 25% of baseline value
Monitoring	Check mean arterial pressure, urinary output, oxygen saturation, direct/indirect signs of circulatory overload (central venous pressure, POCUS of inferior vena cava, pulmonary crackles/radiological signs of pulmonary oedema) and peripheral ischemia (check extremities)
Minimise the risk of side effects	Do not use terlipressin in patients with peripheral oxygen saturation <90%
Minimise the risk of circulatory overload	Use albumin at the dose of 20 grams per day Discontinue albumin infusion if signs of circulatory overload
Conditions that requires special caution	Patients with ACLF grade 3 have poor response and high risk of respiratory failure Patients with sCr > 5 mg/dl have poor response and high mortality

Among other vasoconstrictors, norepinephrine (0.5–3 mg/h) plus albumin was found to have a similar efficacy of terlipressin in three RCTs and a lower efficacy in a recent RCT enrolling patients with HRS–AKI and ACLF (APASL criteria). Norepinephrine should be administered using a central venous line and under continuous monitoring, but it can be considered a valid alternative to terlipressin.

The combination of midodrine (administered orally 7.5–12.5 mg tid) and octreotide (administered subcutaneously 100–200 µg bid) plus albumin showed promising results in a pilot studies and prospective cohorts. However in an RCT the rate of reversal of HRS–AKI was significantly lower in midodrine and octreotide group *vs.* terlipressin group (5% *vs.* 56%).[11] Therefore, midodrine and octreotide is considered a third choice, to be used only in patients with contraindications to terlipressin/norepinephrine.

During treatment with vasoconstrictors patients may develop signs of circulatory overload (increase in central venous pressure [CVP], initial signs of pulmonary oedema). For patients without a central venous catheter, point of care ultrasound of inferior vena cava (IVC) can be helpful to identify patients with increased central venous pressure. Indeed, 95% of patients with a combination of IVC diameter >2.1 cm and IVC collapsibility index ($\frac{IVCmax-IVCmin}{IVCmax}$) <50% have a CVP >10 mmHg. In these patients, albumin administration should be discontinued and a small dose of loop diuretics can be considered.

Liver transplantation

Reversal of HRS–AKI is associated with a significant reduction in mortality, however, the probability of survival in patients achieving reversal of HRS–AKI is still very low (50–60% at 90 days) and liver transplantation (LT) remains the best treatment of HRS–AKI (>85% survival a 12 months).[12] Patients achieving resolution of HRS–AKI before LT have a lower incidence of CKD 12 months after LT. Importantly, after LT the renal function recovers in most of patients with HRS–AKI, even non-responders to vasoconstrictors and albumin. A longer duration of renal replacement therapy (RRT) before LT is the strongest predictor of lack of renal function recovery. Indeed, simultaneous liver and kidney transplantation is indicated in patients with sustained AKI (*e.g.* in those on RRT and/or with an eGFR <25 ml/min/m^2 for >6 weeks).

The introduction of MELD and MELD-Na score has increased the prioritisation of patients with HRS–AKI on the LT waiting list and reduced their mortality in the U.S. Pharmacological treatment with vasoconstrictors and albumin frequently precedes the LT, and LT waiting list prioritisation may be affected in patients achieving a reversal of HRS–AKI, in whom MELD/MELD-Na reduces because of a reduction of sCr. These patients have a higher mortality than other patients on the LT waiting list for any given MELD score. Some European countries, such as Italy and Spain have overcome this issue computing the MELD-Na score using the sCr before treatment of HRS–AKI. However, the impact of this policy is still to be determined.

Renal replacement therapy

RRT should be considered in patients with HRS–AKI not responding to treatment with vasoconstrictors and albumin and in those developing severe complications of AKI (*e.g.* severe metabolic acidosis, severe hyperkalaemia, pulmonary oedema, uremic complications). Patients with HRS–AKI are frequently hypotensive and do not tolerate intermittent RRT, therefore continuous RRT is usually the preferred strategy. RRT should be considered as a bridge to LT, because the outcomes of patients with HRS–AKI undergoing RRT is very poor if they are not suitable for LT (>80% mortality at 90 days). In patients not suitable for LT, RRT should be considered case-by-case, to avoid futility.

Other treatments

Extracorporeal liver support systems have been investigated for the treatment of HRS–AKI without showing a clear benefit and nowadays have no indications for the treatment of HRS–AKI. The placement of a transjugular intrahepatic portosystemic shunt (TIPS) may be a good strategy for treating HRS–AKI, because the reduction of portal pressure can interrupt the chain of events leading to HRS–AKI (splanchnic vasodilation, hyperactivation of endogenous vasoconstrictors systems). In a pilot, uncontrolled study, TIPS placement was associated with a reduction of portal pressure, plasma renin activity and increase in renal plasma flow and glomerular filtration rate. An RCT comparing TIPS *vs.* vasoconstrictors and albumin currently ongoing in patients with HRS–AKI (NCT05346393) and results are expected in 2026.

Conclusions

HRS–AKI is a life-threatening complication of decompensated cirrhosis. HRS–AKI occurs in the context of severe splanchnic vasodilation, systemic inflammation, maximal activation of endogenous vasoconstrictors systems, and kidney hypoperfusion. In the current epidemiological scenario, the differential diagnosis between HRS–AKI and ATN–AKI is tricky and the implementation of urinary biomarkers to be used in clinical practice is warranted.

The combination of vasoconstrictors and albumin represents the first line treatment of HRS–AKI, but it should be handled with caution because of risk of adverse events. LT remains the best treatment of HRS–AKI. New strategies of treatment of HRS-AKI should be explored.

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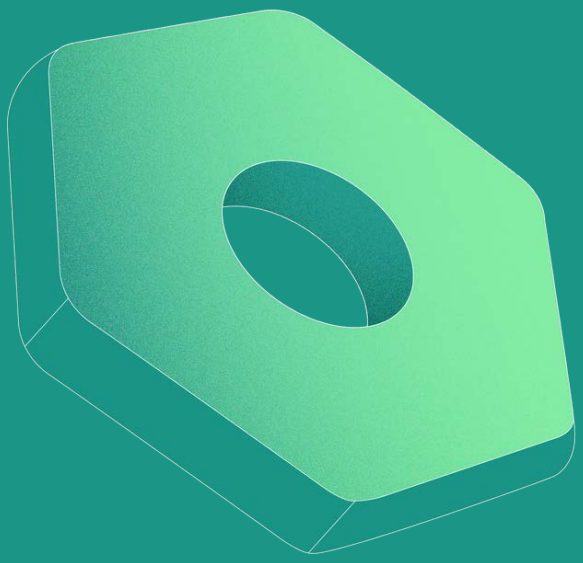

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