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MINIREVIEWS

Advances in the diagnosis and management of clinically significant portal hypertension in cirrhosis: A narrative review

Xiao-Yu Xie, Amine Benmassaoud

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Abstract

Clinically significant Portal hypertension (PH), defined by a hepatic venous pressure gradient (HVPG) greater than 10 mmHg, is a key predictor of decompensation events in cirrhosis, leading to variceal hemorrhage, ascites, and hepatic encephalopathy. This narrative review explores the pathophysiology of PH in cirrhosis, evaluates diagnostic methods for identifying clinically significant PH (CSPH), and discusses guideline-driven strategies to prevent initial and further decompensation. While HVPG remains the gold standard for diagnosing CSPH, non-invasive tools such as liver stiffness measurement and spleen stiffness measurement are increasingly used for initial risk stratification. The combined use of these tools reduces the proportion of patients in the diagnostic "grey zone". Endoscopic ultrasound-guided portal pressure gradient is an emerging diagnostic tool that requires further validation. Non-selective beta-blockers are the cornerstone of primary prophylaxis for decompensation, and their combination with endoscopic variceal ligation is the first-line therapy for secondary prophylaxis of recurrent esophageal variceal bleeding. Statins show promise in reducing PH and preventing decompensation while further studies are still needed. This review also discusses the indications for preemptive transjugular intrahepatic portosystemic shunt and its role in managing refractory ascites and variceal bleeding.

Key Words: Portal hypertension; Cirrhosis; Elastography; Spleen stiffness; Liver stiffness; Endoscopic ultrasound; Portal pressure gradient; Hepatic venous pressure gradient; Decompensation

Core Tip: Portal hypertension (PH) is the main driver of morbidity and mortality in patients with cirrhosis. Over the last decade, there have been many critical developments in the diagnosis and management of this condition. The following review will provide the reader with a state-of-the-art appreciation of the most recent updates in the non-invasive and invasive diagnostic approaches, including the use of liver stiffness, spleen stiffness, and endoscopic ultrasound. A diagnostic algorithm is proposed to guide clinicians. We also discuss the role of pharmacological, endoscopic, and interventional therapeutic options to prevent and manage manifestations of PH.

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INTRODUCTION

Portal hypertension (PH) is characterized by an increased pressure in the portal venous system, primarily due to elevated intrahepatic vascular resistance and increased portal venous flow, most commonly observed in patients with cirrhosis[1]. Clinically significant PH (CSPH), defined by a hepatic venous pressure gradient (HVPG) greater than 10 mmHg, is the main predictor of decompensation events such as variceal bleeding, ascites formation, and hepatic encephalopathy (HE). Early detection and management of CSPH are essential to prevent these life-threatening complications and improve patient outcomes. This narrative review focuses on the pathophysiology, diagnostic approaches, and management of PH in the context of cirrhosis.

CLASSIFICATION OF PH

PH can be classified into prehepatic[2], intrahepatic[3,4] or posthepatic etiologies[5]. The causes of PH are presented in greater detail in Table 1.

PATHOPHYSIOLOGY

In cirrhosis, architectural modifications through collagen deposition and nodule formation alter sinusoidal blood flow, leading to increased fixed vascular resistance. Injured hepatocytes release cytokines which stimulate contraction of myofibroblasts leading to an increased vascular tone. This dynamic component of hepatic resistance is modulated by an excess production of vasoconstrictors and exacerbated by a locally reduced hepatic nitric oxide (NO) bioavailability. Elevated pressure in the portal system causes shear stress on the splanchnic vessels and leads to excessive production of systemic NO and other vasodilators[3]. Systemic vasodilation leads to a reduced effective arterial volume activating the renin-angiotensin-aldosterone system and the antidiuretic hormone. This leads to a hyperdynamic state where salt and water retention contribute to ascites formation. Increased portal pressure and vascular endothelial growth factor-driven angiogenesis result in the creation of portosystemic collaterals, manifesting as varices[6]. HE results from a complex mechanism of accumulation of toxins and ammonia in the systemic circulation *via* portosystemic shunting, impaired liver function, bacterial translocation, and sarcopenia (Figure 1)[5].

DIAGNOSIS OF PH

HVPG

Due to the previous difficulties and complications related to direct measurements of the portal venous pressure, the gold standard to diagnose PH in patients with cirrhosis relies on indirect estimation of portal venous pressure, namely the HVPG[7]. HVPG is calculated from the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). Catheterization of the hepatic vein is performed under local anesthesia usually with a transjugular venous approach. After the installation of a venous introducer, a balloon-tipped catheter is inserted under fluoroscopy guidance in the inferior vena cava and advanced into the hepatic vein[8]. When we measure the WHVP by inflating the balloon and occluding a branch of the hepatic vein, the static column of blood equalizes in pressure with the preceding vessels, which are the hepatic sinusoids (Figure 2)[8]. Due to the obstruction of sinusoidal flow by altered architecture in cirrhosis and the lack of pressure equilibration through inter-sinusoidal communications, the pressure within the sinusoids equilibrates with the portal perfusion pressure. Therefore, WHVP provides an indirect estimate of portal pressure in patients with cirrhosis[8]. FHVP is the measure of the non-occluded hepatic vein allowing the measurement of a pressure gradient across the liver. In cirrhosis, an HVPG above 5 mmHg is diagnostic of sinusoidal PH.

Table 1 Classification of portal hypertension

Classification	Etiologies
Prehepatic	Portal vein thrombosis
	Splenic vein thrombosis
	Congenital venous abnormalities
Intrahepatic	Presinusoidal: Hepatoportal sclerosis; schistosomiasis; myeloproliferative diseases; sarcoidosis; early stage of primary biliary cholangitis; primary sclerosing cholangitis; congenital hepatic fibrosis; arsenic toxicity
	Sinusoidal: Cirrhosis; alcohol-associated hepatitis; nodular regenerative hyperplasia
	Postsinusoidal: Veno-occlusive disease
Posthepatic	Budd-Chiari
	Heart failure
	Pulmonary hypertension
	Constrictive pericarditis

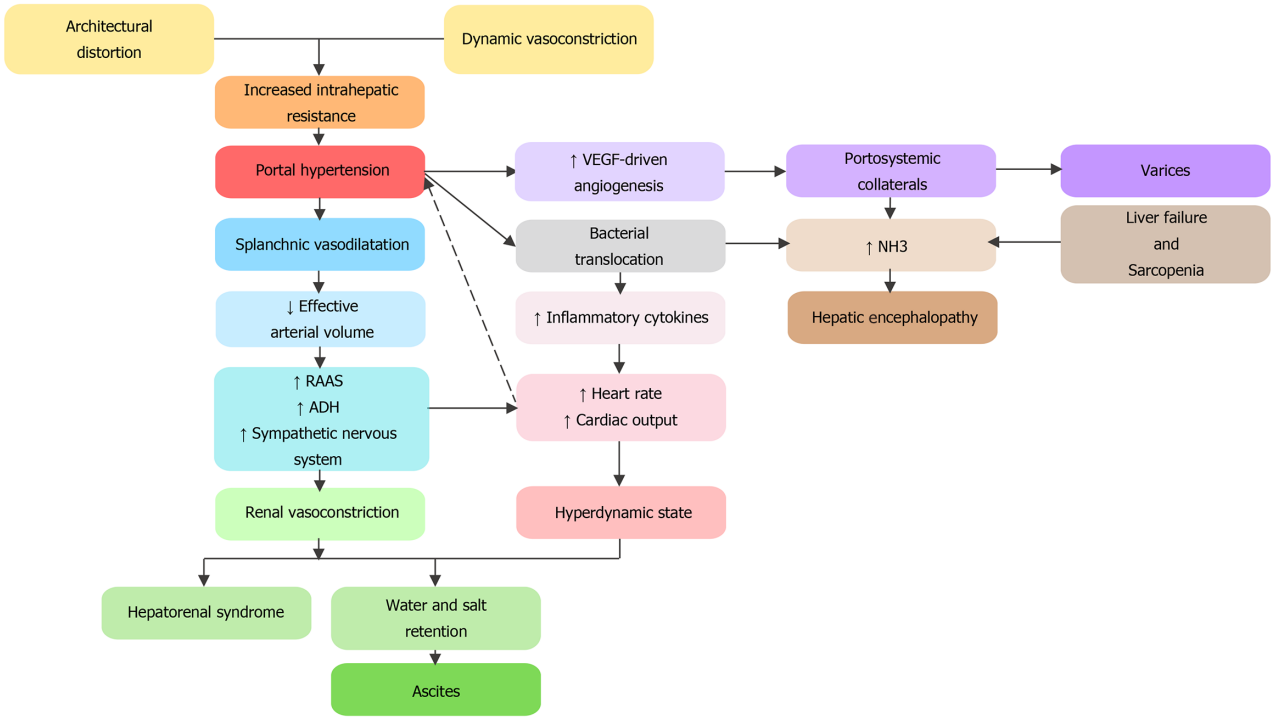

Figure 1 Pathophysiology of cirrhosis. ADH: Antidiuretic hormone; NH3: Ammonia; RAAS: Renin-angiotensin-aldosterone system; VEGF: Vascular endothelial growth factor.

HVPG above 10 mmHg is diagnostic of CSPH and predicts hepatic decompensation[5]. A HVPG above 12 mmHg is associated with variceal hemorrhage and a HVPG above 20 mmHg is associated with a high risk of mortality in variceal hemorrhage[5]. While highly relevant for the risk stratification of patients, the use of HVPG is limited due to a lack of accessibility outside of highly specialized centers. Furthermore, while HVPG remains the gold standard for diagnosis of PH in viral-related and alcohol-related cirrhosis[5], it has limitations in noncirrhotic PH, where WHVP could be normal or slightly elevated, leading to underestimation of portal pressure[9]. This is particularly relevant in conditions like primary biliary cholangitis and metabolic dysfunction-associated steatotic liver disease (MASLD)[5,10]. PH can develop early in the highly variable natural course of MASLD in pre-cirrhotic patients and HVPG can underestimate portal pressure[11]. Data from the large simtuzumab trial reveal that approximately 1 in 7 patients with MASLD who have developed a liver decompensation event had an HVPG < 10 mmHg[12]. In a European multicenter observational cross-sectional study, patients with MASLD and advanced chronic liver disease (ACLD) present with a higher prevalence of liver decompensation at any HVPG value (< 10 mmHg, 10-12 mmHg or > 12 mmHg) than patients with hepatitis C virus (HCV)-ACLD. None of the patients with HVPG < 10 mmHg in the viral group developed a decompensation event, whereas 9% in the MALSD group developed a decompensation event[13]. These findings suggest the need for an adapted risk stratification in MASLD patients with ACLD.

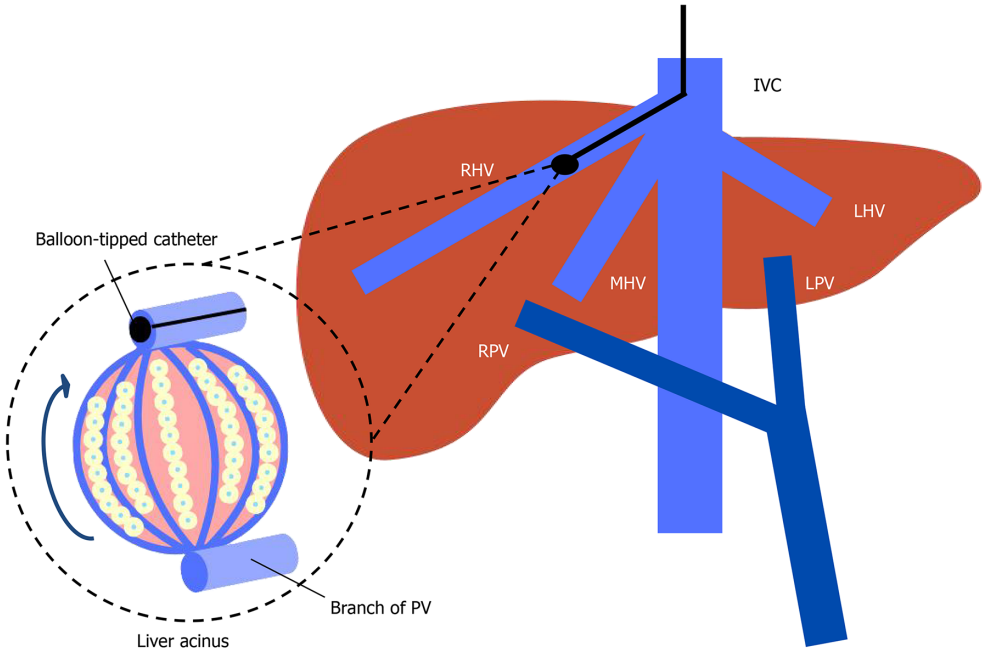

Figure 2 Hepatic vein pressure gradient measurement. IVC: Inferior vena cava; LHV: Left hepatic vein; LPV: Left portal vein; MHV: Middle hepatic vein; PV: Portal vein; RHV: Right hepatic vein; RPV: Right portal vein.

Liver stiffness measurement

Liver stiffness measurement (LSM) using transient elastography (TE) with the combination of platelet count has been validated as a noninvasive tool for ACLD staging and decompensation risk stratification[7,14]. The rule of five using LSM by TE (5-10-15-20-25 kPa) alone or with platelet count is recommended by the BAVENO VII consensus to rule in or rule out compensated ACLD (cACLD) and CSPH (Figure 3)[7]. LSM above 15 kPa rules in cACLD, and below 10 kPa rules out cACLD. Based on the ANTICIPATE study, LSM above 25 kPa presents a positive predictive value of > 90% for CSPH in patients with chronic viral-related or alcohol-related liver disease or MASLD with a body mass index (BMI) below 30 kg/m^2[14]. In patients with MASLD and a BMI above 30 kg/m^2, the positive predictive value decreases to 63%[5], highlighting the need for alternative diagnostic approaches in this population. The ANTICIPATE metabolic dysfunction-associated steatohepatitis model which incorporates LSM, platelet count, and BMI, shows promise but requires further validation[15,16]. LSM below 15 kPa and platelet count above 150 × 10^9/L rule out CSPH. Up to 40%-60% of patients fall into two grey zones associated with indeterminate results[17]: (1) LSM between 20-25 kPa and a platelet count below 150 × 10^9/L; and (2) An LSM between 15-20 kPa and platelet count below 110 × 10^9/L, both correlating with probable CSPH. A validation retrospective multicentric cohort study by Wong *et al*[18] has shown that among the grey zones, viral-related cACLD are associated with a negligible decompensation risk, whereas non-viral cACLD are associated with a higher decompensation risk. However, his study presents a selection bias where 75% of the patients are viral cACLD who have been treated, which questions the applicability of these criteria to other etiologies of cACLD.

Spleen stiffness measurement

Multiple studies have shown that spleen stiffness measurement (SSM) is a promising tool for predicting CSPH and decompensation[19-23]. In the BAVENO VII consensus, SSM by TE may be used in addition to the rule of five in viral-related cACLD [untreated HCV, untreated and treated hepatitis B virus (HBV)] in a dual cutoff model to rule out CSPH in SSM < 21 kPa or rule in CSPH in SSM > 50 kPa[7]. A retrospective validation cohort study by Dajti *et al*[17] has shown that the combination of BAVENO VII criteria using LSM with SSM reduces the grey zone from 48% to 32% using a dual cutoff model (SSM < 21 kPa or SSM > 50 kPa) and to 9% using a single cutoff SSM of 40 kPa while maintaining a predictive positive value above 90%. While the 40 kPa cutoff has shown to be suboptimal for ruling out CSPH in non-viral etiologies (negative predictive value < 90%), it has the most efficient performance at ruling in patients with CSPH [17]. This dual approach of combining LSM with SSM is therefore particularly useful in viral-related cACLD. In a recent posthoc analysis of the PREDESCI trial, Dajti *et al*[24] demonstrated that endoscopic evaluation in patients with inconclusive results after initial CSPH screening by BAVENO VII and American Association for the Study of Liver Diseases (AASLD) criteria (rule in CSPH in LSM ≥ 25 kPa or LSM ≥ 20 kPa + PLT < 150 × 10^9/L and rule out CSPH in LSM ≤ 15 kPa + PLT ≥ 150 × 10^9/L) allows to reduce the grey zone to 22%. The non-invasive BAVENO VII with SSM model was comparable to the BAVENO VII/AASLD criteria with endoscopy and correctly predicted decompensation risk at 3 years. See Figure 4 for the proposed algorithm[24]. This remains a proposed framework, without no definite algorithm established. In patients with CSPH and contraindications or intolerance to non-selective beta-blockers (NSBB) as prophylaxis for decompensation, the BAVENO VII consensus recommends avoiding unnecessary endoscopy in patients with an SSM below 40 kPa and who meet the BAVENO VI criteria for endoscopy (LSM ≥ 20 kPa or platelet ≤ 150 × 10^9/L)[7]. A recent prospective study by Giuffrè *et al*[25] shows that a decreased SSM has better accuracy in correlating

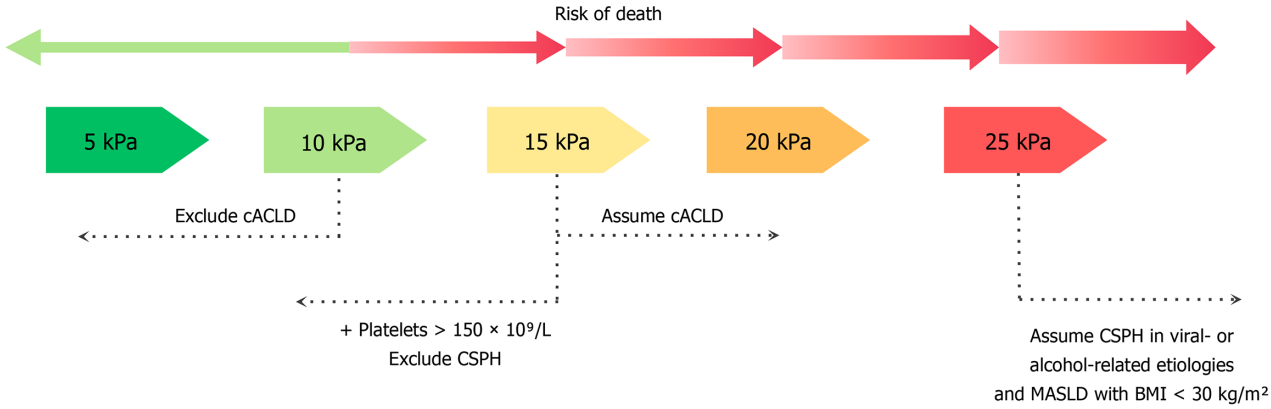

Figure 3 A schematic summary of the rule of five from the BAVENO VII consensus. BMI: Body mass index; cACLD: Compensated advanced chronic liver disease; CSPH: Clinically significant portal hypertension; MASLD: Metabolic dysfunction-associated steatotic liver disease.

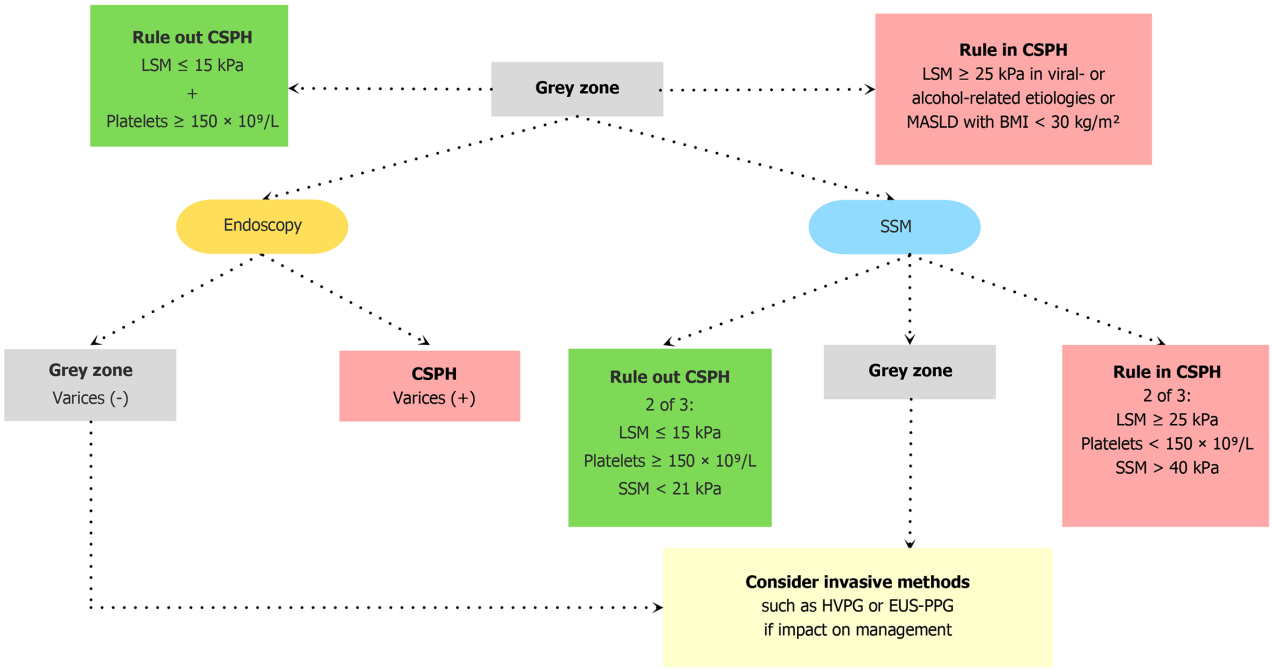

Figure 4 A proposed algorithm for clinically significant portal hypertension screening. BMI: Body mass index; CSPH: Clinically significant portal hypertension; LSM: Liver stiffness measurement; MASLD: Metabolic dysfunction-associated steatotic liver disease; SSM: Spleen measurement; HVPG: Hepatic vein pressure gradient; EUS-PPG: Endoscopic ultrasound-guided portal pressure gradient.

with clinical response to NSBB than LSM and heart rate. Clinical response to NSBB was defined by stability or downstaging of variceal grading at 12 months follow-up[13]. SSM correlates with HVPG pre-transjugular intrahepatic portosystemic shunt (TIPS) and decreases significantly post-TIPS, which suggests the potential use of this non-invasive tool for monitoring TIPS function after the procedure[26]. Technical limitations of SSM are the absence of splenomegaly, a higher BMI, and the accessibility of a dedicated SSM probe as the liver 50 Hz module measures only tissue stiffness up to 15 kPa[7]. A European multicentric prospective study demonstrates that the novel spleen-dedicated 100 Hz module has a significantly higher success rate compared to the standard 50 Hz module in detecting large esophageal varices, and better correlates with HVPG[27]. The use of SSM also needs further validation in prospective studies and non-viral etiologies of cACLD[7].

Endoscopic ultrasound-guided portal pressure gradient

In recent years, endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurements have emerged as a promising tool to assess PH (Table 2). In a recent meta-analysis by Dhindsa *et al*[28], eight cohort studies with a total of 178 patients have shown a technical success rate of 94.6%, a clinical success rate of 85.4%, and a total adverse events rate of 10.9%. The 93.7% of the adverse events are considered mild according to the American Society for Gastrointestinal Endoscopy[28]. Technical success is defined by inserting successfully the needle into the correct vessel and measuring portal and hepatic venous pressures (Figure 5). Clinical success was defined by the correlation of the portal pressure

Table 2 Comparison between hepatic vein pressure gradient and endoscopic ultrasound-guided portal pressure gradient

	HVPG	EUS-guided portal pressure gradient
Technique	Transjugular catheterization of the hepatic vein with a balloon-tipped catheter	Under EUS guidance, fine-needle puncture of the hepatic vein and the portal vein
Principle	HVPG = wedged hepatic venous pressure – free hepatic venous pressure	PPG = portal vein pressure – hepatic vein pressure
Sedation	Usually under minimal (low-dose midazolam) or no sedation	Usually under moderate to deep sedation
Advantages	Well-established as the gold standard for clinically significant portal hypertension assessment	Direct measurement of portal vein pressure. Alternative when HVPG is not accurate such as presinusoidal PH. Can be combined with endoscopic evaluation of varices
Limitations	Indirect measurement of portal vein pressure. May underestimate presinusoidal PH such as primary biliary cholangitis and metabolic dysfunction-associated steatotic liver disease. May be contraindicated in severe coagulopathy	Limited availability and expertise. Requires further validation. Moderate to deep sedation can cause hemodynamic variations and lead to inaccurate PPG measures

EUS: Endoscopic ultrasound; HVPG: Hepatic vein pressure gradient; PH: Portal hypertension; PPG: Portal pressure gradient.

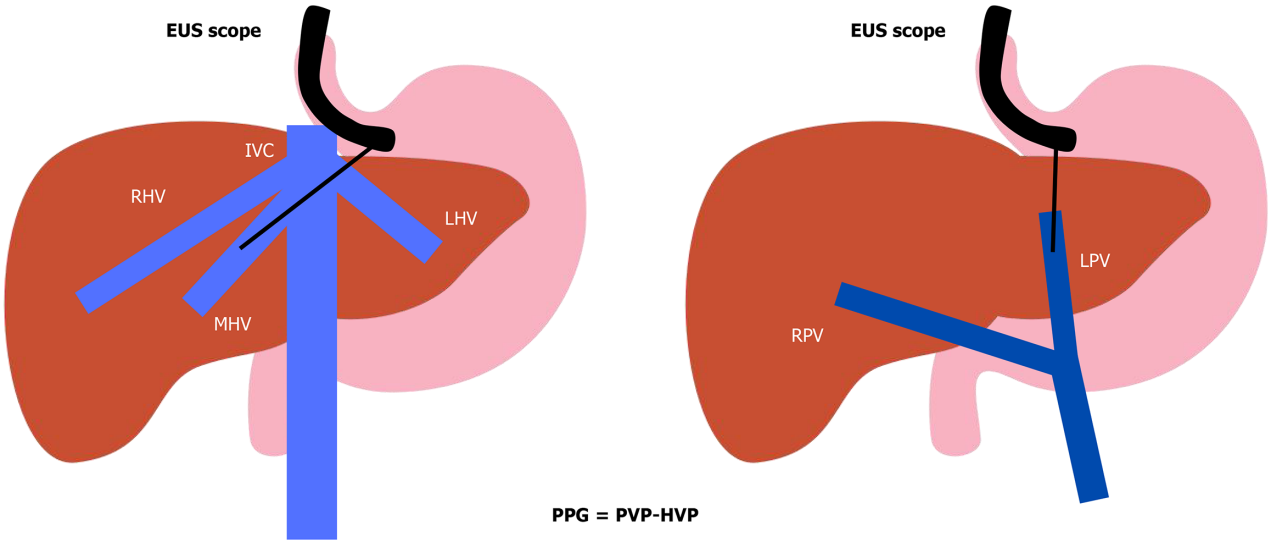

Figure 5 Endoscopic ultrasound-guided portal pressure gradient. EUS: Endoscopic ultrasound; HVP: Hepatic vein pressure; IVC: Inferior vena cava; LHV: Left hepatic vein; LPV: Left portal vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; RPV: Right portal vein; PPG: Portal pressure gradient; PVP: Portal vein pressure.

gradient (PPG) measurement with liver biopsy or HVPG. A few other small prospective studies have also shown a great correlation between EUS-PPG and HVPG[29,30]. We recently highlighted that the use of moderate to deep sedation during EUS-PPG procedures can cause variations in abdominal pressures in different phases of the respiratory cycle[31], and lead to inaccurate PPG measures. This can lead to misclassifying the severity of PH[32]. A case series by Chen *et al* [33] of 3 patients shows the feasibility of EUS-PPG under conscious sedation using ketamine and low-dose midazolam. A large multicentric retrospective study by Kolb *et al*[34] has reported better performance of EUS-PPG as a predictor of histological cirrhosis compared with fibrosis-4 (FIB-4) and aminotransferase to platelet ratio index (APRI) scores. EUS-PPG has also shown great correlation with esophageal varices, portal hypertensive gastropathy and thrombocytopenia. There is a need for large prospective studies and randomized controlled trials before standardizing the practice of EUS-PPG[25]. An ongoing randomized controlled trial will be comparing endoscopic ultrasound (EUS) and transjugular approaches for liver biopsies and PPG/HVPG measurements (NCT 05118308). We also await the results from the Encounter study (NCT 04987034) which will correlate EUS-PPG with HVPG. EUS-PPG has the potential to revolutionize the management of PH by combining hemodynamic assessment, liver biopsy, and endoscopic evaluation in a single procedure. However, large prospective studies and randomized controlled trials are needed to standardize its use and validate its accuracy.

EUS-guided shear wave elastography

Some limitations of the use of LSM and SSM include inflammation, operator-dependent issues, increased BMI, congestion, and presence of ascites. EUS-guided shear wave elastography (EUS-SWE) is an emerging technology for LSM and SSM. A prospective study compared EUS-SWE measurement of SSM in patients with and without CSPH, where CSPH was clinically diagnosed by a hepatologist[35]. In EUS, the spleen is visualized through a transgastric approach

and shear wave elastography (SWE), using an acoustic radiation force, induces shear waves in the interested area of the spleen to estimate tissue stiffness. Patients with CSPH had significantly higher SSM (37.6 kPa ± 8.5 kPa *vs* 29.1 kPa ± 9.9 kPa, P = 0.003)[35]. EUS-SWE measurement of SSM may present theoretical advantages in patients with significant central obesity. In another prospective study, EUS-SWE evaluation of LSM is compared with LSM by TE using EUS-guided liver biopsy as the gold standard. Right lobe SWE strongly correlates to fibrosis stage, and accuracy is comparable to TE[36]. However, left lobe measurements have a 3.5 times higher variance than the right lobe. In a recent multicentric pilot study, EUS-SWE was found to be superior to TE and FIB-4 in predicting advanced liver fibrosis and cirrhosis in patients with MASLD and obesity[37]. Larger prospective studies are necessary to standardize the technique and validate the benefits of this novel approach compared to other noninvasive tools[38].

MANAGEMENT OF PH

Prevention of the first decompensation

Decompensation is defined by events that include overt ascites (or pleural effusion with increased serum ascites albumin gradient > 1.1 g/dL), overt HE (West-Haven ≥ II), and variceal bleeding[7]. Precipitating factors for hepatic decompensation are infections, additional liver injuries such as acute alcoholic hepatitis, acute viral hepatitis, HBV flares, drug-induced liver injury, hepatocellular carcinoma (HCC), and major surgery[7].

Treating the underlying cause

The current BAVENO VII guidelines recommend removing etiological factors of liver disease by obtaining sustained viral response in HCV or HBV suppression in chronic viral-related ACLD, and long-term alcohol abstinence. Treating these underlying etiologies may lead to significant HVPG reduction and prevent hepatic decompensation[7]. In addition to pharmacological and procedural interventions, patient education and lifestyle modifications play a crucial role in managing PH. In the prospective sport diet study, an uncontrolled pilot study, 60 patients with a BMI ≥ 26 kg/m² and HVPG ≥ 6 mmHg underwent a 16-week lifestyle intervention with a personalized hypocaloric diet and 60 minutes of supervised physical activity per week. A total of 50 patients completed the study. Recruited participants were not restricted to those with MASLD but also included those with viral or alcohol-related liver cirrhosis. Results showed significant weight loss was associated with a significant reduction in HVPG. Greater weight loss ≥ 10% was associated with larger HVPG reductions. The intervention was safe, with no clinical decompensation, and weight loss was maintained at 6 months without worsening liver function. The study concluded that 16 weeks of diet and moderate exercise safely reduced body weight and portal pressure in this patient population[39].

NSBB

NSBB reduce cardiac output by blocking beta-1 receptors and induce splanchnic vasoconstriction by blocking beta-2 receptors, resulting in an unopposed effect of alpha-1 receptors[5]. The randomized controlled trial PREDESCI in 2019 demonstrates that long-term use of NSBB increases decompensation-free survival in cirrhosis patients with CSPH[40]. Hemodynamic response to NSBB consists of a decrease of 10%-20% in baseline HVPG or to an HVPG < 12 mmHg[41]. Carvedilol has an additional intrinsic activity of anti-alpha-1 adrenergic activity, inducing splanchnic vasodilatation, which reduces PH. Carvedilol is more effective at reducing HVPG and better tolerated than propranolol[40]. Multiple trials support the greater effectiveness of carvedilol at reducing HVPG than traditional NSBB[42-44]. A prospective study by Reiberger *et al*[45] shows that carvedilol is effective at reducing HVPG in non-responders to propranolol. According to the current guidelines from the AASLD, the use of NSBB and preferably carvedilol to an optimal dose of 12.5 mg per day [5]. A randomized controlled trial by Tripathi *et al*[46] compares carvedilol and endoscopy variceal ligation (EVL) in preventing first variceal bleed and demonstrates lower first variceal bleeding with carvedilol but no difference in mortality on intention-to-treat analysis. Patients with cACLD and CSPH who present contraindications or intolerance to NSBB should undergo endoscopic screening for varices every 2 years (if underlying liver disease etiology remains) or every 3 years (after removal of underlying cause)[5]. Patients with cACLD and low-risk varices (< 5 mm, without red signs, not Child-Pugh C) while having contraindications to NSBB, should repeat endoscopy every year to reassess varices needing treatment[5]. In patients who cannot take NSBBs, primary prophylactic EVL should be performed for high-risk varices, and ligation should be repeated every 2-4 weeks until eradication. Endoscopy should then be repeated at 6 months and every 12 months afterward to reassess varices needing treatment[5]. Patients with cACLD who are on NSBBs for the prevention of decompensation do not need to undergo endoscopic screening to detect varices as there will be no impact on management[7].

Other pharmacological therapy

There are currently no medications that are approved for reducing PH except for beta-blockers. Statins have been demonstrated in various studies to lower PH in patients with cirrhosis. A meta-analysis by Kim *et al*[47] reviewing 10 cohort studies and 3 randomized controlled trials demonstrates that statin use is associated with a 46% lower risk of hepatic decompensation, 46% lower mortality, and 27% lower risk of variceal bleeding or progression of PH. The BAVENO VII consensus encourages the use of statins in patients with cirrhosis and approved indications for statins. Statins should be prescribed at a lower dose (simvastatin at a maximum dosage of 20 mg/day) in Child-Pugh B and C cirrhosis patients and should be monitored for muscular and hepatic toxicity. The benefits of statins in Child-Pugh C have not been well-established[48] and their use should be limited[7].

Management of acute decompensation

Ascites: Ascites occurs in 50% of cirrhotic patients within 10 years[3]. Sodium restriction 2 g/day and diuretics are the first-line therapy to target a negative sodium balance and net fluid loss[49]. Fluid restriction is only recommended in moderate or severe hyponatremia. Aldosterone antagonists and loop diuretics should be tapered to the lowest dose to achieve minimal ascites to prevent adverse effects[49]. Monitoring of body weight and serum creatinine should be regularly performed. Large-volume paracentesis (LVP) combined with hyper oncotic albumin is the mainstay of therapy in grade 3 ascites[49]. A prospective study by Tan *et al*[50] suggests that LVP < 8 L per session and adequate albumin infusion are associated with better preservation of renal function and survival within 2 years. Expert opinion recommends LVP < 8 L and 6-8 g of albumin infusion per liter of removed ascites to reduce the risk of post-paracentesis circulatory dysfunction[49].

HE: HE can be classified into type A occurring in acute liver failure, type B in portosystemic shunt, and type C in cirrhosis [51]. Precipitating events include constipation, infections, gastrointestinal bleeding, dehydration, and diuretics overuse. Alternative causes should be ruled out. Ammonia should be measured in patients with potential concomitant causes of delirium, a normal value would rule out HE[51]. The Animal Naming Test is a screening tool for covert HE in cirrhotic patients without a history of overt HE that needs further validation[51]. Treatment of covert and overt HE is recommended with non-absorbable disaccharides such as lactulose. Albumin dialysis may improve the grade of HE in cirrhosis but needs further validation[52-54].

Variceal bleeding: Acute variceal hemorrhage is a potentially fatal complication of PH. Despite advances in therapeutic strategies, the mortality remains between 10%-15% at 6 weeks[5]. According to the current AASLD 2024 guidelines, the goal of hemodynamic resuscitation is to maintain organ perfusion but to avoid exacerbating PH. Blood transfusions should be given with a targeted hemoglobin at 7-8 g/dL[5]. Patients who present altered consciousness and risk of aspiration should be intubated before endoscopy and extubation is recommended as soon as possible after the procedure. Vasoactive agents (octreotide, somatostatin, or terlipressin) should be promptly started and maintained for 2-5 days[5]. Antibiotic prophylaxis with ceftriaxone 1 g/24 hours or adjusted agent depending on local resistance should be initiated at presentation and maintained until discharge or for 5 days. Although the risk of infection is low in Child-Pugh A cirrhosis, there is a lack of evidence supporting the avoidance of antimicrobial therapy in this group[5]. Considering the risk of aspiration pneumonia, pre-intubation or pre-endoscopic nasogastric tube installation should be avoided[5]. Erythromycin infusion before endoscopy contributes to a better visualization in the absence of contraindications[55,56]. Endoscopy should be performed within 12 hours of presentation. EVL is the first-line therapy for acute esophageal variceal bleeding[5]. For isolated gastric varices (IGV) and gastro-esophageal varices type 2 (GOV 2), treatment with tissue adhesives is recommended (Figure 6)[57]. For GOV 1, ligation or tissue adhesive may be used. Endoscopy treatment using argon, radiofrequency ablation, or band ligation can be used for local treatment of portal hypertensive gastropathy[5]. In refractory hemorrhage, endotracheal tube and balloon tamponade of esophageal stenting are recommended as a bridge to a definite therapy[5]. Self-expandable metal stents have shown to be more effective in bleeding control and safer than balloon tamponade, without significant difference in mortality[58,59] although they are not yet Food and Drug Administration-approved in the United States. In patients actively bleeding on endoscopy and meet specific criteria, pre-emptive TIPS should be considered (see section on TIPS). Balloon-occluded retrograde transvenous obliteration may be considered an alternative therapy in patients with GOV 2, IGV 1, or ectopic varices[5,7].

Preventing further decompensation

Further decompensation is defined by an additional decompensation event (ascites, variceal bleeding, encephalopathy) and/or jaundice, or recurrence of the same decompensation event (recurrent ascites, recurrent variceal bleeding, recurrent encephalopathy), spontaneous bacterial peritonitis, and/or hepatorenal syndrome (HRS)[7].

Preventing further decompensation in patients with ascites: Refractory ascites (RA) develops in 5%-10% of cirrhotic patients with ascites and is defined by ascites that fails to be mobilized or reoccurs after LVP despite dietary sodium restriction and diuretics[5]. A prospective study by Téllez *et al*[60] has measured lower renal perfusion pressure below the critical threshold in patients with RA who receive NSBB and suggests using NSBB with caution or avoiding them in RA. A prospective study by Sersté *et al*[61] has found an association of NSBB with lower survival rates in patients with RA. However, a large post hoc analysis of 3 randomized controlled trials supports the safe use of NSBB in RA[62]. A meta-analysis and multiple retrospective studies have also concluded no significant difference in mortality with the use of NSBB in RA[63-65]. Due to its impact on alpha-1 receptors, carvedilol should be used with caution in patients with RA who often exhibit circulatory dysfunction. Traditional NSBB might be preferable in this context[5]. The current BAVENO VII guidelines support the use of prophylaxis traditional NSBB or carvedilol in patients with ascites and low-risk varices to prevent first variceal bleeding[7]. Patients with ascites and high-risk varices should receive traditional NSBB or carvedilol rather than EVL. NSBB should be temporarily dose-reduced or suspended in patients with ascites and low blood pressure (systolic pressure < 90 mmHg or mean arterial pressure < 65 mmHg) or in the context of HRS[7].

Preventing recurrent HE: Recurrent HE if ≥ 2 episodes occur within 5 months and persistent HE if the patient does not return to his baseline[51]. After a first episode of overt HE, lactulose is recommended as secondary prophylaxis[51]. Rifaximin is recommended as an additional therapy to lactulose after 2 episodes of overt HE within 6 months[51]. Obliteration of portosystemic shunts in patients with cirrhosis and recurrent or persistent HE despite medical treatment should be considered if their model for end-stage liver disease (MELD) score < 11[51].

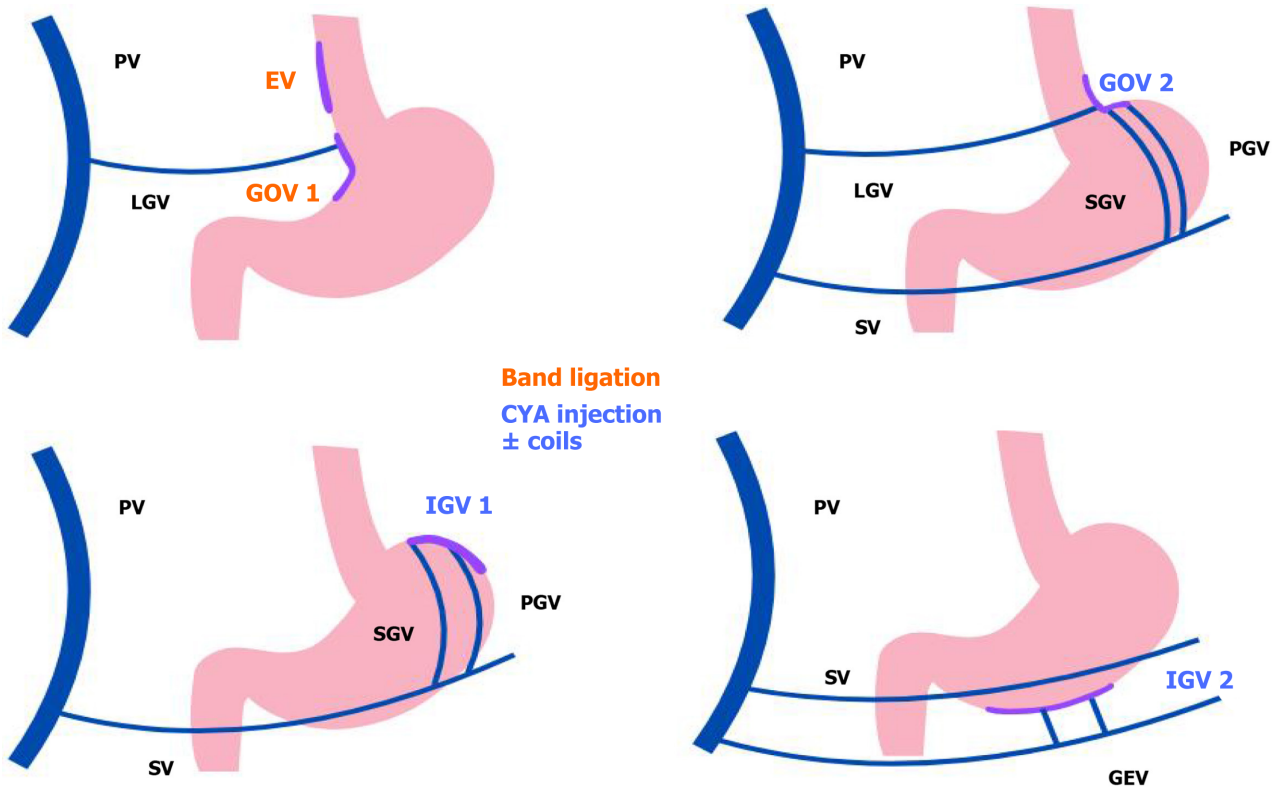

Figure 6 Sarin classification of varices adapted. CYA: Cyanoacrylate; EV: Esophageal varices; GEV: Gastric epiploic vein; GOV 1: Gastro-esophageal varices type 1; GOV 2: Gastro-esophageal varices type 2; IGV 1: Isolated gastric varices type 1; IGV 2: Isolated gastric varices type 2; LGV: Left gastric vein; PGV: Posterior gastric vein; PV: Portal vein; SGV: Short gastric vein; SV: Splenic vein.

Preventing recurrent variceal bleeding: The risk of rebleeding after an initial episode of variceal hemorrhage is up to 60% at one year without prophylaxis[5]. The first 6 weeks after the initial bleed represents a high-risk period[66] and secondary prophylaxis should be initiated as soon as the variceal bleed is controlled, within 7 days of admission[5]. Traditional NSBB or carvedilol with EVL are the first-line secondary prophylaxis to prevent recurrent variceal bleeding [7]. A meta-analysis has shown reduced rebleeding and reduced mortality with combination therapy rather than NSBB alone or EVL alone[67]. Patients who underwent preemptive TIPS do not need prophylaxis combination therapy.

EUS-guided management of varices: Endoscopic injection of cyanoacrylate (CYA) glue remains the most commonly practiced approach to achieve hemostasis in gastric varices. However, some types of gastric varices such as IGV 1 and GOV 2 are more challenging to manage due to their location and size. EUS-guided approach allows direct visualization of these varices and permits precise estimation of their size and identification of feeding vessels[68]. For primary prophylaxis of gastric varices, a randomized controlled trial by Sabry *et al*[69] demonstrates that EUS-guided CYA injection leads to a higher variceal obliteration rate during the index session (77.2% *vs* 38.1%, $P = 0.014$), smaller CYA amount needed (1 mL *vs* 2 mL, $P = 0.027$), and similar adverse events rate (4.5% *vs* 14.3%, $P = 0.345$) compared with direct endoscopic injection. For secondary prophylaxis of gastric varices, a propensity-matched, multicentric study has shown lesser sessions needed to achieve obliteration (1 *vs* 1.5, $P < 0.0001$), re-bleeding episodes (13.8% *vs* 39.1%, $P < 0.0001$) and re-intervention rates (12.1% *vs* 50.4%; $P < 0.001$) with EUS-guided therapy (coils and CYA glue) compared with conventional endoscopic CYA injection[70]. EUS-guided CYA injection for IGV has also shown lesser sessions needed, late rebleeding rates, and postinjection ulcers than conventional endoscopic CYA injection[71]. A small retrospective study has demonstrated the feasibility, safety, and 95% technical success rate for EUS-guided placement of coils in combination with thrombin[72]. A few case reports have described benefits of EUS-guided management of rectal varices[73], ectopic varices[74,75], and parastomal varices[76]. EUS-guided therapy with tissue adhesive with or without coils remains currently in the BAVENO VII consensus's research agenda[7]. The financial implications and the lack of technical expertise remain challenges of EUS-guided therapy *vs* conventional endoscopic therapy[77].

TIPS: TIPS is the creation of an endovascular portosystemic shunt to decrease PPG placed by interventional radiologists under fluoroscopic and ultrasound guidance using a transjugular venous approach under deep sedation or general anesthesia. A hepatic vein is catheterized first and from that vein, the portal vein is punctured followed by dilatation and the installation of a polytetrafluoroethylene-covered stent-graft (Figure 7)[78]. TIPS should be considered for RA regardless of the history of variceal bleeding[7]. TIPS in RA has been shown to improve survival in a meta-analysis by Bai *et al*[79] reviewing 6 randomized controlled trials. Resolution of ascites post TIPS is not immediate but will eventually be in 80% of patients with TIPS[49]. In patients actively bleeding on endoscopy and meet the criteria of Child-Pugh B > 7 points, Child-Pugh C < 14 points, or HVPG > 20 mmHg, preemptive TIPS is recommended within 72 hours and ideally

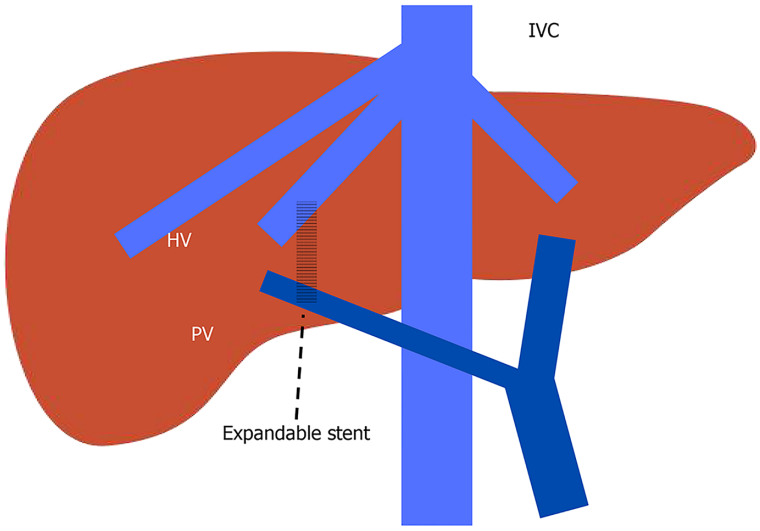

Figure 7 Transjugular intrahepatic portosystemic shunt. HV: Hepatic vein; IVC: Inferior vena cava; PV: Portal vein.

within 24 hours of presentation[7]. Multiple studies have demonstrated improved 1-year survival with preemptive TIPS [80-83]. In acute variceal hemorrhage, the goal is to reduce PPG < 12 mmHg[7]. The lack of benefits in TIPS can be discussed in patients with Child-Pugh score ≥ 14 or MELD score > 30 and lactate > 12 mmol/L, unless liver transplantation (LT) is considered in the short term. TIPS in secondary prophylaxis for variceal bleed reduces rebleeding rates but does not improve mortality compared to combination therapy of NSBB and EVL and increases the risk of HE[5]. Thus, it is recommended as first-line therapy for secondary prophylaxis only in patients with other indications of TIPS such as RA[5]. In patients who rebleed despite combination therapy of NSBB and EVL, TIPS should be considered[7]. Overt HE occurs in 30%-50% post-TIPS. The risk of HE post-TIPS is reduced with a smaller diameter covered stent (< 8 mm)[51]. A randomized controlled trial by Bureau *et al*[84] has shown that the use of rifaximin as prophylaxis (started 14 days before the procedure and maintained for 6 months after TIPS) reduces the rate of HE Post-TIPS compared to placebo and this practice should be considered according to the AASLD guidelines[78]. A MELD score above 18 is associated with higher mortality 3 months after TIPS[85]. According to the AASLD guidelines, absolute contraindications to TIPS are congestive heart failure (stage C, D or ejection fraction < 50%), severe pulmonary hypertension (mean pulmonary artery pressure > 45 mmHg), severe HE, and sepsis[78].

EUS-guided Intrahepatic Portosystemic Shunt: TIPS is generally a safe and effective procedure to alleviate PH. However, in patients at high risk of vascular complications, EUS-guided intrahepatic portosystemic shunt (EIPS) may offer theoretical benefits. EIPS does not require vascular access into the inferior vena cava or the right heart, does not use radiation, and can be concomitantly used as direct portal pressure measurement and for gastric varices management[86]. Schulman *et al*[87] has shown the high feasibility of this technique using a lumen-apposing metal stent with direct portal pressure measurement in a survival animal model. However, the procedure needs further studies in humans, particularly in patients with cirrhosis and a high risk of coagulopathy.

Management of sarcopenia and frailty

Sarcopenia is classically defined as loss of muscle mass and frailty as the loss of muscle contractile function[88]. Sarcopenia affects 40%-70% of patients with cirrhosis and frailty is present in 18%-43% of this population[89]. Computed tomography imaging is currently considered the gold standard to evaluate sarcopenia by measuring the skeletal muscle index (SMI) or the psoas muscle index[88]. Sarcopenia is correlated with poorer mortality pre-LT[90] and post-LT[91], hepatic decompensation[92], development of acute on chronic liver failure (ACLF)[93], longer hospitalization[94], increased infection[95], and reduced of quality of life[96]. According to the AASLD 2021 Practice Guidance for Malnutrition, Frailty, and Sarcopenia, all patients with cirrhosis should be annually assessed for frailty or sarcopenia using the same standardized tool as baseline. Patients with decompensated cirrhosis should be reassessed every 8 weeks to 12 weeks[88]. All patients with cirrhosis should receive nutritional counseling. A personalized prescription of intake should be given to patients who screen positive for malnutrition risk, sarcopenia, or frailty. The recommended caloric intake for patients with cirrhosis is 35 kcal/kg/day[97] and a protein intake of 1.2-1.5 g/kg/day[88]. Patients with cirrhosis and who are critically ill should receive a protein intake of 1.2-2.0 g/kg/day. Protein intake should not be reduced in HE. Early breakfast or late evening snack is recommended to decrease fasting time at night[88]. A combination of aerobic and resistance exercise is recommended[88]. Testosterone levels are usually low in patients with decompensated cirrhosis. A randomized controlled trial by Sinclair *et al*[98] has shown improvements in muscle mass, bone mineral mass, and a decrease in total fat mass in cirrhosis patients receiving testosterone. In the AASLD 2021 guidelines, testosterone therapy may be started in men with low testosterone levels. HCC, a history of other malignancy or thrombosis remains a relative contraindication to this treatment[88]. A prospective study by Benmassaoud *et al*[99] has demonstrated improvements of SMI post-TIPS and no significant correlation between TIPS and de novo HE in patients with sarcopenia.

Liver transplant

LT represents a treatment option for PH-related complications especially when combined with hepatic synthetic dysfunction. Patients with decompensated cirrhosis and a MELD score ≥ 15 should be evaluated for LT as it is associated with an improvement in survival (LT)[100].

Recompensation

Recompensated cirrhosis is defined by the removal of the underlying cause of the liver disease, absence of ascites off diuretics, absence of encephalopathy off lactulose and rifaximin, absence of recurrent variceal bleed for at least 12 months, and sustained improvement in liver function tests[7]. The BAVENO VII consensus currently recommends against removing NSBB unless CSPH is resolved[7]. At this moment, clear definitions are needed to determine the removal of the underlying cause of liver disease in non-alcohol and non-viral etiologies[101].

CONCLUSION

The management of PH in cirrhosis has seen significant advancements in recent years, with non-invasive diagnostic tools and novel therapeutic approaches improving patient outcomes. However, further research is needed to validate emerging techniques such as EUS-PPG and to refine risk stratification algorithms, particularly in non-viral etiologies of cirrhosis. A multidisciplinary approach remains essential to optimize care for patients with complex and refractory PH.

FOOTNOTES

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