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Review Article

Recent Advances in the Pathogenesis and Clinical Evaluation of Portal Hypertension in Chronic Liver Disease

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In chronic liver disease, hepatic stellate cell activation and degeneration of liver sinusoidal endothelial cells lead to structural changes, which are secondary to fibrosis and the presence of regenerative nodules in the sinusoids, and to functional changes, which are related to vasoconstriction. The combination of such changes increases intrahepatic vascular resistance and causes portal hypertension. The subsequent increase in splanchnic and systemic hyperdynamic circulation further increases the portal blood flow, thereby exacerbating portal hypertension. In clinical practice, the hepatic venous pressure gradient is the gold-standard measure of portal hypertension; a value of ≥10 mm Hg is defined as clinically significant portal hypertension, which is severe and is associated with the risk of liver-related events. Hepatic venous pressure gradient measurement is somewhat invasive, so evidence on the utility of risk stratification by elastography and serum biomarkers is needed. The various stages of cirrhosis are associated with different outcomes. In viral hepatitis-related cirrhosis, viral suppression or elimination by nucleos(t)ide analog or direct-acting antivirals results in recompensation of liver function and portal pressure. However, careful follow-up should be continued, because some cases have residual clinically significant portal hypertension even after achieving sustained virologic response. In this study, we reviewed the current and future prospects for portal hypertension. **(Gut Liver 2024;18:27-39)**

Key Words: Portal hypertension; Splanchnic circulation; Hepatitis B; Hepatitis C; Elasticity imaging techniques

INTRODUCTION

The portal vein is the venous trunk formed by the confluence of veins from the abdominal organs, and its branches that flow into the liver eventually form sinusoids, which comprise a capillary bed that drains to the central vein. An increase in vascular resistance or inflow in either of these pathways increases the portal vein pressure and result in various clinical findings, such as enlargement of the portosystemic shunt, including the esophagogastric varices; splenomegaly; pancytopenia secondary to hypersplenism; ascites; and hepatic encephalopathy. Therefore, portal hypertension is not a disease name but a syndrome of various pathologic conditions that increase the portal vein pressure.

Portal hypertension is an important condition that directly affects the prognosis of chronic liver disease. In the natural history of the disease, progression from compensated to decompensated cirrhosis has been considered as a point of no return. However, recent developments in long-term nucleos(t)ide analog treatment in patients with hepatitis B-related cirrhosis as well as direct-acting antiviral (DAA) treatment in patients with hepatitis C-related cirrhosis have enabled us to achieve profound viral suppression and high sustained virologic response (SVR) rates. Consequently, disease regression and recompensation of cirrhosis and portal hypertension have been the focus on studies.

In this article, we reviewed the classification of portal hypertension and outlined its pathogenesis and methods for assessment, with a focus on chronic liver disease. In addition, we summarized the future prospects for portal hypertension.

CLASSIFICATION OF PORTAL HYPERTENSION

Portal hypertension is classified as prehepatic, hepatic, or posthepatic, depending on the site of increased vascular resistance (Table 1). Prehepatic causes include extrahepatic portal venous obstruction (EHPVO), portal vein thrombosis, and portal vein obstruction, which are caused by tumors or inflammation that infiltrates or spreads to the portal vein. Hepatic causes are further subdivided according to their relative location to the sinusoids. Presinusoidal causes include adult polycystic disease, congenital hepatic fibrosis, cholestatic liver disease, schistosomiasis, sarcoidosis, and idiopathic portal hypertension (IPH)/noncirrhotic portal fibrosis (NCPF). Sinusoidal causes account for about 80% of all portal hypertension cases and include alcoholic liver cirrhosis, nonalcoholic fatty liver disease (NAFLD), and viral hepatitis. Postsinusoidal causes include sinusoidal obstruction syndrome and Budd-Chiari syndrome (BCS). Posthepatic causes, such as right heart failure or constrictive pericarditis, are mainly secondary to a congested liver.[1,2] The conditions mentioned above can be differentiated using the hepatic venous pressure gradient (HVPG), which is measured by hepatic venography and is calculated by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. In patients with prehepatic and presinusoidal diseases, the HVPG is normal, because the sinusoidal pressure remains normal, and there is a discrepancy between the HVPG and the actual portal vein pressure. In patients with sinusoidal and postsinusoidal disease, the HVPG is elevated because of an increased intrasinusoidal pressure and is similar to the actual portal vein pressure. In patients with posthepatic disease, the wedged hepatic venous pressure and free hepatic venous pressure are elevated, but the HVPG is normal.

Table 1. Classification of Portal Hypertension and Diseases

Classification	Disease
Prehepatic	Extrahepatic portal venous obstruction Portal vein thrombosis Portal vein obstruction caused by tumor or inflammation
Hepatic	
Presinusoidal	Adult polycystic disease Congenital hepatic fibrosis Cholestatic liver disease Schistosomiasis Sarcoidosis IPH/NCPF
Sinusoidal	Liver cirrhosis
Postsinusoidal	SOS/VOD Budd-Chiari syndrome
Posthepatic	Right heart failure Constrictive pericarditis

IPH, idiopathic portal hypertension; NCPF, noncirrhotic portal fibrosis; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

NONCIRRHOTIC PORTAL HYPERTENSION

1. Extrahepatic portal venous obstruction

EHPVO is a syndrome leading to portal hypertension due to extrahepatic portal vein obstruction. EHPVO is generally a disorder affecting the pediatric or young population and is more prevalent in Asia than that in Western countries. In Japan, the latest nationwide survey in 2015 reported that the male-to-female ratio was 1:1, and the mean age at diagnosis was 33 years, showing no change over 10 years.[3,4] In EHPVO, the development of hepatophilic collateral circulation in the hepatic hilum, so-called cavernous transformation, is observed. Although the cause of primary EHPVO remains largely unclear, angiogenesis, blood coagulation disorders, or myeloproliferative disorders have been implicated.[3] Conversely, the causes of secondary EHPVO include neonatal omphalitis, tumors, cholecystitis, pancreatitis, or intra-abdominal surgery. Pathological findings showed that the lobular structure of the liver was preserved normally, and the intrahepatic portal vein branch is patent. Liver function is generally preserved.

2. IPH/NCPF

IPH/NCPF has been reported globally, particularly in Asian countries, including Japan and India.[5] In Western countries, the incidence of IPH/NCPF has been relatively less; however, it has been increasing.[6] Alternate names for IPH or NCPF include obliterative portal venopathy, nodular regenerative hyperplasia, and hepato-portal sclerosis. The European Association for Vascular Liver Disease Group recently proposed the term "porto-sinusoidal vascular disease" as a concept that includes NCPF/IPH.[7] In Japan, the IPH incidence peaked in 1975 and declined thereafter. In the latest nationwide survey in 2015, the male-to-female ratio was 1:2.3, and the mean age at diagnosis was 47 years, showing no change over 10 years.[3,4] However, previous reports indicated that one of the reasons for the high NCPF incidence is associated with the low socioeconomic strata in India.[5] Owing to improved living standards, NCPF incidence is believed to be declining in India; however, no large multicenter studies have confirmed this notion.[8] Although the cause of IPH/NCPF is largely unknown, environmental chemicals, drugs, or organic compounds have been implicated.[3] Additionally, immune abnormalities, including human immunodeficiency virus

infection, splenic dysfunction, and abnormal coagulopathy, have been reported to be associated with the pathogenesis.[9] The pathological findings of IPH/NCPF are characterized by sclerosis and obliteration of the peripheral branches of the intrahepatic portal vein. The lobular structure and liver function are generally preserved.

3. Budd-Chiari syndrome

BCS is a syndrome that leads to portal hypertension due to obstruction or stenosis of the main hepatic vein or hepatic inferior vena cava. In Japan, according to the latest nationwide survey in 2015, BCS prevalence is increasing.[3] Although the cause of BCS is largely unknown, thrombosis, angiogenic abnormalities, blood coagulation disorders, or myeloproliferative disorders, as well as EHPVO, have been implicated.[3] The clinical manifestations of BCS are highly variable, ranging from no symptoms to fulminant liver failure, and from acute to chronic progression. Hepatic venous outflow obstruction causes increased sinusoidal and portal pressure, which leads to hepatic congestion, necrosis, fibrosis, and ultimately cirrhosis. Moreover, BCS may be complicated by hepatocellular carcinoma (HCC).[10]

4. Management of noncirrhotic portal hypertension

Noncirrhotic portal hypertension including EHPVO, IPH/NCPF, and BCS, may present with pancytopenia due to splenomegaly and hypersplenism, esophagogastric varices, ectopic varices, ascites, and hepatic encephalopathy. In cases with esophagogastric varices, prophylactic procedures using endoscopy, interventional radiology, or surgical treatment are significant. In cases of thrombosis, anticoagulation therapy should be considered. In cases of BCS, interventional radiological treatment, including balloon angioplasty and transjugular intrahepatic portosystemic shunt, or surgical treatment of the occluded area, should be considered; however, in cases of liver failure, early consideration of liver transplantation is significant.[11]

PATHOGENESIS OF PORTAL HYPERTENSION IN CHRONIC LIVER DISEASE

1. Increased intrahepatic vascular resistance

Chronic liver disease is characterized by hepatic parenchymal damage secondary to fibrosis, angiogenesis, and vascular occlusion, with the activation of hepatic stellate cells (HSCs) as the key starting point.[12,13] The extracellular matrix produced by the activated HSCs accumulates in the space of Disse and reduces the sinusoidal diameter.[14] In addition, regenerative nodule-like changes in the liver parenchyma lead to sinusoidal retraction, which result in sinusoidal remodeling. Furthermore, the activated HSCs acquire a myofibroblast-like phenotype and cause sinusoidal contraction.[15] In a normal liver, endothelin 1 is produced by liver sinusoidal endothelial cells (LSECs). As liver injury progresses, endothelin 1 is excessively produced by HSCs and markedly activates the endothelin receptors (i.e., ET_A and ET_B) that are expressed on vascular smooth muscle cells and endothelial cells, which are also involved in sinusoidal contraction.[16-18] In addition to endothelin, vasoconstrictors, such as thromboxane A2, the renin-angiotensin system, and other vasoconstrictor substances, contribute to an increased intrahepatic vascular resistance.[12,19-21]

LSECs have fenestrated structures (i.e., sieve plates) and lack a basement membrane. In a normal liver, LSECs play an important role in the permeation of substances between the space of Disse and the sinusoidal lumen.[22] As hepatic fibrosis progresses, the fenestrations of the LSECs decrease in number, leading to capillarization, progression of hepatic microvascular injury, and increase in intrahepatic vascular resistance.[21,23,24] LSECs express endothelial nitric oxide synthase (eNOS) and produce nitric oxide (NO), which is a vasodilator. If eNOS activity and NO production decrease because of damage in the LSECs, the sinusoids become dilated and tend to increase the vascular resistance.[12,25]

Therefore, in addition to the structural changes secondary to liver fibrosis and the regenerative nodules in the sinusoids, functional changes that are related to vasoconstriction increase intrahepatic vascular resistance and result in portal hypertension (Fig. 1).[23]

2. Systemic inflammation and increased splanchnic and hyperdynamic circulation

A high intrahepatic vascular resistance results in the development of collateral circulation. Although Ohm's law would suggest that the presence of collateral circulation would reduce the vascular resistance of the portal system and lower the portal pressure, portal hypertension persists. Systemic inflammation and increased hyperdynamic circulation are implicated as the cause.[26]

In liver cirrhosis, edema and decreased intestinal motility causes small intestinal bacterial overgrowth and dysbiosis, which reduces the diversity of the intestinal microbiota, leading to increased intestinal permeability and intestinal barrier dysfunction. Consequently, it promotes bacterial translocation from the imbalance in bacterial species. This so-called leaky gut condition increases serum endotoxin concentration.[27-29] Pathogen-associated molecular patterns (PAMPs) are released from the infecting bacteria, resulting in higher PAMP levels in the blood. High levels of lipopolysaccharides and other PAMPs from the leaky gut are delivered to the liver via the portal vein. Furthermore, even in

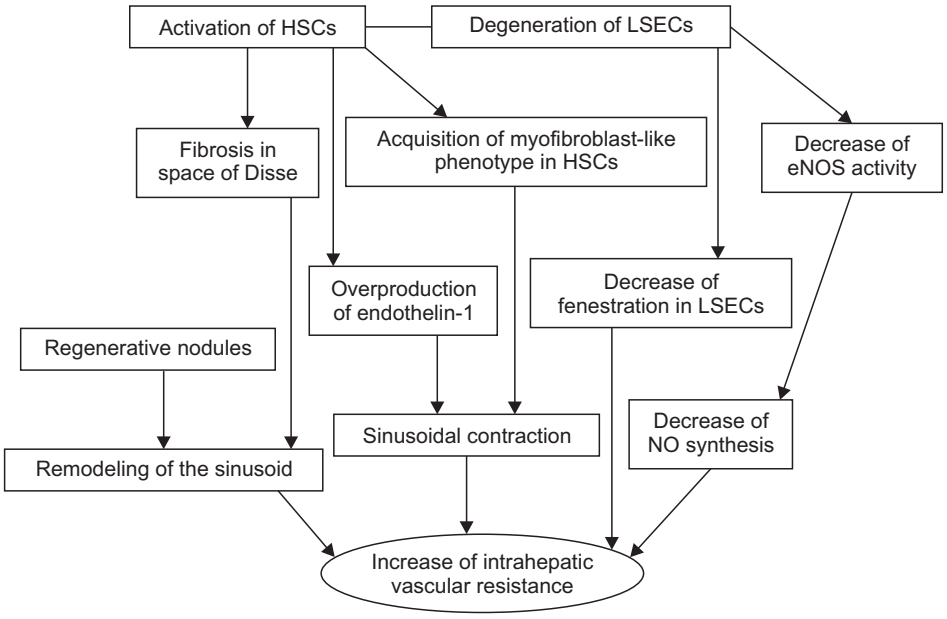

Fig. 1. Pathogenesis of increased intrahepatic vascular resistance in chronic liver disease. HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

the absence of infection or bacterial translocation, systemic inflammation occurs in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure owning to the release of damage-associated molecular patterns from injured organs and tissues. PAMPs and damage-associated molecular patterns in the liver are recognized by toll-like receptors and cause inflammasome activation in the Kupffer cells, hepatocytes, and monocyte-derived pro-inflammatory macrophages. The infiltration of activated neutrophils induces the release of reactive oxygen species, which stresses the mitochondria and causes hepatocyte necrosis and apoptosis.[30] Recently, it has been emphasized that such systemic inflammation is the main actor in acute decompensation or acute-on-chronic liver failure development; large studies, such as APASL-AARC, CANONIC, and PREDICT studies, have reported that bacterial infection is associated with poor clinical course and high mortality.[31-33]

Systemic inflammation-induced endotoxins and the shear stress caused by increased blood flow through the collateral vessels and into the systemic circulation increase the systemic and intestinal NO production from vascular endothelial cells and, conversely, decrease the responsiveness to vasoconstrictors.[26,34] As a result, splanchnic and peripheral arteries dilate, vascular resistance decreases, and systemic and intestinal blood volume increase.[34,35] This increase in systemic circulatory hemodynamics is called hyperdynamic circulation. In addition, when the effective circulating blood volume is reduced by splanchnic vasodilation, the renin-angiotensin system is stimulated[36] and result in sodium and water retention, which increases the circulating blood volume and aggravates hyperdynamic circulation.[37] Other angiogenic factors, such as vascular endothelial growth factor and platelet-derived growth factor, are also involved in eNOS activation and the exacerbating of systemic circulatory hemodynamics.[38,39] In addition to NO, vasodilators, such as glucagon, carbon monoxide, prostacyclin, endocannabinoid, and neuropeptide, have been associated with hyperdynamic circulation.[39-41]

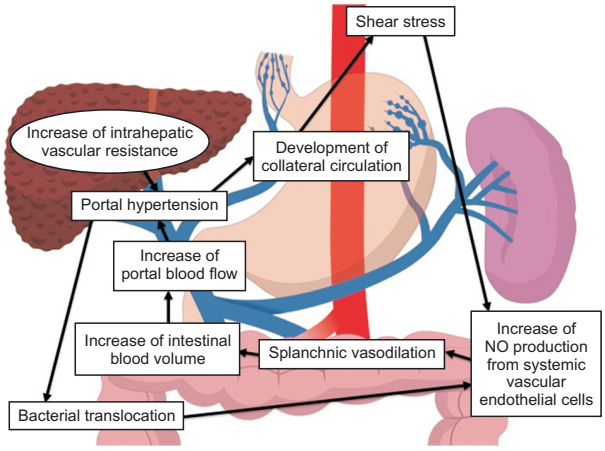

Fig. 2. Pathogenesis of increased splanchnic and hyperdynamic circulation in chronic liver disease. NO, nitric oxide.

Hyperdynamic circulation is characterized by increased circulating blood volume and increased cardiac output and decreased mean arterial pressure, peripheral vascular resistance, and effective circulating blood volume.[40] All of these increase the intestinal blood flow into the portal vein. As a result, portal blood flow increases and portal hypertension worsens (Fig. 2).[12,41,42]

ASSESSMENT OF PORTAL HYPERTENSION

1. Physical examination, noninvasive tests, and altered liver morphology

The first step in evaluating portal hypertension in chronic liver disease is physical examination for signs, such as jaundice, ascites, hepatic encephalopathy, network of large and visible veins around the abdomen (i.e., caput medusae), leg edema, palmar erythema, spider angiomata, coagulopathy, and cutaneous pruritus.[13] Second is screening for liver fibrosis by easily measured; these include N-terminal propeptide of type III collagen, hyaluronic acid, tissue inhibitor of metalloproteinase-1, type IV collagen 7s domain, *Wisteria floribunda* agglutinin-positive Mac-2 binding protein, and autotaxin.[43-50] However, one disadvantage of these fibrosis markers is that they can be modified by other factors, such as pulmonary fibrosis, interstitial pneumonia, diabetes mellitus, or cardiomyopathy. Therefore, a scoring system that comprises several items, such as the fibrosis-4 index,[51] aspartate aminotransferase to platelets ratio index,[52] enhanced liver fibrosis score,[43,53,54] and Lok index,[55] can improve diagnostic performance. Third, liver morphology assessment by abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging, and checking for esophagogastric varices and portal hypertensive gastropathy by upper gastrointestinal endoscopy are important. If these findings are positive, the presence of portal hypertension is suggested.

2. HVPG measurement as a gold standard

In liver cirrhosis, in which intrasinusoidal communication is lost, the HVPG is almost the same as the portal pressure. Therefore, HVPG measurement is the gold standard for the evaluation of portal hypertension not only in research but also in clinical practice.[11] An HVPG of ≤5 mm Hg is normal, whereas a value of >5 mm Hg is diagnostic for portal hypertension. An HVPG of ≥10 mm Hg is diagnosed as clinically significant portal hypertension (CSPH), which has a risk of clinical decompensation (i.e., ascites, variceal bleeding, and hepatic encephalopathy) and HCC.[2] The risk of variceal rupture increases when the HVPG is ≥12 mm Hg. An HVPG of ≥16 mm Hg increases the risk of mortality, and an HVPG of ≥20 mm Hg increases the risks of failed variceal bleeding treatment and mortality.[56] The HVPG can be measured through the transjugular, transfemoral, or peripheral antecubital vein approach.[57] In the clinical settings, most of the measurements are often performed simultaneous with invasive procedures, such as transjugular liver biopsy, transjugular intrahepatic portosystemic shunt, and balloon-occluded retrograde transvenous obliteration. Tolerance should be focused, because HVPG measurement is somewhat invasive. Casu *et al.*[58] reported that hepatic hemodynamic procedures lasting for <35 minutes had >80% probability of being well tolerated. In a report on 41 patients in whom HVPG was measured from the peripheral antecubital veins, Yamamoto *et al.*[59] showed that the median procedure time was 19.1 minutes and the measurement was safe in 98%, without any serious complications, such as large hematoma or nerve injuries. Moreover, the HVPG is a prognostic indicator that can objectively evaluate the therapeutic effect of nonselective beta-blockers or transjugular intrahepatic portosystemic shunt for portal hypertension. HVPG measurement is necessary, but efforts should be made to reduce its invasiveness.

3. Transient elastography

Compensated advanced chronic liver disease (cACLD), which is synonymous to compensated liver cirrhosis, is a chronic liver disorder that has a risk of developing CSPH.[60] As a noninvasive test, the liver stiffness measurement (LSM) using transient elastography (TE) is a useful alternative to HVPG for risk stratification of portal hypertension. LSM <10 kPa may exclude cACLD, >15 kPa is highly suspicious for cACLD, and 10 to 15 kPa is considered as a cACLD gray zone.[60] Furthermore, combining LSM with platelet count allows stratification of CSPH and the risk of varices needing treatment.[61] Screening endoscopy can be avoided in patients with LSM <20 kPa and platelet count >150×10^9/L, because there had been no reported complication of high-risk varices that required treatment.[60] In addition, LSM <15 kPa and platelet count >150×10^9/L can rule out CSPH with >90% sensitivity and negative predictive value.[11,62] Based on the latest Baveno VII consensus, LSM >25 kPa can be used to rule in CSPH, whereas LSM ≤15 kPa and platelet count ≥150×10^9/L can be used to rule out CSPH in most etiologies of cACLD.[11] Although these criteria could be a useful clinical approach for risk stratification of cACLD patients, LSM 15–25 kPa was reported to encompass a CSPH gray zone, which included >40% of eligible patients.[62] Dajti *et al.*[63] reported that the addition of spleen stiffness measurement (SSM), which is measured on TE, to the Baveno VII model dramatically reduced the number of patients in the CSPH gray zone and improved the diagnostic performance for CSPH. SSM not only reflects static hepatic resistance secondary to liver fibrosis but may also capture dynamic presinusoidal vasoconstriction, congestion of the portal blood inflow, and portal hypertension–induced splenic fibrosis.[64-69] SSM is a prognostic indicator of liver-related events and correlates well with HVPG.[70-73] A cutoff value of 41 to 46 kPa for SSM had been useful for identifying high-risk varices and CSPH.[63,74-78]

4. Magnetic resonance elastography

In the past, most reports on LSM and SSM measured these values by TE. In recent years, reports on the use of magnetic resonance elastography (MRE) for the assessment of liver fibrosis and portal hypertension have increased.[77-80] MRE has been reported to be superior to TE in evaluating liver fibrosis.[81,82] The higher accuracy of MRE than of TE for liver fibrosis was attributed to the fact that TE is a single-vector test, whereas MRE provides two-dimensional (2D) or three-dimensional (3D) data of the whole liver.[83] In addition, compared with TE, MRE can measure a larger region of interest in the liver and generated better quality of the elastic waves in patients with obesity or ascites, because compressional and continuous waves were used.[84] Matsui *et al.*[85] showed that a criterion of MRE LSM <4.2 kPa plus platelet count >180×10^9/L had a negative predictive value of 100% for the presence of esophagogastric varices, which are important findings in CSPH. LSM and, especially, SSM obtained by magnetic resonance imaging were shown to have a positive correlation with HVPG.[83,85-87] In addition, in a recent report, the correlation of SSM with HVPG was higher when SSM was obtained by 3D MRE than by 2D MRE.[86,88] Kennedy *et al.*[86] indicated that the correlation of SSM with HVPG was stronger with the use of 3D MRE than with that of 2D MRE and that the best diagnostic performance for CSPH was by 3D MRE SSM, followed by 2D MRE SSM and 3D MRE LSM. On the other hand, Ajmera *et al.*[89] found that a combination of MRE ≥3.3 kPa and FIB-4 ≥1.6 had a robust association with liver-related outcomes in patients with NAFLD. At present, MRE is not universally applied in clinical practice and is an expensive modality. Further studies are needed to accumulate evidence on the value of MRE as a noninvasive alternative to invasive HVPG for evaluating portal hypertension. Hopefully, in the future, the use of MRE will be established and widespread.

5. Other imaging modalities

As a noninvasive test other than TE and MRE, CT angiography images were used by Qi *et al.*[90] to calculate virtual HVPG, which correlated well with invasive HVPG. In addition, the usefulness of ultrasound techniques, such as point shear wave elastography, 2D shear wave elastography, acoustic radiation force impulse quantification and virtual touch tissue quantification, for the diagnosis of portal hypertension has been shown.[70,91-93] Other methods to evaluate portal hypertension include per-rectal portal scintigraphy using Tc-99m-pertechnetate, which has been reported to correlate with the HVPG and be useful in the diagnosis of chronic liver disease or sinusoidal obstruction syndrome after allogeneic hematopoietic cell transplantation.[94,95] Further research on CSPH risk stratification based on noninvasive imaging is warranted. A comparison of each noninvasive imaging modality for assessing CSPH is shown in Table 2.[96-98]

Table 2. Noninvasive Imaging Modalities for Assessing Clinically Significant Portal Hypertension

Assessment method	Sensitivity (95% CI)	Specificity (95% CI)	Pros	Cons
CT/MRI[96]	0.77 (0.71–0.82)	0.81 (0.73–0.87)	Available at several hospitals Useful for collateral blood vessel detection	Exposure to radiation in CT Risk of allergy or nephropathy due to contrast agents
TE-based LSM[96]	0.81 (0.73–0.87)	0.83 (0.77–0.88)	Available at several hospitals Rapidity Easy and reproducible Validated in several etiologies	Somewhat dependent on the skill of the operator Affected by liver inflammation and cholestasis Not measurable in patients with obesity or ascites
SWE-based LSM[96]	0.77 (0.71–0.82)	0.76 (0.65–0.84)	Rapidity Repeatable and reproducible Not limited by ascites	Dependent on the skill of the operator Affected by liver inflammation and cholestasis
US-based SSM[97]	0.85 (0.69–0.93)	0.86 (0.74–0.93)	Less influenced by liver inflammation Reflects not only increased intrahepatic vascular resistance but also splenic hemodynamics and fibrosis	A dedicated device is required Difficult to measure without splenomegaly
MRI-based LSM[98]	0.83 (0.72–0.90)	0.80 (0.70–0.88)	Capable of covering the whole liver Less operator dependence High reproducibility	Expensive modality Not universally applied in clinical practice Affected by liver inflammation and cholestasis
MRI-based SSM[98]	0.79 (0.61–0.90)	0.90 (0.80–0.95)	Capable of covering the whole spleen Less operator dependence High reproducibility	Expensive modality Not universally applied in clinical practice Complexity of repositioning the passive driver from the liver to the spleen

CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; TE, transient elastography; LSM, liver stiffness measurement; SWE, shear wave elastography; US, ultrasound; SSM, spleen stiffness measurement.

6. Artificial intelligence (AI)-based methods

In the field of chronic liver disease, the development of statistical analysis in recent years has led to the creation of diagnostic models using various modalities. Regarding portal hypertension, the development of AI processing technology has led to the creation of noninvasive evaluation models with high diagnostic performance along with studies using traditional radiomics for extracting several quantitative features from medical images to derive information useful for diagnosis.[99-101] Marozas *et al.*[102] predicted CSPH with an accuracy rate of 89.72% using a machine learning algorithm using clinical parameters including TE. Liu *et al.*[103] used a deep convolutional neural network-based model for CT or MR images for predicting patients with CSPH with a high diagnostic ability and an area under the curve value of 0.9 or higher. Moreover, Bosch *et al.*[104] recently showed that a machine learning model using liver biopsy slides was used for predicting CSPH in patients with nonalcoholic steatohepatitis and cirrhosis. Thus, AI-based algorithms are useful techniques for diagnosing portal hypertension; however, their applicability and versatility in clinical practice have not been sufficiently evaluated. In collaboration with pathologists and radiologists, hepatologists should focus on the development of AI-based methods for diagnosing portal hypertension and predicting prognosis as a useful tool that will lead to improved care for patients with chronic liver disease as well as perform appropriate verifications.[105]

CURRENT STATUS AND FUTURE PROSPECTS FOR PORTAL HYPERTENSION IN VIRAL HEPATITIS

1. Chronic hepatitis B

The recent expansion of long-term nucleos(t)ide analog treatment can lead to profound viral suppression, leading to amelioration of necroinflammation in patients with chronic hepatitis B. Additionally, several reports state that nucleos(t)ide analog treatment contributes to portal hypertension regression in patients with hepatitis B-related cACLD.[106-111] Manolakopoulos *et al.*[106] reported that lamivudine therapy reduced HVPG in patients with hepatitis B-related cirrhosis during 12-month treatment. Wang *et al.*[107] reported that 120-week treatment with entecavir resulted in recompensation in more than 50% of patients with hepatitis B-related decompensated cirrhosis. Farina *et al.*[108] followed up with the patients with hepatitis B-related compensated cirrhosis treated with tenofovir or entecavir and observed that esophageal varices had regressed in 58% of patients who had low-risk varices at baseline. Conversely, even if the activity of hepatitis is controlled by nucleos(t)ide analog treatment, the risk of decompensation remains in cases of higher liver stiffness. Lee *et al.*[109] investigated 818 patients receiving antiviral treatment who had an LSM of ≥10 kPa and compensated liver disease with chronic hepatitis B and identified that 3.9% of patients developed hepatic decompensation and 5.9% of patients fulfilling the Baveno VI criteria developed decompensation. Jachs *et al.*[110] reported that hepatitis B virus (HBV)-infected patients with CSPH who achieved long-term viral suppression using nucleos(t)ide analog treatment were protected from decompensation if the LSM was <25 kPa; however, an LSM of ≥25 kPa indicated a persisting risk of decompensation despite long-term HBV suppression.

Regarding HCC development, hepatitis B-related markers, including hepatitis B e antigen, HBV-DNA, and hepatitis B core-related antigen, are the risk factors for HCC development in patients with chronic hepatitis B.[112-114] In contrast, an association between HCC development and portal hypertension has also been reported. Wong *et al.*[115] reported that a combined score of LSM, age, serum albumin and HBV-DNA level is accurate for predicting HCC in patients with chronic hepatitis B. Additionally, Marzano *et al.*[116] reported that portal hypertension before antiviral therapy and liver stiffness-spleen size-to-platelet value following therapy were predictive factors for the risk of HCC. Papatheodoridis *et al.*[117] showed that a liver stiffness of ≥12 kPa at year 5 was associated with increased HCC risk following a 5-year antiviral therapy. Notably, in patients with hepatitis B-related cACLD, the benefit of nucleos(t)ide analog treatment reduces the risk of decompensation and HCC development; however, the risk remains if the portal hypertension persists.

2. Chronic hepatitis C

Among patients with hepatitis C, both chronic hepatitis and compensated cirrhosis can now be treated with DAAs, which can eliminate the virus and has a high SVR rate.[118-122] More recently, good treatment results with DAAs have been reported, even in patients with decompensated cirrhosis secondary to hepatitis C.[123-125] Given these developments, attention has been focused on the changes in portal hypertension after SVR and improvement of prognosis. Previous reports have shown that HVPG decreases when SVR was achieved in patients with hepatitis C-related cirrhosis.[126-130] In a report on patients with hepatitis C-related cirrhosis with portal hypertension, Mandorfer *et al.*[128] indicated that after interferon-free treatment, HVPG decreased after SVR; notably, the number of patients in whom this outcome was demonstrated was lower in Child–Pugh stage B cases than in Child–Pugh stage A cases. Lens *et al.*[129] showed that DAA

treatment of patients with hepatitis C virus-associated cirrhosis and CSPH decreased the HVPG after achieving SVR, but the CSPH in 78% after 24 weeks of treatment completion. In another study with longer follow-up period, HVPG decreased further, but the CSPH persisted in 53% after 96 weeks of treatment completion.[130] Semmler *et al.*[131] clarified that after DAA treatment, LSM <12 kPa and platelet count >150×10^9/L ruled out CSPH with 99.2% sensitivity, whereas LSM ≥25 kPa ruled in CSPH with 93.6% specificity. In the most recent report, DAA treatment of patients with hepatitis C-related decompensated cirrhosis improved the hepatic accumulation rate of Tc-99m-galactosyl human serum albumin and decreased the percentage of patients with severe portal hypertension (i.e., HVPG ≥12 mm Hg) from 92% to 58%; however, the HVPG did not decrease in patients with large splenic volume.[132] Therefore, in patients with hepatitis C-related cirrhosis and achieve SVR, HVPG decreases in the short term, but CSPH persists in many patients.

Several data on the long-term prognosis of hepatitis C-related cirrhosis after achieving SVR have been accumulated.[129,133-137] Verna *et al.*[138] reported that after a median of four years of DAA treatment of 642 patients with advanced/decompensated cirrhosis, improvements in the MELD score, total bilirubin, and albumin were only marginalt. In particular, patients with portal hypertension have a high-risk of liver-related events, even after achieving SVR.[129] Nagaoki *et al.*[139] found that among 87 patients with DAA-treated compensated cirrhosis, aggravation of esophagogastric varices and portosystemic encephalopathy was more frequent in those who had large feeding vessels for the esophagogastric varices and portosystemic shunts at the time of SVR. Lens *et al.*[140] found that the risk of clinical decompensation was high when CSPH persisted after achieving SVR 24. Moreover, a recent report indicated the incidence of HCC among patients who achieved SVR after DAA treatment was higher in those with CSPH than in those without CSPH.[141] Based on these findings, careful follow-up after DAA treatment is required to monitor the development of liver-related complications, regardless of whether or not SVR was achieved.

3. Future prospects for portal hypertension

The recent Baveno VII consensus recommended the use of elastography indices, including LSM and SSM, or noninvasive tests, such as serum circulating markers and a combined score, as a strategy in the clinical management of portal hypertension, although HVPG remains the gold standard.[11] In patients with viral hepatitis-related cACLD who have residual CSPH following viral suppression or elimination, periodic checkups are necessary because the risk of decompensation remains even after the dismissal of the primary etiologic factor. Therefore, we underscore the importance of preventing both initial and recurrent decompensation. In other conditions, such as alcoholic liver disease and NAFLD, the important strategies to remove the primary etiologic factors include abstinence and mental programs, and aerobic and resistance exercise, respectively. With the advent of new drugs and evaluation methods, we can expect a paradigm shift in the clinical management of portal hypertension.

CONCLUSIONS

This review presented the classification of portal hypertension and outlined the pathogenesis of portal hypertension in chronic liver disease and the current status of assessment methods. High intrahepatic vascular resistance and increased splanchnic and systemic hyperdynamic circulation result in a complex combination of structural and functional changes that cause portal hypertension. Although HVPG remains the gold standard measurement for portal hypertension, establishment of evidence on the usefulness of noninvasive tests, including elastography and serum biomarkers, for the evaluation of CSPH and risk stratification of liver-related events can be expected in the future. Toward the future of portal hypertension in chronic liver disease, ensuring the removal of the primary etiologic factors to recompensate liver function and portal pressure and implementation of meticulous personalized medicine are important.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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