Received: 26 March 2022 | Accepted: 21 April 2022

DOI: 10.1002/poh2.8

REVIEW

PH&C PORTAL HYPERTENSION & CIRRHOSIS

Portal hypertension in nonalcoholic fatty liver disease: Challenges and perspectives

Lei Miao[1] | **Giovanni Targher**[2] | **Christopher D. Byrne**[3] | **Luca Valenti**[4,5] | **Xiaolong Qi**[6] | **Ming-Hua Zheng**[7,8]

[1]Department of Gastroenterology, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

[2]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

[3]Southampton National Institute for Health Research Biomedical Research Centre, Southampton General Hospital, University Hospital Southampton, Southampton, UK

[4]Translational Medicine, Department of Transfusion Medicine and Hematology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

[5]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milano, Italy

[6]CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, Gansu, China

[7]Department of Hepatology, NAFLD Research Center, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

[8]Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, Zhejiang, China

Correspondence
Ming-Hua Zheng, NAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou, Zhejiang, 325000, China.
Email: zhengmh@wmu.edu.cn

Managing Editor: Ningning Wang

Funding information
National Natural Science Foundation of China, Grant/Award Number: 82070588; Agenzia Italiana del Farmaco, Ministero della Salute, Grant/Award Number: RF-2016-02364358

Abstract

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide. NAFLD-related cirrhosis is often complicated by portal hypertension (PHT). Recent evidence showed that portal venous pressure (PVP) starts to rise in the early stages of NAFLD, even in absence of advanced fibrosis or cirrhosis. However, the precise pathological mechanisms of this process are still poorly understood. Lipid accumulation, hepatocellular ballooning, sinusoidal endothelial cell dysfunction, capillarization, microthrombosis, increased angiogenesis, and pericellular fibrosis may all be involved in the early development of increased PVP in NAFLD. Direct measurement of PHT is invasive and impractical in noncirrhotic NAFLD individuals and may also underestimate its severity. Thus, the development and validation of noninvasive and more accurate measurements, including new serum biomarkers, scoring models, and imaging techniques (such as ultrasonography, elastography, and magnetic resonance imaging), are urgently needed. Owing to the increasing morbidity, challenges in the prevention and management of PHT in NAFLD are unprecedented. This review article aims to briefly discuss these challenges and summarizes the mechanisms, diagnosis, and emerging therapies for PHT in people with NAFLD.

KEYWORDS

metabolic dysfunction-associated fatty liver disease, nonalcoholic fatty liver disease, novel noninvasive measurement, portal hypertension

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as one of the commonest causes of chronic liver disease, affecting up to 25%–30% of the global population.[1–3] The histological spectrum of NAFLD ranges from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis.[4] From 10% to 25% of patients with NASH progress to cirrhosis within 8–14 years, and the risks of developing portal hypertension (PHT), liver failure, and hepatocellular carcinoma are significantly increased.[5] Increasing evidence suggests that patients with NAFLD may develop increased portal pressure even in the early stages of NAFLD when advanced fibrosis or cirrhosis is absent.[6–10] Recent evidence also suggests that increased portal venous pressure (PVP) can promote fibrosis development in NAFLD.[11,12] These data suggest that increased PVP is not just a consequence of NAFLD, but may also contribute to the pathogenesis of NAFLD.[8] However, the underlying pathophysiological mechanisms for PHT remain incompletely understood.

Measurement of the hepatic venous pressure gradient (HVPG) is the most commonly used method for invasively detecting PHT, and HVPG is calculated as the difference between free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP).[5,13] However, recent observations suggest that HVPG may underestimate the true PVP in patients with NAFLD.[9,14] Furthermore, liver decompensation may develop at lower HVPG in patients with NAFLD than in those with viral liver disease, underscoring differences in disease pathophysiology.[15] Therefore, this gold standard invasive method might not be accurate for assessing PHT in people with NAFLD. Thus, there are currently a large number of questions and challenges that arise in the detection of PHT in this patient population. These questions include (a) What is the underlying pathological mechanism? (b) How does the increase in portal pressure contribute to NAFLD progression? (c) How can subclinical PHT be detected? (d) How should patients with PHT be managed? (e) What treatment is appropriate and what candidate drugs are available?

This review article briefly discusses and summarizes recently discovered mechanisms, novel measurements for assessment and therapies for PHT, and the review also provides our perspective as to how best to address these coming challenges.

2 | CHALLENGE IN PATHOPHYSIOLOGY: THE PATHOLOGICAL MECHANISMS ARE UNCLEAR

The main pathophysiological mechanisms of PHT in NAFLD-related cirrhosis appear to be similar to other etiologies of cirrhosis, such as viral hepatitis, autoimmune liver disease, and schistosomiasis.[6] The increase in portal pressure is mainly due to increased intrahepatic vascular resistance (IHVR).[7] However, in contrast to other etiologies, clinically significant portal hypertension (CSPH) may develop early in the natural history of NAFLD, even before the development of advanced fibrosis or cirrhosis. Changes in hepatic blood flow may also occur during the early stages of hepatic fibrosis in NAFLD patients because of impaired outflow in liver sinusoids.[16] Several mechanisms that may impair sinusoidal hemostasis and contribute to the rise of IHVR in NAFLD are schematically illustrated in Figure 1.

2.1 | Hepatocellular enlargement and sinusoidal narrowing

Hepatocellular enlargement, caused by lipid accumulation (steatosis) and ballooning, is thought to play a key

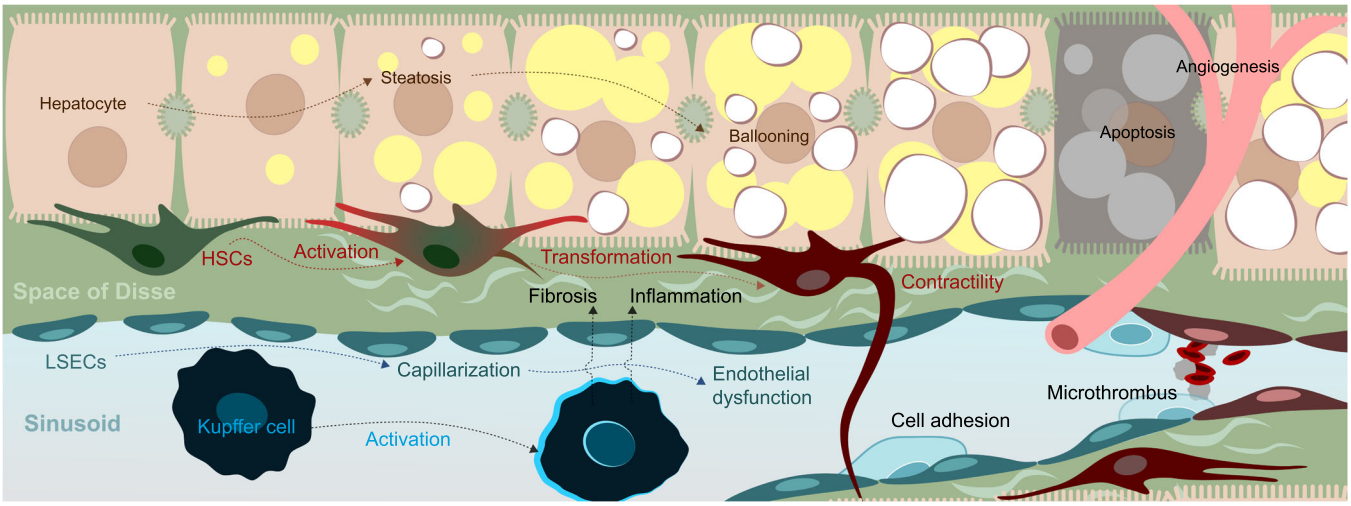

FIGURE 1 Due to steatosis and hepatocellular ballooning, enlarged fatty hepatocytes reduce sinusoidal flow and promote endothelial dysfunction, contributing to further shear stress. In response to these structural and functional changes, LSECs become defenestrated and develop a basement membrane (capillarization) that causes hypoxia and hepatocellular injury. HSCs reside in the space of Disse and Kupffer cells in the sinusoids. Defenestrated LSECs stimulate the contractility and transformation of HSCs into myofibroblasts leading to increased liver fibrogenesis and angiogenesis. Hepatocellular injury and apoptosis activate Kupffer cells leading to advancing inflammation, fibrosis, and angiogenesis, which further narrows the sinusoid. Augmented inflammatory changes include the recruitment of additional cellular components such as polymorphonuclear leukocytes promoting adhesion and microthrombosis. HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells.

role in the development of both increased IHVR and PHT in the early stages of NAFLD. This process of hepatocellular enlargement reduces the space of liver sinusoids, hindering circulation from sinusoids to liver cells because the diameter of swollen hepatocytes is enlarged about 1.5–2.0 times and causes sinusoidal narrowing, which may induce sinusoidal endothelial cell dysfunction.[8,17] Furthermore, steatotic hepatocytes are susceptible to lipotoxicity, which affects several cellular signaling pathways, and induces reactive oxygen species formation and endoplasmic reticulum stress.[18] Furthermore, the ballooned hepatocytes, as a characteristic feature of lipotoxicity-induced NASH, may activate the sonic hedgehog signaling pathway, which promotes liver fibrogenesis.[19]

2.2 | Sinusoidal endothelial cell dysfunction

A disrupted balance between vasodilator and vasoconstrictor products of sinusoidal vessels has been observed in the early stages of NAFLD.[20–22] Liver sinusoidal endothelial cells (LSECs) play a key role in both sensing and regulating hepatic blood flow, not only regulating portal and hepatic vascular resistance but also inhibiting the activation of Kupffer cells and hepatic stellate cells (HSCs).[23] Endothelial nitric oxide synthase (eNOS) is the key vasodilator that regulates sinusoidal blood flow and LSECs are the main source of nitric oxide (NO).[23] In an experimental study, Wistar Kyoto rats were fed with cafeteria diet (65% of fat) to develop liver steatosis and metabolic syndrome features.[8] Later, the cafeteria diet-fed rats developed higher in vivo hepatic vascular resistance and greater portal perfusion pressure. Because the decrease of endothelium-dependent vasodilation is due to a decrease in eNOS phosphorylation and NOS activity, the results of this experimental study suggest that liver steatosis may impair the function of LSECs and limit NO release, causing endothelial cell dysfunction in the early stages of NASH.[8] HSCs, located in the space of Disse, are inhibited by NO release from LSECs in healthy livers.[24] HSCs are activated by liver injury and cause contraction of the sinusoids and decrease sinusoidal blood flow. Kupffer cells may also regulate liver injury, inflammation, and fibrosis, as well as participate in the pathogenesis of NAFLD.[25] Kupffer cells are also activated by injured hepatocytes and activate-HSCs.[24] Activated Kupffer cells release multiple chemokines, eicosanoid derivatives, and reactive oxygen species, which may further aggravate liver inflammation.[26]

2.3 | Sinusoidal capillarization, fibrosis, and angiogenesis

Sinusoidal capillarization of LSEC, as an early manifestation of endothelial dysfunction in NAFLD, happens before the synergistic activation of Kupffer cells and HSCs.[27] The capillarization of LSEC that leads to sinusoidal dysfunction may promote liver steatosis by blocking the transfer of chylomicron remnants from portal vessels to hepatocytes, potentially stimulating hepatic cholesterol, and triglyceride synthesis.[28] In response to liver injury, LSECs undergo gradual defenestration by forming a perisinusoidal basement membrane with deposits of extracellular matrix proteins, such as fibronectin and laminin, in the space of Disse. Capillarization impairs hepatic perfusion and induces chronic hypoxia, which may aggravate steatosis and promote the progression of NAFLD to NASH and cirrhosis, leading to activation of hypoxia-inducible factors and increased transcriptional gene regulation of angiogenesis and proliferation.[29–31] Increasing evidence suggests that sinusoidal capillarization and angiogenesis play a key role in the progression of NAFLD. The vascular endothelial growth factor is the key regulator in this process, which is activated by the hypoxia-inducible factor and may further promote fibrosis development.[17] Chronic hypoxia activates HSCs, collagen begins to accumulate in the space of Disse and with capillarization and hypoxia development, fibrous bridging occurs near the hepatic sinusoids, eventually leading to the formation of cirrhotic nodules.[28] Moreover, it is known that fibrosis in NAFLD usually begins to develop in the intercellular space around the central vein and in the perisinusoidal area of zone 3, where HSCs are the main driver of the process.[4,32] This fibrosis pattern is different from other forms of chronic liver disease and potentially causes PHT before patients with NAFLD develop overt cirrhosis.[31]

2.4 | Cell adhesion and microthrombosis

In NAFLD, enlarged hepatocytes (caused by steatosis and ballooning) initially reduce sinusoidal flow in zone 3, and this effect then spreads across the entire lobule, thereby resulting in increased shear stress in LSECs. Furthermore, LSECs respond by facilitating the adhesion of blood cells. When the sinusoids narrow enough to trap blood cells, such as leukocytes, the effect usually occurs first in the centrilobular region, constraining the sinusoidal space and exacerbating the negative impact of steatosis.[33]

It has been hypothesized that microthrombosis could also increase IHVR in NAFLD. In a cohort of obese/overweight individuals, it was found that patients with biopsy-proven NASH had higher plasma plasminogen activator inhibitor-1 (PAI-1) concentrations than those with normal livers.[34] Levels of PAI-1 increased significantly with the histological severity of NAFLD, whereas other coagulation factors were unaltered. An increase in fibrinogen, factor VIII, and von Willebrand factor and a decrease in anti-thrombin III were correlated with metabolic features, including fasting C-peptide and waist circumference, but not with liver histology. This finding might, in part, explain why microthrombosis and PHT are associated with NAFLD.[34]

2.5 | Microbiota and gut–liver axis

Gut microbiota and bacterial translocation may also play an important role in the development of NAFLD-related cirrhosis and its complications, such as PHT,

spontaneous bacterial peritonitis, and hepatic encephalopathy.[35–37] Gut microbiota products, such as secondary bile acids, may affect intestinal permeability and PHT, mainly through the farnesoid-X receptor (FXR) and the G protein-coupled bile salt receptor-1, which mediate antisteatotic, anti-inflammatory, and antifibrotic effects. In contrast, cirrhosis and PHT affect gut microbiota and increase translocation.[37] Therefore, pharmacological regulation of the gut–liver axis may be an effective strategy for the prevention and management of NAFLD-related PHT, although this needs to be tested in randomized clinical trials.

2.6 | Genetic mechanisms

Inherited risk factors predisposing to NAFLD development in individuals with metabolic risk factors may directly contribute to fibrogenesis and PHT independently of their effect on hepatic fat accumulation.[38] In particular, the common rs738,409 polymorphism encoding for the p.I148M variant of *PNPLA3* accounts for a large fraction of the interindividual susceptibility to NAFLD in the population and is strongly enriched in patients with severe NAFLD and NASH.[39,40] Furthermore, the p.I148M *PNPLA3* variant has been identified as one of the main determinants of susceptibility to endothelial activation and inflammation.[41] Besides promoting intracellular fat accumulation in hepatocytes, PNPLA3 plays a key role in the trans-activation of HSCs,[42] and the *PNPLA3* variant triggers a pro-fibrogenic and pro-inflammatory phenotype in HSCs.[43,44] In keeping, carriage of the *PNPLA3* variant has been associated with the risk of decompensation in patients with PHT due to fatty liver disease.[45] These data suggest that a large fraction of patients with severe NAFLD may be predisposed to develop PHT due to genetic mechanisms.

3 | CHALLENGE IN THE DETECTION AND ASSESSMENT OF PHT

To assess the degree of PHT, PVP is traditionally measured by an invasive method like HVPG, which is costly and performed only in some specialized centers.[13] But there have been significant efforts to find novel diagnostic approaches for the assessment of PVP and replace traditional HVPG measurements, such as less invasive or noninvasive techniques, to indirectly estimate PVP (Figure 2). But none of these noninvasive techniques has entered clinical practice as a substitute for HVPG with the exception of endoscopic ultrasound-guided portal pressure gradient measurement (EUS-PPG).[46,47]

3.1 | Shortage and inaccuracy of conventional measurements

WHVP represents the hepatic sinusoid pressure, which indirectly reflects portal vein pressure in PHT.[13] Clinical signs of PHT may be present in about 25% of patients when patients have advanced fibrosis or cirrhosis.[6] However, a recent study involving 40 patients with NAFLD-related cirrhosis treated with a trans-jugular intrahepatic portosystemic shunt in three European centers showed discrepancies in the measurements of WHVP and portal pressure occurred in up to 15% of patients, thus suggesting that PVP could be significantly underestimated by WHVP. These data suggest that WHVP in patients with NAFLD-related cirrhosis is not as accurate as in cirrhotic patients; this is due to other etiologies.[14]

HVPG is defined as the difference between WHVP and FHVP, and can better reflect PVP.[13] As early as 2005, the Baveno IV consensus proposed that monitoring HVPG can identify the beneficiaries of nonselective beta-blockers.[48] The new Baveno VII consensus pointed out that HVPG ≥10 mmHg is still the gold standard for the diagnosis of CSPH.[13,49,50] This consensus also indicated that in patients with NAFLD-related cirrhosis, although an HVPG >10 mmHg is strongly associated with the presence of clinical signs of PHT such as esophageal varices,[51] these signs can also be present in a small proportion of patients with HVPG values <10 mmHg.[13] In an observational study investigating the prevalence and the noninvasive predictors of PHT in 354 patients with NAFLD, the authors found that signs of CSPH were present in about 25% of these patients at the time of diagnosis of NAFLD, and most of these patients had advanced fibrosis or cirrhosis. However, these authors also found that PHT could occur in a small proportion of patients with mild or no fibrosis, and was associated with the extent of steatosis.[6] A discrepancy was found between HVPG and PPG in noncirrhotic NAFLD.[14] A retrospective analysis showed that about 15% of patients with CSPH, whose HVPG was >10 mmHg, did not have cirrhosis.[7] In two phase 2b, placebo-controlled trials of simtuzumab (combined) that involved a total of 475 individuals with NASH with bridging fibrosis or compensated cirrhosis (F3–F4 stage), the authors found that seven patients with subclinical PHT (median HVPG: 7.5 mmHg; range: 4.0–9.5 mmHg) without cirrhosis developed the symptoms of decompensation, and patients with higher HVPG at baseline had the greater increase in HVPG over time.[52] All these observations suggest that HVPG may underestimate the fibrosis stage and severity of NAFLD. Actually, the effects and manifestations of subclinical PHT, which was defined as HVPG ≥5 mmHg and HVPG < 10 mmHg, on the natural course of NAFLD, are not well understood, and the effects of subclinical PHT may have been largely overlooked.[53] That said, measurements of WHVP and HVPG are invasive and require technical expertise from the operator and equipment. Thus, these measurements are rarely used in clinical practice.

3.2 | The novel invasive and noninvasive measurements

As shown in Figure 2, the EUS-PPG is one of the novel techniques that can directly measure the portal and hepatic vein pressure.[46] Theoretically, EUS-PPG is more accurate than WHVP and HVPG in patients with

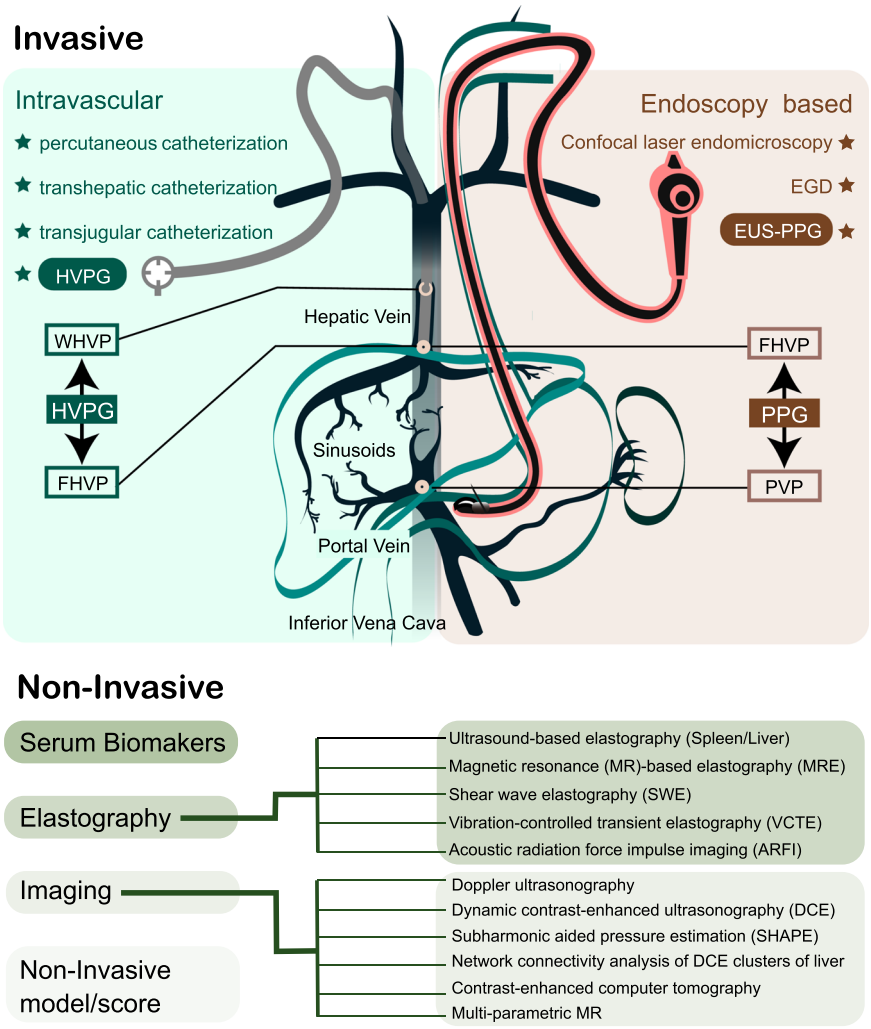

FIGURE 2 Old and new invasive and noninvasive methods for the assessment of PHT. Traditional methods (indicated by the blue area) include HVPG measurement, which uses a balloon-tipped central vein catheter inserted into a hepatic vein tributary that detects WHVP and FHVP. With the development of EDG technology (indicated by the red area), EUS-PPG is an emerging method to provide a safe and direct measurement of PPG. Analysis of mucosal vascular pattern and flow by confocal endomicroscopy is another novel method. Several noninvasive methods (indicated by the green area), for example, serum biomarkers, models or risk scores, tissue stiffness assessment of the liver, and spleen by elastography based on ultrasound or MR, are in development. EDG, endoscopy; EUS-PPG, endoscopic ultrasound-guided portal pressure gradient measurement; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; MR, magnetic resonance; PHT, portal hypertension; PPG, portal pressure gradient; PVP, portal venous pressure; WHVP, wedged hepatic venous pressure.

presinusoidal PHT because WHVP and HVPG tend to underestimate PVP in these patients. This ultrasound technique is suitable for patients with advanced NAFLD and for other patients with indications for endoscopy (e.g., surveillance of esophageal and gastric varices, portal hypertensive gastropathy screening, EUS-guided liver biopsy, or duodenal mucosal analysis by confocal endomicroscopy). Hence, other traditional techniques for portal pressure measurement that included intra-splenic puncture, trans-hepatic portal catheterization, operative portal pressure measurements, and umbilical vein catheterization are now being gradually replaced. Thus, novel noninvasive measurements that accurately measure PVP in a safe and simple way are urgently needed.[47] Novel noninvasive measurements such as serum markers,[54–59] the subharmonic-aided pressure estimation based, dynamic contrast-enhanced ultrasonography, liver and spleen stiffness elastography[60–65] based on recent doppler ultrasound and imaging technology,[66–70] contrast-enhanced computer tomography,[71,72] and multiparametric magnetic resonance imaging (MRI),[73,74] which require further investigation to test their utility in the investigation of PHT in NAFLD (Figure 2).

4 | CHALLENGE IN PREVENTION AND MANAGEMENT: THERE IS NO SPECIFIC THERAPY

To date, there are no specific pharmacotherapies for NAFLD-related PHT. In noncirrhotic NAFLD, prevention is usually the best therapeutic strategy, so lifestyle modifications are still the first-line recommended treatment.[51,75] In cirrhotic NAFLD-related PHT, current drugs used for management of PHT and its complications are substantially similar to those used for cirrhosis due to other etiologies, such as prevention of variceal bleeding by using nonselective beta-blockers or vasoconstrictor drugs, such as terlipressin, vasopressin, or octreotide.[13,49] However, these pharmacotherapies have

not been yet tested for management of PH in the early stages of NAFLD. Most drug candidates for PHT management in the early stages of NAFLD have only been tested in animal models.[76] However, there are some promising drugs for PHT in NAFLD as outlined below.

4.1 | NO modulation

It is known that NO plays an important role in the modulation of IHVR in liver sinusoids, thus NO modulation might be a promising therapeutic option in the early stage of NAFLD.[8] In a pilot human study, vardenafil, that is, an NO modulator that can prevent the breakdown of the NO mediator cyclic guanosine monophosphate, was found to reduce HVPG.[77] In an animal model in cirrhotic rats, portal pressure was decreased by the use of tetrahydrobiopterin and AVE9488, which increase NOS transcription or activity, respectively. NO modulation may inhibit HSC activation.[78,79] However, NO donors might cause hypotension due to the decrease in systemic vascular resistance.[80] Thus, clinical trials in patients are needed to prove its effect on PHT and to investigate side effects.

4.2 | Statins

Statins have been demonstrated to have some beneficial effects on steatosis, inflammation, and fibrosis in NAFLD.[81] Furthermore, statins may lower PVP in patients with cirrhosis and reduce the increased postprandial portal pressure.[81,82] Some studies have shown that simvastatin had a positive effect on decreasing PVP in NAFLD.[68] This effect in NAFLD might be partially due to the statins' function to modulate IHVR by enhancing eNOS expression, which may improve endothelial dysfunction, and reduce HSC contractility.[68] Moreover, statins have been also reported to reduce angiogenesis, which might also be beneficial for PHT.[83]

4.3 | Farnesoid-X nuclear receptor

FXR, as a modulator of IHVR in NAFLD, affects bile acid metabolism, lipid metabolism, inflammation, and fibrosis.[84] FXR agonists stimulate eNOS activity and inhibit the endothelin-1 (ET-1)-mediated contraction of HSCs.[85] Obeticholic acid is a promising steroidal FXR agonist, which may reduce PHT in rats by upregulating eNOS and rho-kinase.[86] Another nonsteroidal FXR agonist PX20606 may reduce PHT by improving liver sinusoidal cell dysfunction, fibrosis, and vascular remodeling.[87] In addition, obeticholic acid has been shown to reduce bacterial translocation and intestinal inflammation in cirrhotic rats with ascites.[88] Therefore, FXR is now emerging as a promising therapeutic target for reducing PHT in NAFLD. However, the precise biological mechanisms of FXR-induced reduction of liver fibrosis need to be further explored.

4.4 | Peroxisome proliferator-activated receptor (PPAR) agonists

PPAR agonists play a key role in fatty acid and lipid metabolism, inflammation, and fibrogenesis. Promising agents such as pan-PPAR agonist (lanifibranor) showed some beneficial effects on liver fibrosis.[89–91] Moreover, the PPAR-α agonist fenofibrate could reduce PVP in cirrhotic rats by improving endothelial function mainly through increased NO bioavailability and reduced leukocyte recruitment.[92] However, further research is needed to examine the efficacy of PPAR agonists on PHT in humans.

5 | CONCLUSIONS AND FUTURE PERSPECTIVES

PHT is the underlying cause of many liver-related complications that drive poor clinical outcomes. With the potential pathophysiological significance of increased PVP in NAFLD indicating that PHT may promote NAFLD/NASH fibrosis progression and vice versa, it is clinically important to find noninvasive and accurate methods that allow early detection and monitoring of PHT. The role of metabolic risk factors in the pathogenesis of PHT in the early stages of NAFLD is poorly studied and is worth further exploration. Likewise, we believe that the recently proposed change in the nomenclature from NAFLD to metabolic-dysfunction associated fatty liver disease (MAFLD) may help to better understand the role of metabolic risk factors in PHT and facilitate new drug development to reduce PVP and fibrosis in patients with NAFLD, possibly through the improvement of multiple metabolic pathways.

AUTHOR CONTRIBUTIONS

Conception and design: Lei Miao, Ming-Hua Zheng, and Xiaolong Qi. *Collection and assembly of articles*: Lei Miao. *Manuscript writing, intellectual input, critical evaluation, proofreading, and final approval of the manuscript*. All authors.

ACKNOWLEDGMENT

This study was supported by grants from the National Natural Science Foundation of China (No. 82070588), High Level Creative Talents from the Department of Public Health in Zhejiang Province (No. S20321026 00032), Project of New Century 551 Talent Nurturing in Wenzhou. G. T. is supported in part by grants from the University School of Medicine of Verona, Verona, Italy. C. D. B is supported in part by the Southampton NIHR Biomedical Research Centre (IS-BRC-20004), United Kingdom. This study is a part of the PERSONS study. L. V. is supported by the Italian Ministry of Health (Ministero della Salute), Ricerca Finalizzata RF-2016-02364358, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Ricerca corrente, “Liver BIBLE” (PR-0391), Innovative Medicines Initiative 2 joint undertaking of European Union's Horizon 2020 research, and innovation programme and EFPIA European Union

(EU) Programme Horizon 2020 (under grant agreement No. 777377) for the project LITMUS, the European Union, programme "Photonics" under grant agreement "101016726."

CONFLICTS OF INTEREST

Xiaolong Qi is the Editor-in-Chief and Ming-Hua Zheng is the Editorial Board Member of *Portal Hypertension & Cirrhosis*. They are, therefore, excluded from the peer-review process and all editorial decisions related to the publication of this manuscript. The remaining authors declare that there are no conflict of interest.

ORCID

Xiaolong Qi http://orcid.org/0000-0002-3559-5855
Ming-Hua Zheng http://orcid.org/0000-0003-4984-2631

REFERENCES

1. Younossi Z, Koenig A, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84. doi:10.1002/hep.28431
2. Younossi ZA. Non-alcoholic fatty liver disease—a global public health perspective. *J Hepatol*. 2019;70:531-544. doi:10.1016/j.jhep.2018.10.033
3. Le MH, Yeo YH, Li X, et al. 2019 global NAFLD prevalence: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;S1542-3565:1280-1285. doi:10.1016/j.cgh.2021.12.002
4. Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *Lancet*. 2021;397:2212-2224. doi:10.1016/s0140-6736(20)32511-3
5. Goh GBB, McCullough AJ. Natural history of nonalcoholic fatty liver disease. *Dig Dis Sci*. 2016;61:1226-1233. doi:10.1007/s10620-016-4095-4
6. Mendes F, Suzuki A, Sanderson S, Lindor K, Angulo P. Prevalence and indicators of portal hypertension in patients with non-alcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2012;10(9):1028–1033.e2. doi:10.1016/j.cgh.2012.05.008
7. Rodrigues SG, Montani M, Guixé-Muntet S, De Gottardi A, Berzigotti A, Bosch J. Patients with signs of advanced liver disease and clinically significant portal hypertension do not necessarily have cirrhosis. *Clin Gastroenterol Hepatol*. 2019;17(10):2101–2109.e1. doi:10.1016/j.cgh.2018.12.038
8. Pasarín M, La Mura V, Gracia-Sancho J, et al. Sinusoidal endothelial dysfunction precedes inflammation and fibrosis in a model of NAFLD. *PLoS One*. 2012;7:e32785. doi:10.1371/journal.pone.0032785
9. Sourianarayanane A, Talluri J, Humar A, McCullough A. Stage of fibrosis and portal pressure correlation in nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol*. 2017;29:516-523. doi:10.1097/meg.0000000000000825
10. Cremonese C, Schierwagen R, Uschner FE, et al. Short-term western diet aggravates non-alcoholic fatty liver disease (NAFLD) with portal hypertension in TGR(mREN2)27 rats. *Int J Mol Sci*. 2020;21:3308. doi:10.3390/ijms21093308
11. Bravo M, Raurell I, Hide D, et al. Restoration of liver sinusoidal cell phenotypes by statins improves portal hypertension and histology in rats with NASH. *Sci Rep*. 2019;9:20183. doi:10.1038/s41598-019-56366-2
12. Hilscher MB, Sehrawat T, Arab JP, et al. Mechanical stretch increases expression of CXCL1 in liver sinusoidal endothelial cells to recruit neutrophils, generate sinusoidal microthombi, and promote portal hypertension. *Gastroenterology*. 2019;157(1):193-209.e9. doi:10.1053/j.gastro.2019.03.013
13. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII—renewing consensus in portal hypertension. *J Hepatol*. 2021;76:959-974. doi:10.1016/j.jhep.2021.12.022
14. Ferrusquía-Acosta J, Bassegoda O, Turco L, et al. Agreement between wedged hepatic venous pressure and portal pressure in non-alcoholic steatohepatitis-related cirrhosis. *J Hepatol*. 2021;74:811-818. doi:10.1016/j.jhep.2020.10.003
15. Bassegoda O, Olivas P, Turco L, et al. Decompensation in advanced nonalcoholic fatty liver disease may occur at lower hepatic venous pressure gradient levels than in patients with viral disease. *Clin Gastroenterol Hepatol*. 2021;S1542-3565:1136-1138. doi:10.1016/j.cgh.2021.10.023
16. Hirooka M, Koizumi Y, Miyake T, et al. Nonalcoholic fatty liver disease: portal hypertension due to outflow block in patients without cirrhosis. *Radiology*. 2015;274:597-604. doi:10.1148/radiol.14132952
17. Iwakiri Y, Shah V, Rockey D. Vascular pathobiology in chronic liver disease and cirrhosis – Current status and future directions. *J Hepatol*. 2014;61:912-924. doi:10.1016/j.jhep.2014.05.047
18. Luci C, Bourinet M, Leclère PS, Anty R, Gual P. Chronic inflammation in non-alcoholic steatohepatitis: molecular mechanisms and therapeutic strategies. *Front Endocrinol (Lausanne)*. 2020;11:597648. doi:10.3389/fendo.2020.597648
19. Rangwala F, Guy CD, Lu J, et al. Increased production of sonic hedgehog by ballooned hepatocytes. *J Pathol*. 2011;224:401-410. doi:10.1002/path.2888
20. Coulon S, Francque S, Colle I, et al. Evaluation of inflammatory and angiogenic factors in patients with non-alcoholic fatty liver disease. *Cytokine*. 2012;59:442-449. doi:10.1016/j.cyto.2012.05.001
21. Gonzalez-Paredes FJ, Hernández Mesa G, Morales Arraez D, et al. Contribution of cyclooxygenase end products and oxidative stress to intrahepatic endothelial dysfunction in early non-alcoholic fatty liver disease. *PLoS One*. 2016;11:e0156650. doi:10.1371/journal.pone.0156650
22. Francque S, Laleman W, Verbeke L, et al. Increased intrahepatic resistance in severe steatosis: endothelial dysfunction, vasoconstrictor overproduction and altered microvascular architecture. *Lab Invest*. 2012;92:1428-1439. doi:10.1038/labinvest.2012.103
23. Gracia-Sancho J, Caparrós E, Fernández-Iglesias A, Francés R. Role of liver sinusoidal endothelial cells in liver diseases. *Nat Rev Gastroenterol Hepatol*. 2021;18:411-431. doi:10.1038/s41575-020-00411-3
24. Friedman S. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev*. 2008;88:125-172. doi:10.1152/physrev.00013.2007
25. Baffy G. Kupffer cells in non-alcoholic fatty liver disease: the emerging view. *J Hepatol*. 2009;51:212-223. doi:10.1016/j.jhep.2009.03.008
26. Maher JJ, Leon P, Ryan JC. Beyond insulin resistance: innate immunity in nonalcoholic steatohepatitis. *Hepatology*. 2008;48:670-678. doi:10.1002/hep.22399
27. Miyao M, Kotani H, Ishida T, et al. Pivotal role of liver sinusoidal endothelial cells in NAFLD/NASH progression. *Lab Invest*. 2015;95:1130-1144. doi:10.1038/labinvest.2015.95
28. Hammoutene A, Rautou PE. Role of liver sinusoidal endothelial cells in non-alcoholic fatty liver disease. *J Hepatol*. 2019;70:1278-1291. doi:10.1016/j.jhep.2019.02.012
29. Shao Y, Wang K, Xiong X, et al. The landscape of interactions between hypoxia-inducible factors and reactive oxygen species in the gastrointestinal tract. *Oxid Med Cell Longev*. 2021;2021:8893663-8893669. doi:10.1155/2021/8893663
30. Kietzmann T, Görlach A. Reactive oxygen species in the control of hypoxia-inducible factor-mediated gene expression. *Semin Cell Dev Biol*. 2005;16:474-486. doi:10.1016/j.semcdb.2005.03.010
31. Li S, Fujino M, Takahara T, Li X. Protective role of heme oxygenase-1 in fatty liver ischemia-reperfusion injury. *Med Mol Morphol*. 2019;52:61-72. doi:10.1007/s00795-018-0205-z
32. Kumar S, Duan Q, Wu R, Harris E, Su Q. Pathophysiological communication between hepatocytes and non-parenchymal cells in liver injury from NAFLD to liver fibrosis. *Adv Drug Deliv Rev*. 2021;176:113869. doi:10.1016/j.addr.2021.113869
33. McCuskey RS. Morphological mechanisms for regulating blood flow through hepatic sinusoids. *Liver*. 2000;20:3-7. doi:10.1034/j.1600-0676.2000.020001003.x
34. Verrijken A, Francque S, Mertens I, et al. Prothrombotic factors in histologically proven nonalcoholic fatty liver disease and

nonalcoholic steatohepatitis. *Hepatology*. 2014;59:121-129. doi:10.1002/hep.26510
35. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol*. 2016;13:412-425. doi:10.1038/nrgastro.2016.85
36. Aron-Wisnewsky J, Vigliotti C, Witjes J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat Reviews Gastroenterol Hepatol*. 2020;17:279-297. doi:10.1038/s41575-020-0269-9
37. Arab J, Martin-Mateos R, Shah V. Gut-liver axis, cirrhosis and portal hypertension: the chicken and the egg. *Hepatol Int*. 2018;12:24-33. doi:10.1007/s12072-017-9798-x
38. Trépo E, Valenti L. Update on NAFLD genetics: from new variants to the clinic. *J Hepatol*. 2020;72:1196-1209. doi:10.1016/j.jhep.2020.02.020
39. Bianco C, Jamialahmadi O, Pelusi S, et al. Non-invasive stratification of hepatocellular carcinoma risk in non-alcoholic fatty liver using polygenic risk scores. *J Hepatol*. 2021;74:775-782. doi:10.1016/j.jhep.2020.11.024
40. Jamialahmadi O, Bianco C, Pelusi S, Romeo S, Valenti L. Reply to: "polygenic risk score: a promising predictor for hepatocellular carcinoma in the population with non-alcoholic fatty liver disease". *J Hepatol*. 2021;74:1494-1496. doi:10.1016/j.jhep.2021.02.030
41. Paré G, Ridker PM, Rose L, et al. Genome-wide association analysis of soluble ICAM-1 concentration reveals novel associations at the NFKBIK, PNPLA3, RELA, and SH2B3 loci. *PLoS Genet*. 2011;7:e1001374. doi:10.1371/journal.pgen.1001374
42. Pirazzi C, Valenti L, Motta BM, et al. PNPLA3 has retinyl-palmitate lipase activity in human hepatic stellate cells. *Hum Mol Genet*. 2014;23:4077-4085. doi:10.1093/hmg/ddu121
43. Pingitore P, Dongiovanni P, Motta BM, et al. PNPLA3 overexpression results in reduction of proteins predisposing to fibrosis. *Hum Mol Genet*. 2016;25:5212-5222. doi:10.1093/hmg/ddw341
44. Bruschi FV, Claudel T, Tardelli M, et al. The PNPLA3 I148M variant modulates the fibrogenic phenotype of human hepatic stellate cells. *Hepatology*. 2017;65:1875-1890. doi:10.1002/hep.29041
45. Mandorfer M, Scheiner B, Stättermayer AF, et al. Impact of patatin-like phospholipase domain containing 3 rs738409 G/G genotype on hepatic decompensation and mortality in patients with portal hypertension. *Aliment Pharmacol Ther*. 2018;48:451-459. doi:10.1111/apt.14856
46. Bazarbashi A, Ryou M. Portal pressure measurement: have we come full circle? *Gastrointest Endosc*. 2021;93:573-576. doi:10.1016/j.gie.2020.08.007
47. Zhou Y, Wong V, Zheng M. Consensus scoring systems for nonalcoholic fatty liver disease: an unmet clinical need. *Hepatobiliary Surg Nutr*. 2021;10:388-390. doi:10.21037/hbsn-21-80
48. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2005;43:167-176. doi:10.1016/j.jhep.2005.05.009
49. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743-752. doi:10.1016/j.jhep.2015.05.022
50. Bosch J, Iwakiri Y. The portal hypertension syndrome: etiology, classification, relevance, and animal models. *Hepatol Int*. 2018;12:1-10. doi:10.1007/s12072-017-9827-9
51. Zheng KI, Liu C, Li J, et al. Validation of Baveno VI and expanded Baveno VI criteria to identify high-risk varices in patients with MAFLD-related compensated cirrhosis. *J Hepatol*. 2020;73:1571-1573. doi:10.1016/j.jhep.2020.06.042
52. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology*. 2019;70:1913-1927. doi:10.1002/hep.30664
53. Baffy G, Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: is it real and how to measure it? *J Hepatol*. 2022;76:458-463. doi:10.1016/j.jhep.2021.09.029
54. Tang LJ, Ma HL, Eslam M, et al. Among simple non-invasive scores, Pro-C3 and ADAPT best exclude advanced fibrosis in Asian patients with MAFLD. *Metabolism*. 2022;128:154958. doi:10.1016/j.metabol.2021.154958
55. Ferlitsch M, Reiberger T, Hoke M, et al. von Willebrand factor as new noninvasive predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis. *Hepatology*. 2012;56:1439-1447. doi:10.1002/hep.25806
56. Pind M, Bendtsen F, Kallemose T, Møller S. Indocyanine green retention test (ICG-r15) as a noninvasive predictor of portal hypertension in patients with different severity of cirrhosis. *Eur J Gastroenterol Hepatol*. 2016;28:948-954. doi:10.1097/meg.0000000000000611
57. Sandahl TD, McGrail R, Møller HJ, et al. The macrophage activation marker sCD163 combined with markers of the enhanced liver fibrosis (ELF) score predicts clinically significant portal hypertension in patients with cirrhosis. *Aliment Pharmacol Ther*. 2016;43:1222-1231. doi:10.1111/apt.13618
58. Leeming DJ, Veidal SS, Karsdal MA, et al. Pro-C5, a marker of true type V collagen formation and fibrillation, correlates with portal hypertension in patients with alcoholic cirrhosis. *Scand J Gastroenterol*. 2015;50:584-592. doi:10.3109/00365521.2014.996590
59. Wang L, Feng Y, Ma X, et al. Diagnostic efficacy of noninvasive liver fibrosis indexes in predicting portal hypertension in patients with cirrhosis. *PLoS One*. 2017;12:e0182969. doi:10.1371/journal.pone.0182969
60. Valente G, Rinaldi L, Moggio G, Piai G. Point shear wave elastography and vibration controlled transient elastography for estimating liver fibrosis in a cohort of liver transplant patients. *Eur Rev Med Pharmacol Sci*. 2020;24:7357-7365. doi:10.26355/eurrev_202007_21903
61. Song J, Ma Z, Huang J, et al. Reliability of transient elastography-based liver stiffness for diagnosing portal hypertension in patients with alcoholic liver disease: a diagnostic meta-analysis with specific cut-off values. *Ultraschall Med*. 2020;41:60-68. doi:10.1055/a-0731-0178
62. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol*. 2017;67:399-411. doi:10.1016/j.jhep.2017.02.003
63. Elkrief L, Ronot M, Andrade F, et al. Non-invasive evaluation of portal hypertension using shear-wave elastography: analysis of two algorithms combining liver and spleen stiffness in 191 patients with cirrhosis. *Aliment Pharmacol Ther*. 2018;47:621-630. doi:10.1111/apt.14488
64. Takuma Y, Nouso K, Morimoto Y, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. *Radiology*. 2016;279:609-619. doi:10.1148/radiol.2015150690
65. Hu X, Huang X, Hou J, Ding L, Su C, Meng F. Diagnostic accuracy of spleen stiffness to evaluate portal hypertension and esophageal varices in chronic liver disease: a systematic review and meta-analysis. *Eur Radiol*. 2021;31:2392-2404. doi:10.1007/s00330-020-07223-8
66. Gupta I, Eisenbrey JR, Machado P, et al. Diagnosing portal hypertension with noninvasive subharmonic pressure estimates from a US contrast agent. *Radiology*. 2021;298:104-111. doi:10.1148/radiol.2020202677
67. Berzigotti A, Reverter E, García-Criado A, et al. Reliability of the estimation of total hepatic blood flow by Doppler ultrasound in patients with cirrhotic portal hypertension. *J Hepatol*. 2013;59:717-722. doi:10.1016/j.jhep.2013.04.037
68. Ayoola O, Bolarinwa R, Aderibigbe A, Onigbinde S, Oguntade B. Portal hypertension evolving from sickled hepatopathy: Could hepatic venous Doppler ultrasound be beneficial in its evaluation? *Med Hypotheses*. 2020;135:109450. doi:10.1016/j.mehy.2019.109450
69. Qi X, Berzigotti A, Cardenas A, Sarin S. Emerging non-invasive approaches for diagnosis and monitoring of portal hypertension. *Lancet Gastroenterol Hepatol*. 2018;3:708-719. doi:10.1016/s2468-1253(18)30232-2
70. Bolognesi M, Di Pascoli M, Sacerdoti D. Clinical role of non-invasive assessment of portal hypertension. *World J Gastroenterol*. 2017;23:1-10. doi:10.3748/wjg.v23.i1.1

71. Lee DH, Ahn JH, Chung JW, et al. Varices on computed tomography are surrogate of clinically significant portal hypertension and can predict survival in compensated cirrhosis patients. *J Gastroenterol Hepatol*. 2019;34:450-457. doi:10.1111/jgh.14319
72. Qi X, Li Z, Huang J, et al. Virtual portal pressure gradient from anatomic CT angiography. *Gut*. 2015;64:1004-1005. doi:10.1136/gutjnl-2014-308543
73. Singh R, Wilson M, Katlariwala P, Murad M, McInnes M, Low G. Accuracy of liver and spleen stiffness on magnetic resonance elastography for detecting portal hypertension: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2021;32:237-245. doi:10.1097/meg.0000000000001724
74. Palaniyappan N, Cox E, Bradley C, et al. Non-invasive assessment of portal hypertension using quantitative magnetic resonance imaging. *J Hepatol*. 2016;65:1131-1139. doi:10.1016/j.jhep.2016.07.021
75. Eslam M, Sarin SK, Wong VW, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int*. 2020;14:889-919. doi:10.1007/s12072-020-10094-2
76. Miao L, Xu J, Targher G, Byrne C, Zheng M. Old and new classes of glucose-lowering agents as treatments for non-alcoholic fatty liver disease: a narrative review. *Clin Mol Hepatol*. 2022. doi:10.3350/cmh.2022.0015
77. Deibert P, Schumacher YO, Ruecker G, et al. Effect of vardenafil, an inhibitor of phosphodiesterase-5, on portal haemodynamics in normal and cirrhotic liver—results of a pilot study. *Aliment Pharmacol Ther*. 2006;23:121-128. doi:10.1111/j.1365-2036.2006.02735.x
78. Biecker E, Trebicka J, Kang A, Hennenberg M, Sauerbruch T, Heller J. Treatment of bile duct-ligated rats with the nitric oxide synthase transcription enhancer AVE 9488 ameliorates portal hypertension. *Liver Int*. 2008;28:331-338. doi:10.1111/j.1478-3231.2008.01664.x
79. Bosch J, Groszmann R, Shah V. Evolution in the understanding of the pathophysiological basis of portal hypertension: how changes in paradigm are leading to successful new treatments. *J Hepatol*. 2015;62:S121-S130. doi:10.1016/j.jhep.2015.01.003
80. Farah C, Michel LYM, Balligand JL. Nitric oxide signalling in cardiovascular health and disease. *Nat Rev Cardiol*. 2018;15:292-316. doi:10.1038/nrcardio.2017.224
81. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. *J Hepatol*. 2015;63:705-712. doi:10.1016/j.jhep.2015.05.006
82. Pollo-Flores P, Soldan M, Santos UC, et al. Three months of simvastatin therapy *vs.* placebo for severe portal hypertension in cirrhosis: a randomized controlled trial. *Dig Liver Dis*. 2015;47:957-963. doi:10.1016/j.dld.2015.07.156
83. Chang CC, Wang SS, Hsieh HG, et al Rosuvastatin improves hepatopulmonary syndrome through inhibition of inflammatory angiogenesis of lung. *Clin Sci (Lond)*. 2015;129:449-460. doi:10.1042/cs20140622
84. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385:956-965. doi:10.1016/s0140-6736(14)61933-4
85. Li J, Kuruba R, Wilson A, Gao X, Zhang Y, Li S. Inhibition of endothelin-1-mediated contraction of hepatic stellate cells by FXR ligand. *PLoS One*. 2010;5:e13955. doi:10.1371/journal.pone.0013955
86. Verbeke L, Farre R, Trebicka J, et al. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats. *Hepatology*. 2014;59:2286-2298. doi:10.1002/hep.26939
87. Schwabl P, Hambruch E, Seeland BA, et al. The FXR agonist PX20606 ameliorates portal hypertension by targeting vascular remodelling and sinusoidal dysfunction. *J Hepatol*. 2017;66:724-733. doi:10.1016/j.jhep.2016.12.005
88. Úbeda M, Lario M, Muñoz L, et al. Obeticholic acid reduces bacterial translocation and inhibits intestinal inflammation in cirrhotic rats. *J Hepatol*. 2016;64:1049-1057. doi:10.1016/j.jhep.2015.12.010
89. Han X, Wu Y, Yang Q, Cao G. Peroxisome proliferator-activated receptors in the pathogenesis and therapies of liver fibrosis. *Pharmacol Ther*. 2021;222:107791. doi:10.1016/j.pharmthera.2020.107791
90. Francque S, Szabo G, Abdelmalek MF, et al. Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors. *Nat Rev Gastroenterol Hepatol*. 2021;18:24-39. doi:10.1038/s41575-020-00366-5
91. Ratziu V, Harrison SA, Francque S, et al Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. *Gastroenterology*. 2016;150(5):1147–1159. doi:10.1053/j.gastro.2016.01.038
92. Rodríguez-Vilarrupla A, Laviña B, García-Calderó H, et al. PPARα activation improves endothelial dysfunction and reduces fibrosis and portal pressure in cirrhotic rats. *J Hepatol*. 2012;56:1033-1039. doi:10.1016/j.jhep.2011.12.008

How to cite this article: Miao L, Targher G, Byrne CD, Valenti L, Qi X, Zheng M-H. Portal hypertension in nonalcoholic fatty liver disease: challenges and perspectives. *Port Hypertens Cirrhos*. 2022;1:57-65. doi:10.1002/poh2.8