Editorial Commentary

Managing portal hypertension in patients with liver cirrhosis and hepatocellular carcinoma: non-invasive diagnosis and systemic treatment considerations

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Comment on: Thabut D, Kudo M. Treatment of portal hypertension in patients with HCC in the era of Baveno VII. J Hepatol 2023;78:658-62.

Keywords: Portal hypertension (PH); hepatocellular carcinoma (HCC); elastography; bevacizumab; variceal bleeding

Submitted Oct 21, 2023. Accepted for publication Nov 02, 2023. Published online Nov 09, 2023.
doi: 10.21037/hbsn-23-551
View this article at: https://dx.doi.org/10.21037/hbsn-23-551

Portal hypertension (PH) represents a crucial complication of liver cirrhosis that significantly impacts a patient's prognosis. Controlling portal venous pressure requires a combination of medical and interventional treatments. However, it's important to note that the presence of other conditions in patients, such as hepatocellular carcinoma (HCC), can influence the treatment approaches for PH and subsequently affect the overall outcomes. Clinicians should consider that condition when developing treatment strategies to enhance patient outcomes (1).

The increased life expectancy of patients with PH, as a result of reduced complications of decompensated liver cirrhosis due to improved PH management, may have contributed to the relative increase in HCC incidence. However, the aggravation of PH and bleeding risk as a side effect of recent advances in the systemic therapy of HCC must also be considered before the treatment. The Baveno consensus was first held in 1986 and publishes consensus statements that play an important role in the management of PH and its complications. In the recent workshop held in 2021, it covered various aspects of managing patients with compensated advanced chronic liver disease (cACLD) and clinically significant PH (CSPH) (2). Significantly, the guidelines provide consensus statements regarding the treatment of PH in individuals with HCC, including strategies to prevent decompensation and how to manage PH when it is associated with portal venous tumor thrombosis (3).

Non-invasive diagnosis and monitoring of PH

In the past, the assessment of portal venous pressure primarily relied on the measurement of hepatic venous pressure gradient (HVPG) to directly gauge intrasinusoidal pressure and monitor the development of varices. While HVPG remains a widely accepted gold standard, the contemporary approach to non-invasively diagnosing PH in cACLD patients encompasses diagnostic methods that eliminate the need for invasive procedures such as repetitive endoscopy or HVPG measurement.

The term "cACLD" means the spectrum of severe fibrosis and cirrhosis in patients with ongoing chronic liver disease. A practical definition of cACLD, based on liver stiffness measurement (LSM) under non-invasive diagnosis of liver fibrosis and PH, helps to assess the risk of CSPH and decompensation in a point-of-care manner regardless of histological stage or the ability of LSM to pinpoint the fibrosis stages.

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A "rule of 5" based on LSM by transient elastography (10-15-20-25 kPa) can indicate increasing risks of decompensation and liver-related mortality regardless of the underlying cause of chronic liver disease. Gray zones exist for cACLD (10–15 kPa) and CSPH (20–25 kPa), where gastroscopy to detect esophageal varices is recommended, following Baveno VII guidelines (2). The acoustic radiation force impulse technique, including point shear wave elastography (SWE) and 2D-SWE, demonstrates comparable accuracy in predicting decompensation (4,5). However, it faces challenges due to varying threshold values across different ultrasound equipment from different manufacturers (6).

Non-invasive diagnosis of PH offers a significant benefit by simplifying the process of monitoring PH progression through longitudinal LSM. This longitudinal assessment of LSM in individuals with PH carries crucial clinical significance (7). PH is frequently linked to chronic liver conditions and is dynamic, making the condition vulnerable to severe complications such as variceal bleeding and ascites (8). Therefore, the ability to continuously track changes in liver stiffness over time, achieved through the elastography technique empowers clinicians to evaluate disease progression and assess the effectiveness of treatment.

When LSM exceeds 25 kPa as determined by transient elastography, this is indicative of CSPH. In such cases, beta-blockers are recommended for primary prevention, regardless of whether esophageal varices have been confirmed through endoscopy. This approach is also applicable to patients with HCC. In addition to beta-blockers, carvedilol is considered a preferred treatment for the primary prevention of decompensation related to PH (3). For patients who cannot undergo surgical and locoregional treatments due to refractory ascites or decompensated liver cirrhosis, the consideration of transjugular intrahepatic portosystemic shunt (TIPS) is justified. However, it is important to mention that the use of TIPS for this particular purpose is not very common in Korea.

PH with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs)

TKIs target the vascular endothelial growth factor (VEGF) receptor and can potentially affect PH. Nevertheless, TKIs can cause ascites but do not increase the risk of bleeding; however, the combination of atezolizumab and bevacizumab increases the risk of bleeding compared to sorafenib (9). Bevacizumab is an antibody that targets VEGF, which increases the risk of bleeding due to inhibition of wound healing and increased PH. ICIs do not increase the risk of bleeding. Portal vein obstruction can increase the risk of acute variceal bleeding.

It is essential to thoroughly evaluate PH before initiating atezolizumab/bevacizumab treatment for patients not already on primary prophylaxis. Beta-blockers should be initiated as necessary. Surveillance should be more frequent, possibly with endoscopies every six months. The need for these recommendations with new immune checkpoint therapies without bevacizumab remains uncertain. In cases of a history of acute variceal bleeding, these new ICI regimens may be preferred. After variceal banding for primary prophylaxis, a delay of two weeks (for post-banding ulcer healing) before starting atezolizumab/bevacizumab therapy is considered reasonable.

Although the patients in curative anticoagulation have been excluded from IMbrave 150 study (9), it is recommended to keep it because there was no evidence that anticoagulation causes bleeding when using drugs other than bevacizumab, and using bevacizumab for treatment of malignancies of other organs, anticoagulation therapy is not a contraindication (3). For patients who have undergone banding, they recommended prioritizing low-molecular-weight heparin rather than oral anticoagulants.

In conclusion, the review paper by Thabut and Kudo emphasizes the importance of non-invasive diagnosis of PH in patients with both HCC and liver cirrhosis. When selecting systemic treatments for HCC, such as TKIs and ICIs, it's crucial to assess their effects on PH and bleeding risks. Notably, the authors exaggerate the need for caution when considering bevacizumab due to its potential to increase the risk of bleeding. A comprehensive approach to managing PH and its interactions with other medical conditions is indispensable for improving patient outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://hbsn.

amegroups.com/article/view/10.21037/hbsn-23-551/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Jeong WK. Managing portal hypertension in patients with liver cirrhosis and hepatocellular carcinoma: non-invasive diagnosis and systemic treatment considerations. HepatoBiliary Surg Nutr 2023;12(6):960-962. doi: 10.21037/hbsn-23-551