Editorial Commentary

Relationship between portal hypertension and liver stiffness measurements in the treatment of hepatocellular carcinoma from the surgeon's point of view in the Baveno VII era

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide (1). It often arises from the backgrounds of damaged liver due to viral hepatitis, alcoholic, or non-alcoholic liver disease. Although the proportion of patients with HCC of non-hepatitis B and C origins has increased in recent years, hepatitis B and C viruses still cause more than half of all carcinogenesis in patients with HCC (2). Patients with HCC often develop portal hypertension (PHT) from cirrhosis due to the deterioration of the background liver, which proves to be the greatest obstacle to various types of treatments for HCC. The results of the latest consensus meeting to improve the understanding of PHT and disseminate evidence on its diagnosis, natural history, and treatment were published in 2022 as Baveno VII (3). Baveno VII updated the diagnostic criteria for PHT and the definition of clinically significant portal hypertension (CSPH) indicated non-invasive screening for PHT and management of CSPH. However, Baveno VII did not mention PHT associated with HCC. Thabut and Kudo reviewed and recommended the management of PHT in patients with HCC based on the latest data and Baveno VII (4). We respect their work and reviewed their reports with great interest. As hepatologists involved in the daily practice for HCC and as hepatic surgeons, we would like to make a few comments on their report on hepatectomy and PHT in the era of Baveno VII.

In the Baveno VII consensus, patients with CSPH are recommended to receive prophylactic beta-blockers to prevent worsening of PHT and its associated complications, regardless of the esophago-gastric varix status. Although CSPH is defined as a hepatic venous pressure gradient (HVPG) >10 mmHg as the gold standard, liver stiffness measurement (LSM) using the transient elastography is recommended as a non-invasive alternative in clinical practice. LSM ≤10 kPa in the absence of other clinical/image signs can rule out compensated advanced chronic liver disease, while LSM ≤15 kPa plus platelet count ≥150×10^9/L ($150,000/mm^3$) can rule out CSPH with a sensitivity and negative predictive value of >90% (3). Baveno VII omitted the indications for screening endoscopy in this category of patients. Contrasting with Baveno VII, Thabut and Kudo recommend screening endoscopy in patients with HCC, even in those with platelet count ≥$150,000/mm^3$ and LSM ≤15 kPa, considering that the criteria do not always rule out high-risk varices accurately. However, they agreed with Baveno VII in avoiding upper gastrointestinal endoscopy in HCC patients with LSM >25 kPa receiving beta-blockers,

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regardless of the esophageal variceal status. It is now widely recognized that beta-blockers, especially non-selective beta-blockers, reduce HCC-related mortality (5). They also argued that HCC patients with PHT should be monitored regularly, including the use of upper gastrointestinal endoscopies, since PHT may progress faster due to the occurrence of vascular invasion or worsening liver disease from HCC and its corresponding therapies (6). According to the report of the IMbrave 150 study, bleeding events occurred more frequently in the combination treatment with atezolizumab and bevacizumab group compared to the sorafenib group, even in well-selected patients (high-risk patients who developed PHT-related bleeding within six months before treatment were excluded) (7). Considering the increased bleeding risk associated with Bevacizumab use (8), Thabut and Kudo recommended a strict work-up of PHT before starting treatment with atezolizumab and bevacizumab in all patients and periodic surveillance more frequently than that recommended in patients without systemic therapy. They stated that, in their personal opinion, other regimens may be favored for patients with a history of bleeding from esophageal varices (4).

LSM by transient elastography is an excellent non-invasive and accurate diagnosis of cirrhosis (9). From the perspective of hepatic surgeons who perform surgery for HCC occasionally with PHT, several reports have suggested that LSM measurement can be useful in predicting complications and liver failure after hepatectomy (10-14). Kim *et al.* first showed the relationship between liver stiffness and postoperative liver failure (total bilirubin level >5 mg/dL for more than five days after surgery or postoperative death) and proposed a LSM cutoff value of 25.6 kPa (10). Cescon *et al.* suggested the cut-off value of LSM ≥15.7 kPa predicting the postoperative liver failure, which was mainly defined as: the occurrence of refractory ascites causing a delay in the removal of the drainage; an increase of bilirubin levels of more than 3 mg/dL; alteration of coagulation factors requiring fresh frozen plasma infusion, renal impairment, etc. (11). Furthermore, other researchers suggested the LSM cut-of values predicting postoperative liver failure according to the International Study Group of Liver Surgery definition (15) as 9.5–12 kPa (12-14). Rajakannu *et al.* defined persistent postoperative hepatic decompensation (PHD) as unresolved ascites, jaundice, and/or encephalopathy within three months after surgery and reported that LSM ≥22 kPa was strongly correlated with the occurrence of PHD (16). Although the cut-off values of LSM are variable and patient backgrounds differ in each report, it is certain that LSM measurement is useful in predicting the development of complications after hepatic resection.

Our group has long argued that patients with HCC and PHT can undergo hepatic resection if the indication is carefully determined, and the complications associated with PHT are managed (17,18). However, the Barcelona Clinic Liver Cancer (BCLC) and other Western groups maintain that PHT is not an indication for hepatectomy (19). Although CSPH is defined as HVPG >10 mmHg, a strong correlation between HVPG and liver stiffness has been reported, and several reports on LSM values and the presence of CSPH have predicted LSM cut-off values of CSPH as 13.6–21.1 kPa (11,20-22). Robic *et al.* stated that LSM can help avoid unnecessary invasive hepatic vein catheterization and/or endoscopic screening or CSPH since LSM shows a strong correlation with HVPG (22), while Llop *et al.* reported that HVPG is still a non-replaceable method in detecting CSPH because. This is demonstrated in their validation report for each criterion, wherein LSM <13.6 kPa may have a high sensitivity but a low specificity, and LSM >21 kPa with a high specificity but a low sensitivity (23). Several studies have shown a relationship between indocyanine green (ICG) retention test and LSM. Fung *et al.* reviewed 44 liver resection cases and found that the ICG retention test at 15 min (ICG R15) and LSM had a significant correlation and were associated with early postoperative complications (24). Wong *et al.* stated that LSM is superior to ICG R15 in predicting postoperative complications in liver resection (25); however, LSM is still not a quantitative standard and is not comparable to a quantitative ICG test in determining the precise extent of resectability of a damaged liver (26).

LSM measurement is a non-invasive procedure that may replace HVPG in the diagnosis of PHT. As reported by Wu *et al.*, endoscopic screening prior to liver resection may be omitted in some patients according to the Baveno VII criteria (27), but the sensitivity of the diagnosis of risky varices is not 100%. We have encountered mortality due to variceal rupture in the perioperative period of liver resection (18). Therefore, for a safe liver resection, it is still recommended to perform endoscopy in patients with HCC associated with cirrhosis. We would also recommend endoscopic screening when administering bevacizumab to patients with HCC and cirrhosis, similar to the endoscopic procedure performed prior to liver resection. ICG R15 is also deemed essential in determining the extent of safe hepatic resection, but in the case of partial hepatic resection

with minimal loss of normal liver parenchyma, it may be possible to omit the ICG test in HCC with background liver damage within LSM ≤10 kPa, in the absence of other clinical/imaging signs described in the Baveno VII criteria. To gain widespread acceptance of our opinion that the presence of PHT is not a contraindication for hepatic resection, we need to continue to advocate for the possibility of hepatic resection of HCC with PHT presenting with LSM results.

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