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Editorial

Transient elastography can be integrated into routine clinical practice for the evaluation of portal hypertension?

Beom Kyung Kim[1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul; [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

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Portal hypertension (PH) is a major consequence of liver tissue fibrogenesis in chronic liver disease (CLD).[1] During progression of CLD, the intrahepatic vasculature is remodeled and excess endogenous vasodilators are released, causing splanchnic arteriolar vasodilatation. Consequently, blood flow in the portal venous system would be increased, leading to PH. As the degree of PH becomes severe, it can result in complications such as the development of esophageal varices, variceal bleeding, ascites, spontaneous bacterial peritonitis and hepatorenal syndrome.[2] Particularly in patients with decompensated cirrhosis, PH is responsible for significant morbidity and mortality.[1-4] In this regard, precise assessment of PH allows accurate prediction of prognosis and is essential for managing CLD appropriately. Measurement of the hepatic venous pressure gradient (HVPG), the gradient between the wedged (i.e., balloon-occluded) hepatic venous pressure and the free hepatic venous pressure, has been accepted as the reference standard for assessing the degree of PH. Clinically significant PH (CSPH) defined as HVPG ≥10 mmHg, has been associated with formation of esophageal varices and poor prognosis.[5-7] However, the routine use of this method in the clinical setting has been limited by its invasiveness and the need for expertise and specialized equipment such as angio-intervention unit. Thus, alternative approaches with acceptable diagnostic performance that allow clinicians to assess PH in patients with cirrhosis noninvasively have been needed.

Liver stiffness (LS) assessed using transient elastography (TE) was recently demonstrated to be a reliable and accurate noninvasive tool for assessing the degree of liver fibrosis.[8,9] Recent large-scale longitudinal studies also showed a significant association between LS value and the risk of development of hepatocellular carcinoma (HCC) or cirrhotic complication in patients with chronic hepatitis B (CHB).[10,11] Theoretically, TE also reflects a progressive rise in portal pressure due to increased hepatic vascular resistance related to hepatic fibrosis. Accumulating evidence suggests that TE adequately reflects the findings of HVPG, indicating that it is a useful modality for evaluating PH and cirrhotic complications.[12-18] TE has good performance for discriminating between patients with and without CSPH (area under the receiver operating characteristic curve [AUROC] 0.82–0.94).[19] In addition, a TE value

Abbreviations:

CHB, Chronic hepatitis B; CLD, Chronic liver disease; CSPH, Clinically significant portal hypertension; HCC, Hepatocellular carcinoma; HVPG, Hepatic venous pressure gradient; LS, Liver stiffness; PH, Portal hypertension; TE, Transient elastography

Corresponding author : Beom Kyung Kim
Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1930, Fax: +82-2-393-6884
E-mail: beomkkim@yuhs.ac

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<13 kPa reliably excludes CSPH, while values >21 kPa have an accuracy equal to that of HVPG ≥10 mmHg for prediction of first clinical decompensation in patients with compensated cirrhosis.[20] As variceal bleeding is the most important complication of PH, the relationship between TE values and the presence of esophageal varices has been also investigated in several studies,[13,21,22] which reported significant correlations between TE values and the presence of esophageal varices. Furthermore, Kim et al.[23] conducted a systematic review and meta-analysis to identify the clinical usefulness of non-invasive TE for assessing PH as an alternative to HVPG in patients with CLD. The diagnostic accuracy of TE for CSPH was high (correlation 0.7480, 95% confidence interval: 0.6464; 0.8236, $P<0.0001$). Furthermore, the sensitivity and specificity were 0.85 (range: 0.63–0.97) and 0.71 (range: 0.50–0.93), respectively; the AUROC was 0.88 (range: 0.76–0.99). Therefore, TE shows promise as a reliable and non-invasive procedure that should be integrated into clinical practice for the evaluation of PH. In contrast, Llop et al.[24] demonstrated a moderate correlation between TE and HVPG (r=0.552) and patients with a TE value of 13.6–21 kPa had insufficient sensitivity and specificity to detect CSPH (HVPG >10 mmHg). Thus, TE is not sufficiently accurate to replace HVPG due to its insufficient sensitivity or specificity. Furthermore, TE has limitations for clinical applications because of the wide range of cutoff values (ranges: 13.9–21.5 kPa) and variability in performance among studies (AUROC 0.76–0.85).[13,21,22] Since PH is initiated by an increase in intrahepatic resistance, TE appropriately reflects mild-to-moderate PH or the initiation of CSPH. However, the severity of PH is more dependent on the amount of portal blood inflow and peripheral hemodynamic changes than the stiffness of the hepatic parenchyma; thus, the predictive power of TE for PH might be limited.[12] This explanation was also supported by the fact that the hemodynamic response to a non-selective β blocker could not be accurately predicted using TE.[25]

To overcome such shortcomings of TE alone in evaluating the PH, several studies have shown that the combination of TE, platelet count and spleen size by ultrasound has a superior diagnostic value for CSPH and esophageal varices than any of the three methods individually in patients with compensated cirrhosis of different etiologies.[19] Kim et al.[26] recently proposed a novel prediction model, the LS-spleen diameter to platelet ratio score (LSPS); this uses TE values and the spleen diameter to platelet ratio, which reflect PH in patients with CHB. This model showed excellent diagnostic performance for the prediction of high-risk esophageal varices (AUROC 0.953; negative predictive value 94.7%, positive predictive value 93.3%). Another prospective study showed that LSPS was a reliable predictor of the development of variceal bleeding. CHB patients with an LSPS ≥5.5 had a higher cumulative incidence rate of esophageal variceal bleeding during follow-up, and an LSPS score ≥6.5 was an independent risk factor for variceal bleeding from high-risk esophageal varices, indicating that prophylactic treatment should be considered in these high-risk patients.[10] However, these two studies had a limitation in that HVPG was not measured and that the correlation between HVPG and LSPS could not be evaluated. A recent validation study reported that ≥80% of patients were accurately classified using LSPS. Additionally, in this study, a modified LS-based score, (the varices risk score) was found to be superior to all other noninvasive tests for identifying patients with esophageal varices (AUROC 0.909); it classified 85% of patients correctly.[18] The better performance of LSPS might be primarily due to the combination of different methods reflecting the various pathophysiological components of PH. Splenomegaly in cirrhotic patients is most likely the result of vascular disturbances, which are almost always due to greater portal pressure, whereas thrombocytopenia might be caused by either PH-induced splenic sequestration, or other mechanisms such as decreased thrombopoietin synthesis, shorter mean platelet lifetime, or myelotoxic effects of drugs or hepatitis viruses.[27-29]

Although a systematic review and meta-analysis by Kim et al.[23] showed the overall clinical usefulness of non-invasive TE for assessing PH as an alternative to HVPG in patients with CLD, that study had potential limitations. First, only eight studies were included, so the robustness of the conclusions in terms of the evaluation of the usefulness and performance of TE might be limited. Second, the characteristics of the included studies, such as patient characteristics, etiologies of cirrhosis and diagnostic thresholds, were various. Third, it included only studies published in English, potentially leading to a language bias.

In conclusion, based on the positive results of TE for assessing PH, TE can be integrated into routine clinical practice for the evaluation of PH. However, LS itself might not be sufficient to estimate and replace the HVPG accurately; therefore, complementary methods are required.

Conflicts of Interest

The author has no conflicts to disclose.

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