Application of point shear wave elastography in alcohol-related liver disease

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According to the Global Burden of Disease project, around 1,256,900 deaths were due to cirrhosis and chronic liver disease in 2016, among which 334,900 (27%) were attributable to alcohol [1]. There is considerable geographical variability in alcohol consumption. Alarming, Asia has witnessed a particularly sharp increase in alcohol consumption. In 2017, the annual per-capita consumption of pure alcohol was 7.3 L (3.1 L in female and 11.1 L in male) in East Asia, 4.7 L (1.6 L in female and 7.7 L in male) in South Asia, and 4.5 L (1.7 L in female and 7.2 L in male) in Southeast Asia [2].

In all chronic liver diseases, fibrosis stage carries important prognostic information, with progression to cirrhosis representing a pivotal step towards complications of portal hypertension and hepatocellular carcinoma. Accurate diagnosis of cirrhosis allows the selection of patients for surveillance of hepatocellular carcinoma and varices. In addition, alcoholic hepatitis is a specific complication of alcohol-related liver disease (ALD). Alcoholic hepatitis is characterized by jaundice, malaise, malnutrition, high aminotransferase levels (usually higher aspartate aminotransferase than alanine aminotransferase levels), and/or fever. In patients with alcoholic hepatitis and high Maddrey discriminant function of 32 or above (calculated from prothrombin time and total bilirubin), current guidelines recommend using systemic corticosteroids to improve the short-term survival [3].

One difficulty clinicians often face is how to distinguish severe alcoholic hepatitis from other causes of hepatic decompensation. Because bacterial infection is a common cause of hepatic decompensation in patients with alcohol-related cirrhosis, the misdiagnosis of alcoholic hepatitis and consequent prescription of systemic corticosteroids can be

catastrophic. Although liver biopsy can be performed in case of diagnostic uncertainty, this invasive procedure is not without risk in patients with hepatic decompensation and coagulopathy.

With this background, the paper by Cho and colleagues in this issue of *Hepatology International* is particularly relevant [4]. In this cross-sectional study, the authors performed point shear wave elastography (pSWE) using the Siemens Acuson S3000 Virtual Touch ultrasound system (Siemens AG, Erlangen, Germany) within 72 h from liver biopsy in 251 Korean patients with ALD. One hundred forty-four (57%) patients had cirrhosis, and 146 (58%) had moderate to severe steatohepatitis. Overall, pSWE had excellent accuracy for each fibrosis stage (area under the receiver-operating characteristics curve [AUROC] 0.90–0.93). At the proposed cutoffs based on the Youden indexes (maximal combined sensitivity and specificity) and maximal positive likelihood ratios, pSWE had 85–97% sensitivity and 94–96% specificity in diagnosing each fibrosis stage. Interestingly, when stratified by the presence of cirrhosis, pSWE was also highly accurate in diagnosing alcoholic steatohepatitis. In non-cirrhotic patients, pSWE had an AUROC of 0.93 for steatohepatitis (sensitivity 68%, specificity 93% at a cutoff of 1.49 m/s). Likewise, among cirrhotic patients, the AUROC for steatohepatitis was 0.92 (sensitivity 61%, specificity 97% at a cutoff of 2.52 m/s). The authors thus proposed an algorithm using pSWE and the Maddrey discriminant function to diagnose alcoholic hepatitis and make decisions on the use of systemic corticosteroids.

The findings of this study are in keeping with observations using other physical measurements of liver stiffness. In an individual patient data meta-analysis of 10 studies comprising 1026 patients with alcohol-related liver disease, transient elastography also showed good accuracy in diagnosing liver fibrosis [5]. In that study, non-severe alcoholic hepatitis was again associated with increased liver stiffness. The latter reflects the direct effect of hepatic inflammation

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on liver stiffness, which has been repeatedly demonstrated in different acute and chronic liver diseases.

Although the study by Cho and colleagues is interesting and clinically relevant, a few issues deserve clarification in future studies [4]. Above all, the proposed cutoffs require independent validation. Furthermore, although pSWE could accurately diagnose alcoholic steatohepatitis when the analysis was stratified by cirrhosis, it is worth noting that there was considerable overlap in the liver stiffness measurement by pSWE in non-cirrhotic patients with steatohepatitis and cirrhotic patients without steatohepatitis. The AUROC of pSWE in distinguishing these two groups was only 0.55 (95% CI 0.43–0.68). In other words, for a liver stiffness measurement-based diagnostic algorithm for alcoholic hepatitis to work, clinicians must be able to diagnose cirrhosis confidently in the first place. This cannot be achieved with liver stiffness measurement alone because of the confounding effect of hepatic necroinflammation. In the current paper, Cho and colleagues propose radiological diagnosis of cirrhosis as the first step followed by pSWE examination. However, the diagnosis of cirrhosis and the subsequent stratified

analysis were based on histology. The algorithm should be tested in a prospective manner.

Moreover, alcoholic hepatitis is largely a clinical diagnosis in routine practice, whereas the current study defined alcoholic steatohepatitis by histology. Therefore, a significant proportion of patients in this study would not be considered for the diagnosis of alcoholic hepatitis in the usual clinic setting. The inclusion of patients with very mild disease (having neither advanced fibrosis nor alcoholic hepatitis) would introduce spectrum bias and make pSWE look more discriminating. Nevertheless, the diagnosis would be more challenging if the target population is restricted to patients with acute or subacute onset of jaundice in whom alcoholic hepatitis is suspected. The combination of pSWE and other proposed biomarkers such as keratin 18-based cell death markers deserves further evaluation [6].

Compared with other ultrasound-based liver stiffness measurement (transient elastography and two-dimensional shear wave elastography), pSWE has a smaller fixed region of interest with no color display (Table 1) [7]. In contrast, two-dimensional shear wave elastography allows real-time measurements of liver stiffness in larger regions of interest,

Table 1 Shear wave elastography

Type	Model	Source of stress or vibration	Region of interest	Structural examination	Availability
Transient elastography	FibroScan 502/630 (Echosens, France)	External by probe	Cylinder of 1 cm in diameter and 4 cm in length	No, only M mode ultrasound for localization	High
Point shear wave elastography	Aduson S2000 and 3000 (Siemens Healthineers, Germany) iU22, Epiq series, Affiniti (Philips Healthcare, The Netherlands) HI-VISION Ascendus, Arietta 70/850 (Hitachi Ltd, Japan) MyLab 9 (Esaote, Italy) HS70 A, RS80 A (Samsung Medison, South Korea)	Internal acoustic push by ultrasound beam itself	1 × 0.5 cm fixed area	Yes	Moderate
Two-dimensional shear wave elastography	Aixplorer (SuperSonic Imagine, France) Epiq series (Philips Healthcare, the Netherlands) Acuson S3000 (Siemens Healthineers, Germany) Aplio 500, i-series (Canon Medical Systems, Japan) Resona series, DC-80 system (Mindray, China)	External by probe	Real-time measurement in larger regions of interest than point shear wave elastography	Yes	Moderate

and transient elastography is more widely available, particularly in Europe and Asia. In a study involving head-to-head comparison of the three techniques in 291 patients with nonalcoholic fatty liver disease, pSWE was least likely to have failed measurements but also had lower accuracy [8]. In the current study, Cho and colleagues adopted the transient elastography approach and defined reliable measurements as ten valid measurements and an interquartile range-to-median ratio of 30% or less [4]. It would be important to test if this is the best definition of reliability for pSWE. In addition, the effect of current or recent alcohol consumption on pSWE measurements should be scrutinized.

Finally, as the authors correctly pointed out, the current study used liver histology as the reference standard. It would be important to validate the prognostic significance of pSWE measurements against hard clinical outcomes. Previous studies have already demonstrated the role of liver and/or spleen stiffness measurements in predicting portal hypertension and varices needing treatment [9]. In one Korean study, the change in spleen stiffness measurement by pSWE could also reflect hepatic venous pressure gradient response in patients with esophageal varices receiving carvedilol treatment [10]. The additional clinical question would be how pSWE may change decisions on liver biopsy and treatment and impact on outcomes.

In summary, this important study by Cho and colleagues offers another non-invasive test of fibrosis and cirrhosis in patients with ALD. Non-invasive diagnosis of alcoholic hepatitis is an unmet need. The use of pSWE and/or other biomarkers for this purpose deserves further studies.

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Compliance with ethical standards

Conflict of interest Vincent Wong has served as a consultant or advisory board member for 3 V-BIO, AbbVie, Allergan, Boehringer Ingelheim, Center for Outcomes Research in Liver Diseases, Echosens, Gilead Sciences, Intercept, Novartis, Novo Nordisk, Perspectum Diagnostics, Pfizer, TARGET-NASH, and Terns; and a speaker for AbbVie, Bristol-Myers Squibb, Echosens, and Gilead Sciences. He has also received an unrestricted grant from Gilead Sciences for fatty liver research.

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