Editorial

Two-dimensional shear wave elastography: promises for the future

Arka De, Yogesh K. Chawla

Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to: Yogesh K. Chawla. Professor and Head, Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. Email: ykchawla@gmail.com.

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The prognostication and therapeutic decision making in patients of chronic liver disease is greatly influenced by the degree of liver fibrosis and presence of cirrhosis. Liver biopsy has traditionally been considered the "gold standard" for this purpose. However, it is invasive with rare but potentially serious complications and is prone to sampling errors (1,2). The increasing availability of non-invasive tests with good diagnostic accuracy and high reproducibility has led to their inclusion in several guidelines for the assessment of fibrosis and diagnosis of cirrhosis (3-5).

Among the different non-invasive tests, transient elastography (TE), a technique for measuring liver stiffness using ultrasound (USG) based shear wave elastography (SWE) has been widely studied with good to excellent accuracy for the diagnosis of significant fibrosis and cirrhosis (6,7). However, there is no B-mode orientation for localising the measurement site and the region of interest (ROI) cannot be selected. Moreover, it cannot be used in patients with ascites and a special XL probe is required in obese patients (3). Two-dimensional shear wave elastography (2D-SWE) uses real time, high frequency ultrasound acquisition of propagated shear waves generated by a radiation force impulse induced by focused ultrasonic beams. Unlike TE, 2D-SWE is integrated into a conventional USG machine thereby allowing ROI localisation under B-mode in real time. Moreover, its applicability is not limited by obesity or ascites (8).

Previously 2D-SWE has been evaluated in several small-medium size trials in patients of chronic hepatitis C (CHC) (9,10), chronic hepatitis B (CHB) (11,12), nonalcoholic fatty liver disease (NAFLD) (13,14) and pooled etiologies (15,16) and has been reported to have comparable accuracies vis-à-vis TE and p-SWE for the assessment of fibrosis. There is however a dearth of large multicentre data and Herrmann *et al*. recently conducted a meta-analysis by pooling individual patient data to study the role of 2D-SWE in staging fibrosis using liver biopsy as the reference and also compared the diagnostic performance of 2D-SWE with TE (17). It should be noted however, that this meta-analysis was not a systematic review of published results. On the contrary, centres with experience in using the Airexplorer® ultrasound equipment were requested to provide the data of patients from their respective centres. Patients data which had previously been published as centre based studies were thus accepted (10-12,15,16,18). Selection criteria included adult patients with chronic liver disease who had undergone 2D-SWE using Airexplorer® and had recent liver biopsies (within 24 weeks of 2D-SWE) with samples ≥10 mm in length and with ≥6 portal tracts.

The data of 1,134 patients from 13 clinical centres were finally analysed. Valid TE measurements (IQR/med <0.3) were available in 665 patients. The predominant etiologies were CHB in 35.27%, CHC in 33.42% and NAFLD in 13.76% patients. Alcoholic liver disease accounted for majority of the remaining cases. There was a significant difference in the distribution of etiologies across various centres. A strong correlation was noted between 2D-SWE measurements and stages of fibrosis. Though 2D-SWE results in NAFLD patients were found to be comparable to HCV patients with respect to fibrosis stages, the sample size was too small to reliably estimate cut-off values in NAFLD patients. For other patients, the cut-off point for diagnosing significant fibrosis (Metavir stage ≥2) was 7.1 kPa. The cut-off values for severe fibrosis and cirrhosis (Metavir stage ≥3

and 4 respectively) were lower in CHB patients (8.1 and 11.5 kPa respectively) than in other patients (9.2 and 13.4 kPa respectively).

The AUROCs for CHC, CHB and NAFLD were 86.3%, 90.6% and 85.5% for diagnosing significant fibrosis and 92.9%, 95.5% and 91.7% for diagnosing cirrhosis. Thus, like TE (3), 2D-SWE was better in the detection of cirrhosis than significant fibrosis. Moreover, the negative predictive values (NPVs) were higher than the positive predictive values (PPVs) suggesting that 2D-SWE performs better in ruling out as opposed to ruling in cirrhosis, similar to that reported with TE (3). 2D-SWE AUROCs were higher than that that of TE for detecting both significant fibrosis and cirrhosis. However, though statistically significant, the absolute increase in AUROC values was small (0.022–0.084 for significant fibrosis and 0.003–0.034 for cirrhosis respectively). Overall, the increase was highest in CHB patients and lowest in CHC.

The authors have used refined statistical techniques to circumvent some of the biases that are inherent to these types of studies. To account for a possible "spectrum effect" due to the wide variation in the prevalence of fibrosis stages across different centres, Obuchowski analysis was used to detect an ordinal, non-binary scaled endpoint for estimated cut-off values. Thus, the optimal cut-off values for significant fibrosis was estimated from patients with fibrosis stage 0 to 2 while those for severe fibrosis and cirrhosis were estimated from patients with fibrosis stages 2 to 3 and 3 to cirrhosis respectively. Obuchowski analysis enables the correct interpretation of AUROCs as the gold standard here (liver biopsy) was not binary. However, this focus on neighbouring fibrosis stages was used only during the selection of cut-off values and not during their final evaluation. This was prudent as comparing all stage combinations potentially reduces bias by avoiding prioritisation of any single binary comparison (19). Funnel plots of individual AUROC estimates negated the risk of bias from centres with small number of patients. The exclusion of 147 cirrhotics from centres with a policy of avoiding liver biopsy in patients with clinically apparent cirrhosis could have led to a focus on patients with less advanced disease. However, an additional analysis that included these patients resulted in AUROCs above 95% for the diagnosis of cirrhosis irrespective of the etiology.

While non-invasive tests certainly have a role as a surrogate of liver biopsy, the best manner of their integration at the community level to optimise the diagnosis and prognostication of chronic liver disease patients remains hotly debated. As reported in previous studies (11-13), 2D-SWE performed better than TE in the non-invasive staging of liver fibrosis particularly in CHB patients in this retrospective meta-analysis of individual patient data. However, several issues remain particularly the lack of consensual criteria for defining failure and unreliable results with 2D-SWE. This precludes the estimation of its applicability which is the sum of reliability (percentage of interpretable tests) and failure rate. The number of measurements taken with 2D-SWE per patient varied from 1 to 10 across different centres participating in this study (17), thereby suggesting a lack of standardised practice protocols. Calculation of PPV, NPV and overall correct classification results are dependent on the pre-test probability. Thus, the reported values should be interpreted with caution as the prevalence of significant fibrosis, severe fibrosis and cirrhosis varied from 15.9% to 22.1% and may far exceed the prevalence of disease in the community. Liver biopsy specimens ≥10 mm was taken as the reference standard in this study. However, it should be remembered that even biopsy specimens 25 mm long misclassify fibrosis stages in up to 25% cases when compared to specimens that are >50 mm in length (typically obtained in surgical biopsies) (2,20). An increasing body of evidence is supporting the role of TE in predicting the prognosis and complication in cirrhotics (21). While 2D-SWE is expected to give similar results, longitudinal studies are needed to confirm this. The effect of steatosis and necroinflammation on 2D-SWE values also remains to be ascertained.

Nonetheless, the future looks promising. Anatomic orientation with B-mode and the larger ROI of 2D-SWE (2 cm × 2 cm) gives it a potential edge over TE. Moreover, the integration of 2D-SWE in conventional ultrasound systems thereby allowing simultaneous HCC surveillance has financial implications in resource poor settings. On the flip side, the performance of 2D-SWE requires more training and expertise as compared to TE though the interpretation of findings should be done by clinicians with expertise in liver disease. Apart from Airexplorer® of Supersonic Imagine, other companies are also coming out with their own equipments. While the technology used is largely similar, they use different proprietary calculation algorithms and thus extrapolating the results from one equipment to another may be hazardous (22). Further studies are needed to standardise the quality criteria of 2D-SWE and to explore its prognostic value.

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Footnote

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References

1. West J, Card TR. Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology 2010;139:1230-7.
2. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-57.
3. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.
4. Cosgrove D, Piscaglia F, Bamber J, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall Med 2013;34:238-53.
5. Ferraioli G, Filice C, Castera L, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. Ultrasound Med Biol 2015;41:1161-79.
6. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960-74.
7. Tsochatzis EA, Gurusamy KS, Ntaoula S, et al. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. J Hepatol 2011;54:650-9.
8. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans Ultrason Ferroelectr Freq Control 2004;51:396-409.
9. Bavu E, Gennisson JL, Couade M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. Ultrasound Med Biol 2011;37:1361-73.
10. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56:2125-33.
11. Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. Radiology 2013;269:910-8.
12. Zeng J, Liu GJ, Huang ZP, et al. Diagnostic accuracy of two-dimensional shear wave elastography for the non-invasive staging of hepatic fibrosis in chronic hepatitis B: a cohort study with internal validation. Eur Radiol 2014;24:2572-81.
13. Cassinotto C, Boursier J, de Lédinghen V, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016;63:1817-27.
14. Petta S, Maida M, Macaluso FS, et al. The severity of steatosis influences liver stiffness measurement in patients with nonalcoholic fatty liver disease. Hepatology 2015;62:1101-10.
15. Cassinotto C, Lapuyade B, Mouries A, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan®. J Hepatol 2014;61:550-7.
16. Deffieux T, Gennisson JL, Bousquet L, et al. Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography. J Hepatol 2015;62:317-24.

17. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by 2D-shear wave elastography: An individual patient data based meta-analysis. Hepatology 2017. [Epub ahead of print].
18. Guibal A, Renosi G, Rode A, et al. Shear wave elastography: An accurate technique to stage liver fibrosis in chronic liver diseases. Diagn Interv Imaging 2016;97:91-9.
19. Obuchowski NA. Estimating and comparing diagnostic tests' accuracy when the gold standard is not binary. Acad Radiol 2005;12:1198-204.
20. Poynard T, Lenaour G, Vaillant JC, et al. Liver biopsy analysis has a low level of performance for diagnosis of intermediate stages of fibrosis. Clin Gastroenterol Hepatol 2012;10:657-63.e7.
21. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
22. Piscaglia F, Salvatore V, Mulazzani L, et al. Ultrasound Shear Wave Elastography for Liver Disease. A Critical Appraisal of the Many Actors on the Stage. Ultraschall Med 2016;37:1-5.

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