Liver Ultrasound Elastography: Review of Techniques and Clinical Applications

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ABSTRACT

Chronic liver disease remains a substantial worldwide problem. Accurate estimation of liver fibrosis is crucial for determining the stage of the disease, assessing the patient's prognosis and predicting treatment response. Staging hepatic fibrosis has traditionally been done with liver biopsy but clinical practice has been changing, partly because liver biopsy has several disadvantages: it is invasive; it is associated with rare but serious complications; and it is prone to sampling error representing a tiny portion of the total liver volume. An increasing number of non-invasive liver fibrosis assessment have been developed. These include elastographic methods involving ultrasound (US) and magnetic resonance (MR) imaging. In this review article we discuss the different ultrasound-based elastography techniques, their clinical applications and various confounding factors in the assessment of hepatic fibrosis that may affect the accuracy of the measurements.

KEYWORDS: ultrasound, fibrosis, elastography, shear wave, liver, hepatitis

INTRODUCTION

Chronic liver disease remains a substantial worldwide problem. Although the underlying etiologies differ, with viral hepatitis, non-alcoholic fatty liver disease (NA-FLD) and alcohol remain common causes, the end result is similar – increasing deposition of fibrous tissue within the liver, leading to progressive fibrosis and development of hepatic cirrhosis and subsequently to portal hypertension, hepatic insufficiency and carcinogenesis.[1,2]

Hepatic fibrosis is a dynamic process leading to a progression of disease stages from no fibrosis to cirrhosis. Accurate estimation of liver fibrosis is crucial for determining the stage of the disease, assessing the patient's prognosis and predicting treatment response.[3] Although percutaneous liver biopsy is considered the reference standard for the assessment of hepatic fibrosis, it has several inherent limitations, and its use has been declining over recent years.[2] Liver biopsy is an invasive procedure having potential complications including pain and bleeding which can be severe in 1% of the cases,[4,5] and a procedural mortality rate of approximately 0.01%,[6,7] which reduce patient's acceptance and limit its suitability for repeated measurements and disease monitoring. Also, liver biopsy is prone to sampling error representing approximately 1/50,000th of the total liver volume.[8,9] An increasing number of non-invasive liver fibrosis assessment have been developed. These include elastographic methods involving ultrasound (US) and magnetic resonance (MR) imaging.

The aim of this review is to discuss the different ultrasound-based elastography techniques, their clinical applications and various confounding factors in the assessment of hepatic fibrosis that may affect the accuracy of the measurements.

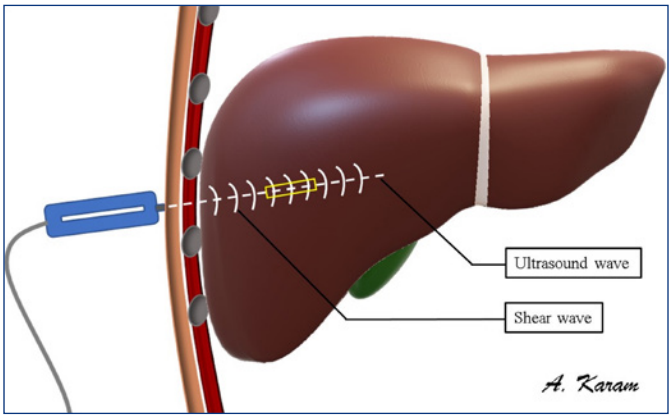
ULTRASOUND-BASED ELASTOGRAPHY

There are three main ultrasound-based elastography methods to evaluate tissue stiffness: transient elastography (TE); point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D SWE). In each of these techniques, the patient is placed in the supine position with the right side slightly elevated (approximately 30 degrees) and the right arm raised above the head to increase the intercostal acoustic window.

TE technique

The FibroScan® system (Echosens, Paris, France) was the first commercially available TE system, introduced in Europe in 2003 and was approved by the Food and Drug Administration in the United States of America in 2013. TE is an inexpensive system used as a "point of care" tool. Although it is an US-based technique, it does not provide direct imaging guidance – the probe is typically positioned based on anatomic landmarks at the level of the dullest point over the liver, typically in the 9th–11th intercostal along the right axillary line. Different frequency probes are available to allow the evaluation of different size patients including children. TE uses a mechanical piston to generate a resulting shear wave that propagates into the underlying liver. The ultrasound probe provides an image showing the propagation of the shear wave over time (shear wave speed) in the region of interest (ROI) called the elastogram box, placed approximately 6 cm deep (**Figure 1**). The shear wave speed is converted to elasticity utilizing Young's modulus and displayed

Figure 1. Schematic of transient elastography system showing a shear wave, created by a mechanical piston, propagating through the liver. The speed of the shear wave is measured by the ultrasound wave in the elastogram box (yellow rectangle).



in Kilopascals (KPa). The software determines whether the obtained measurement is valid or not; the machine will not report a value if inadequate. The procedure is considered to have failed when no value could be obtained following at least 10 attempts. The examination is deemed valid when: (1) at least 10 valid measurements are obtained; (2) The ratio of valid measurements/ the total number of shots is > 0.6; (3) the interquartile ratio (IQR)/ median value < 0.3 – the IQR is the difference between the 75th and 25th percentiles, essentially the middle 50% of the data.

Since TE has been available since 2003, there have been many studies supporting its use. Thresholds for the differentiation of the degree of fibrosis all the way to cirrhosis have been provided with TE based on many original works using histology as the reference standard.[10] Limitations of this technique are: (1) the lack of grayscale images to guide the placement of the elastogram box and to provide diagnostic images of the liver parenchyma i.e. potential liver lesion(s), biliary tree and hepatic vasculature; (2) the probe needs recalibration every 6–12 months for reliable measurements; (3) inability to use it in patients with ascites and large body habitus.

pSWE technique

At present, most ultrasound manufacturers have developed their own liver stiffness quantification technologies. They all share the capacity to assess tissue deformation and to measure the speed of shear waves travelling perpendicular to the axis of an applied force consisting of ultrasound energy known as acoustic radiation force impulse (ARFI). These technologies are collectively known as shear-wave elastography (SWE) with the two main categories being pSWE (point shear wave elastography) and 2D SWE (two-dimensional shear wave elastography).[2,11] In pSWE the shear wave speed is calculated in a small selected ROI measuring approximately 0.5 to 1cc (**Figure 2**) in meters per second and is converted to elasticity utilizing Young's modulus and displayed in kPa.[2] Advantages of this technique over TE are its ability to acquire real-time grayscale images allowing the operator to avoid placing the ROI over potential masses, blood vessels and bile ducts, and to perform a diagnostic ultrasound examination at the same setting. With both pSWE and 2D SWE

Figure 2. Grayscale ultrasound image from a pSWE study showing the white box representing the ROI where the measurement is obtained. Note the adjacent vessels (white arrows) that were avoided during the placement of the ROI. HV: Hepatic vein. IVC: Inferior vena cava.

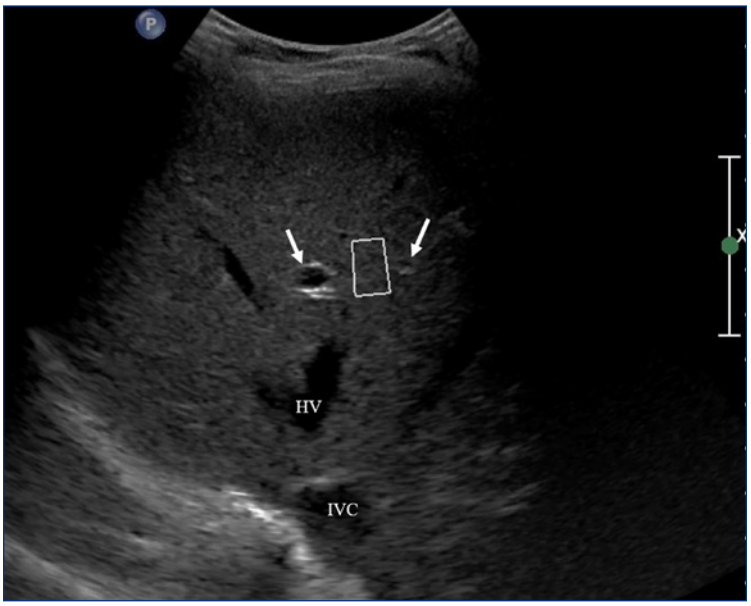
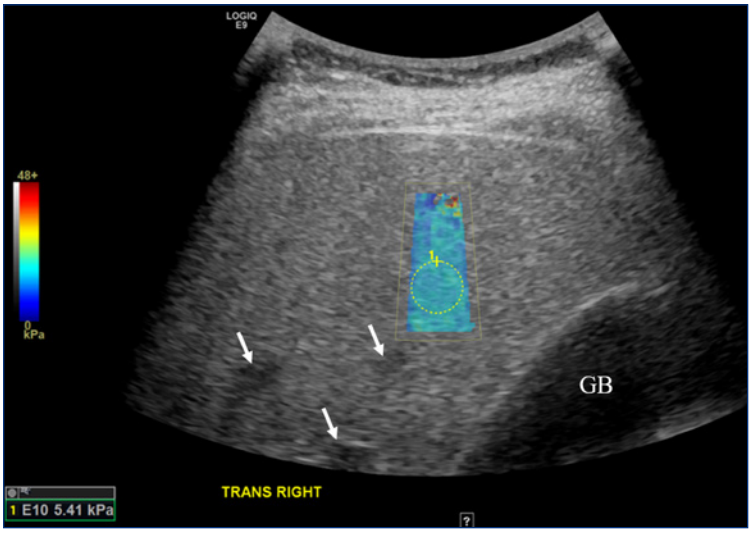


Figure 3. 2D SWE image in a 41-year-old female patient with history of chronic hepatitis C. Note the rectangular box placed in the right lobe of the liver away from major vessels (arrows), which is the field of view where shear waves are measured and color coded. The round circle is the ROI where the measurement is obtained (measurement # 10 is shown). The software provides the median, the IQR and IQR/median (5.4 KPa, 0.55 KPa and 0.10 respectively in this patient). GB: gallbladder.



technologies, the consensus recommendation is to obtain 10 measurements from the right lobe of the liver and confirm the IQR/median value < 0.3 if the reported stiffness value is > 7.1 KPa (1.5 m/sec).

2D SWE

In 2D SWE the shear wave speed is calculated in a relatively large field of view (FOV), of approximately 14 to 20 cc. Within this FOV an ROI is placed to obtain measurements from this location (**Figure 3**). Like with pSWE, the speed of the shear waves is calculated in meters per second and is converted to elasticity utilizing Young's modulus and displayed in KPa. Advantages of 2D SWE are its ability to acquire real-time grayscale images allowing the operator to place the FOV avoiding potential masses, vessels and bile ducts and to perform a diagnostic ultrasound examination like in pSWE. The larger area of measurements compared to pSWE allows for a larger ROI for the averaging of measurements.[2] 2D SWE is proven a highly accurate method in hepatitis B virus (HBV) and hepatitis C virus (HCV) infected populations.[12,16] Although less well studied than pSWE and TE as it is a newer technique, 2D SWE has been found to be equivalent if not better than both technologies,[13,16] and can be used with equivalent diagnostic accuracy.

Clinical applications of liver ultrasound elastography

Current guidelines including the AASLD and EASL recommend the use of ultrasound elastography to assess the degree of hepatic fibrosis.[17,18] Apart from chronic hepatitis B and C, ultrasound elastography has also been used to assess hepatic fibrosis in patients with alcoholic liver disease, nonalcoholic fatty liver disease, primary sclerosing cholangitis and others. One major benefit of noninvasive ultrasound elastography is that the examination can be readily repeated, as a standalone test or during diagnostic liver ultrasound examination.

Early studies proved a positive correlation between hepatic fibrosis and portal hypertension, which in turn is correlated with the development of gastric and esophageal varices.[19] Recent international guidelines recommend a TE elasticity of 20 KPa and a platelet count of 150,000/μL as a threshold to obviate the need for gastroscopic examination in cirrhotic patients.[17,18]

Initial studies suggest that ultrasound elastography can play a role in establishing the prognosis of patients with chronic liver disease; patients with higher hepatic elasticity are at greater risk to develop hepatocellular carcinoma, gastric varices with or without hemorrhage, hepatic decompensation and have a higher mortality.[20]

Confounding factors in the assessment of hepatic fibrosis

While SWE techniques are relatively easy for an experienced sonographer to learn and perform, a good intercoastal window allowing adequate visualization of the right lobe of the liver and the push of a button are not the only considerations. It is crucial to consider different technical and patient related factors that can affect the stiffness values, the main ones are summarized in **Table 1**. Most patient-related confounding factors increase the stiffness values therefore, a normal value of elastography (< 5 KPa) can be accepted as normal, whereas an increased value must be taken in clinical context.[1,2] Several studies comparing different technologies on the same patient cohort have demonstrated inter-system variation for SWE estimation of liver fibrosis. Furthermore, machines from different manufacturers are based on proprietary technologies, resulting in different calibration and stiffness ranges among each other and in comparison to TE.[1,13] A general conclusion we can draw is that normal levels of stiffness firmly indicate the absence of any significant fibrosis, irrespective of the manufacturer and are obtained with high reproducibility. Conversely, thresholds for higher levels of stiffness and therefore higher fibrosis stages are strictly related to each technology and manufacturer.

Table 1. Confounding factors in liver ultrasound elastography.

Confounding factors	Liver stiffness	Comments
Right heart failure	Increased	Evidence of right heart failure and liver congestion can be seen on grayscale and Duplex ultrasound.
Biliary obstruction	Increased	Can be seen on grayscale ultrasound.
Necro-inflammatory activity	Increased	Elevated transaminase levels > 5 times normal values. Increased liver stiffness associated with severe hepatic steatosis is attributed to increased necroinflammatory activity.
Digestion	Increased	Liver stiffness measurements obtained within 0 to 3 hours from a meal may overestimate the degree of liver fibrosis. Examination should be obtained after fasting.
Amyloidosis	Increased	
Alcohol consumption	Increased	In patients with alcoholic hepatitis, it is recommended to ascertain the quantity and recency of alcohol consumption related to the timing of the examination.
Alcohol abstinence	Decreased	In patients with alcoholic hepatitis, it is recommended to ascertain the quantity and recency of alcohol consumption related to the timing of the examination.
Anti-viral therapy	Decreased	
Subcapsular and left lobe measurements	Increased	ROI should be placed 1.5–2 cm deep to the liver capsule to avoid reverberation artifacts and increased subcapsular stiffness within 1 cm from the capsule. Measurements obtained in the left lobe are affected by the cardiac activity.

CONCLUSION

Liver ultrasound elastography has evolved into an accurate method for noninvasive diagnosis and monitoring of liver fibrosis of various etiologies. There are several methods for performing liver elastography, including TE, pSWE, and 2D SWE. While each method may be appropriate, they differ in how the shear wave is generated and in what measurements are taken, with pSWE and 2D SWE having the advantage of real-time ultrasound imaging for accurate measurement placement and performing a diagnostic ultrasound surveying for the sequelae of chronic liver disease. Interpretation of the results should consider potential confounding factors and technical limitations.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383(9930):1749-1761.
2. Barr RG, Ferraioli G, Palmeri ML, et al. Elastography assessment of liver fibrosis. Society of radiologists in ultrasound consensus conference statement. Radiology 2015;276:845-861.
3. Martinez SM, Foucher J, Combis JM, et al. Longitudinal liver stiffness assessment in patients with chronic hepatitis C undergoing antiviral therapy. PloS ONE 2012;7(10):e47715.
4. Steff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8(10):877-883.
5. Stotland BR, Lichtenstein GR. Liver biopsy complications and routine ultrasound. Am J Gastroenterol 1996;91(7):1295-1296.
6. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. Ann Intern Med 1993;118:96-98.
7. Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. Hepatology 2009;49:1017-1044.
8. Regev A, Berho M, Jeffers LJ, et al. Sampling error and interobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97(10):2614-2618.
9. Mahraj B, Mahraj RJ, Leary WP, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523-525.
10. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gasrtoenterol 2008; 134(4):960-974.
11. Zelesco M, Abbott S, O'Hara S. Pitfalls and sources of variability in two dimensional shear wave elastography of the liver: An overview. Sonography 2017;5:20-28.
12. 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(3):910-918.
13. 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(6):2125-2133.
14. Verlinden W, Bourgeois S, Gigase P, et al. Liver fibrosis evaluation using real-time shear wave elastography in hepatitis C-monoinfected and human immunodeficiency virus/hepatitis C-coinfected patients. J Ultrasound Med 2016;35(6):1299-1308.
15. 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(10):2572-2581.
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(2):317-324.
17. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
18. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461-511.
19. Wang JH, Chuah SK, Lu SN, et al. Transient elastography and simple blood markers in the diagnosis of esophageal varices for compensated patients with hepatitis B virus-related cirrhosis. J Gastroenterol Hepatol 2012;27:1213-1218.
20. Singh S, Fujii LL, Murad MH, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1573-840.

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