REVIEW PAPER: DIFFUSE LIVER DISEASE

Ultrasound-based liver elastography: current results and future perspectives

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Abstract
Chronic liver disease affects 185 million population worldwide. It encompasses a heterogenous disease spectrum, but all can lead to the development of liver fibrosis. The degree of liver fibrosis is not only a prognosticator, but has also been used to guide the treatment strategy and to evaluate treatment response. Traditionally, staging of liver fibrosis is determined on histological analysis using samples obtained from an invasive liver biopsy. Ultrasound-based liver elastography is a non-invasive method of assessing diffuse liver disease in patients with known chronic liver disease. The use of liver elastography has led to a significant reduction in the number of liver biopsies performed to assess the severity of liver fibrosis and a liver biopsy is now reserved for only select sub-groups of patients. The aim of this review article is to discuss the key findings and current evidence for ultrasound-based elastography in diffuse liver disease as well as the technical challenges and to evaluate the potential research direction.

Keywords Liver elastography · Transient elastography · Fibrosis · Hepatitis · Cirrhosis · Chronic liver disease

Introduction

Chronic liver disease affects 185 million people worldwide [1]. It encompasses many disease aetiologies with the vast majority of cases secondary to viral hepatitis, alcohol induced, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH). The common pathological consequence for all these different aetiologies involves the development of liver fibrosis; a result of chronic inflammation. Untreated, liver fibrosis can lead to end stage liver disease and cirrhosis both of which are associated with a high morbidity and mortality. Assessment of the degree of liver fibrosis is clinically relevant in guiding treatment, evaluating response and predicting associated complications. Ultrasound-based elastography is an adjunctive tool to traditional B-mode ultrasound for assessing patients with chronic liver disease. It is inexpensive, quick to perform and has a short period of training for the operator.

Liver elastography guidelines are available from European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [2], World Federation for Ultrasound in Medicine and Biology (WFUMB) [3, 4] and Society of Radiologists in Ultrasound Consensus [5]. The aim of this review article is to discuss the key findings and current evidence for ultrasound-based elastography in diffuse liver disease as well as technical challenges and potential further research.

Types of elastography

Elastography is a method of studying tissue stiffness. The differences in tissue stiffness between healthy and pathological tissue allows for the inference of the presence and severity of disease. There are two types of ultrasound-based elastography techniques; strain elastography (SE) and shear wave elastography (SWE).
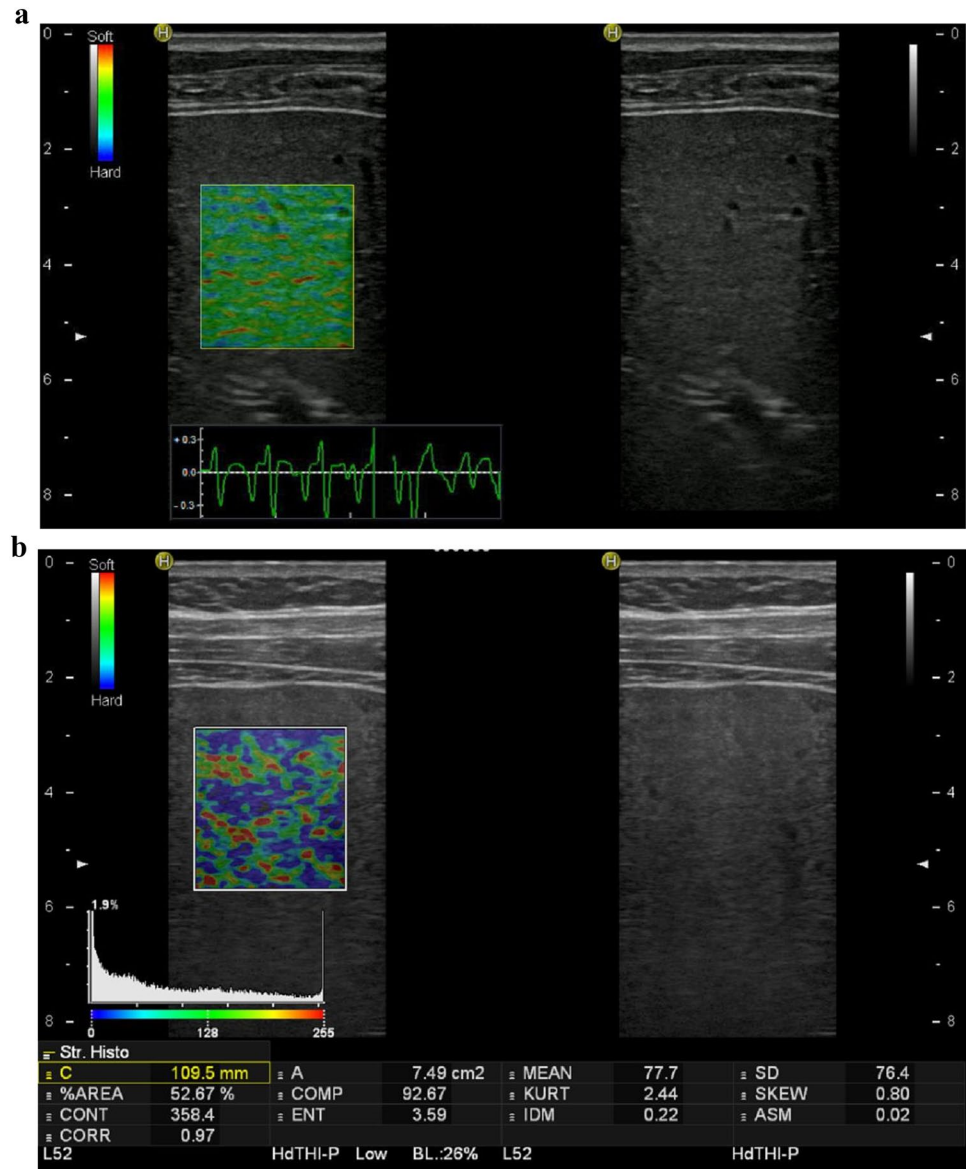
Strain elastography

In SE the elasticity of the tissue of interest is assessed by comparing the degree of distortion with adjacent healthy tissue induced by an external manual compression or cardiac

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Fig. 1 Two strain elastography studies performed using Real-time Tissue Elastography (Hitachi Medical Corporation, Japan). **a** Liver elastogram from a 21-year-old male with chronic hepatitis B infection demonstrates "soft" liver texture indicated by relatively homogenous green colour. **b** Liver elastogram from a 59-year-old male with chronic hepatitis C infection demonstrates "hard" liver texture which corresponding to severe fibrosis on histological analysis. The parameters underneath the pictures can be used to compute semi-quantitative liver fibrosis index

pulsation [6, 7]. The output is a colour coded map of tissue elastogram super-imposed on the B-mode image (Fig. 1). This shows the relative degree of distortion between the tissue of interest and adjacent tissue. Therefore, the stain ratio between the pathological and healthy tissue is a relative measure of tissue elasticity.

Strain elastography was first available commercially on the Hitachi platform also known as Real-time Tissue Elastography (RTE™, Hitachi Inc, Japan). Semi-quantitative analysis can be performed by calculating the liver fibrosis index (LFI) from 11 imaging features including mean relative strain value (MEAN), standard deviation of relative strain value (SD), percentage of lower strain area (% of blue colour area − % area), complexity of lower strain area, Skewness (SKEW), Kurtosis (KURT), Entropy (ENT), textural complexity, inverse difference moment (IDM), angular second moment, contrast (ASM), and correlation (COR) [8] (Fig. 1). The results from a RTE™ study is more operator-dependent and requires additional training when compared to using the SWE techniques [9]. There have been far fewer publications using SE compared to SWE and these studies were predominantly performed in East Asian populations, where obesity is less prevalent. Meta-analysis showed the AUROC for significant fibrosis (F > 2), advanced fibrosis (F > 3) and cirrhosis (F = 4) were 0.79, 0.94 and 0.85 using LFI [10]. Furthermore, few studies have compared diagnostic performance of RTE™ against SWE [9, 11]. The use of RTE™ in assessing stages of liver fibrosis has not been incorporated in EASL, EFSUMB [6], SRU [5] and WFUMB guidelines [3, 4].

Assessment of liver stiffness using both SWE (2D-SWE) and SE can be simultaneously performed on ARIETTA

Hitachi 850 known as Combi-Elasto (Hitachi Medical Corporation). Assessing liver stiffness using combined RTE™ and the shear wave technique could potentially identify the influence of any confounding factors on liver stiffness such as acute inflammation, biliary obstruction or hepatic congestion. During follow-up studies changes in relative strain during RTE™ examination is thought to be rarely affected by these factors [9].

Shear wave elastography

In SWE, an acoustic impulse is generated by the transducer and transmitted from the transducer to the region of interest (ROI) where the propagation speed of the resultant shear wave is measured. Tissue elastic modulus is calculated through the equation, $E = 3\rho c^2$, where E is tissue elasticity, C is shear wave velocity, and ρ is the density of the tissue in kg/m^3. Therefore, shear wave velocity is a quantitative method of determining the absolute tissue elasticity. Shear wave elastography encompasses several different methods of measuring shear wave velocities: transient elastography (TE), point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE). There are many commercially available machine platforms allowing users to perform a liver elastography study are listed, but not exclusively, in Table 1.

TE is more commonly known by the brand name Fibro-Scan™ (Echosens, Paris, France). TE displays shear wave velocity by converting this to kilopascals (kPa) but does not have the capability of forming a B-mode image of the liver during the elastography examination. This cannot be used in patients with abdominal ascites as measurements will be unreliable and has technical limitations with obese patients. This may be overcome by using a different transducer, the XL transducer, which is designed for obese patients.

pSWE and 2D-SWE are performed with conventional ultrasound machines which allows simultaneous B-mode imaging allowing for a comprehensive liver assessment. The difference between pSWE and 2D-SWE is that the former emits a single shear wave at a single frequency for each measurement, while the latter emits multiple shear waves simultaneously. Conventionally the measurements are expressed as a velocity, although many manufacturers are able to also display measurements in kPa. Conversion from velocity measurements to kPa results in additional inaccuracies but TE and FibroScan™ have established the kPa as a readily identifiable measurement in hepatology practice.

Elastography examination techniques

Patients are required to fast for at least a minimum of 2 h and rest for 10 min prior to the examination to avoid falsely elevated liver stiffness measurements [12]. The examinations are performed with patients lying in supine position with their right arm extended over their head to increase intercostal space. Measurement should be taken from the right lobe of the liver via intercostal costal approach. Using the FibroScan™ technique, there is no region of interest to

Table 1 Examples of current available commercial systems (applications)

Commercially available systems	Software name	Reliability indication
Transient elastography		
Fibroscan™ (Echosens, France)	Fibroscan™	IQR/M ≤ 30%
Point shear wave elastography		
ACUSON™ (S2000/S3000/Sequoia), (Siemens Healthineers, Germany)	Virtual Touch™ Quantification (VTQ™)	IQR/M ≤ 30%
EPIQ series, Affinity—(Philips Healthcare, Netherlands)	ElastPQ™	IQR/M ≤ 30%
Ascendus™, Arietta series—(Hitachi Medical Corporation, Japan)	Hi-VISION™	Net amount of effective shear wave velocity percentage (VsN) ≥ 50%
MyLab™ Twice (Esaote SpA, Italy)	QElaXto	IQR/M ≤ 30%
RS80, HS70A (Samsung Medison, South Korea)	S-Shearwave	Reliable measurement index (RMI) > 80%
2D-shear weave elastography		
Aixplorer™—(Aix-en-Provence, France)	SuperSonic Imaging (SSI™)	Stability index
LOGIQ (E9, E10)—(GE Healthcare, USA)	2D comb-push	IQR/M ≤ 30%
ACUSON™ (Sequoia), (Siemens Healthineers, Germany)	Virtual Touch™ Quantification (VTQ™)	IQR/M ≤ 30%
MyLab™ 9eXP (Esaote SpA, Italy)	QElaXto -2D	Quality colour map
RS85—(Samsung Medison, South Korea)	S-Shearwave	Reliable measurement index (RMI) > 80%
Aplio 500™—(Toshiba, Japan)	Acoustic Structure Quantification (ASQ)	Shear Wave Propagation map
EPIQ series—(Philips Healthcare, Netherlands)	ElastPQ™ imaging	Confidence map

place as there is no visualization of the liver, and readings are obtained from the perceived correct area of liver. With ultrasound-based techniques, where the liver is visualized, operators should place the region of interest (ROI) box in the right lobe of the liver avoiding any rib shadows, large blood vessels and the biliary tree. There are a number of commercial systems which incorporate both pSWE and 2D-SWE examinations within the machine functionality, as summarized in a recent review [13].

For pSWE examination, the ROI box should be placed 1–2 cm below the liver capsule to avoid reverberation arte-fact and the subcapsular liver parenchyma which is stiffer, a consequence of the proximity to the liver capsule tissue (Fig. 2). This is not strictly necessary for 2D-SWE, as a colour map of tissue elastogram will be displayed for the
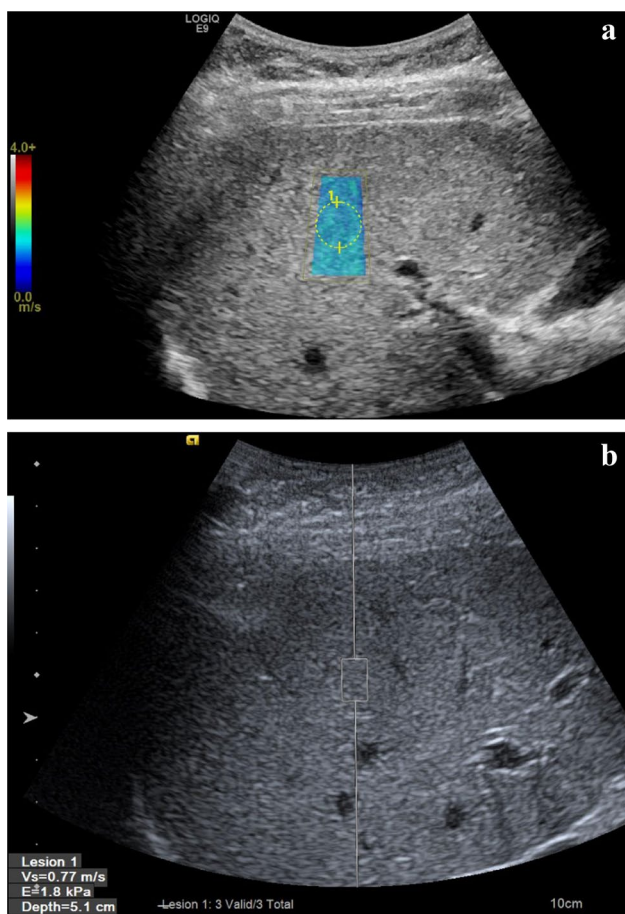

Fig. 3 50-year-old male with alcohol-related liver disease. 2D-SWE (GE) showed heterogeneous mixed green, yellow and red colour elastogram box. The centre round dotted region of interest box was placed to calculate the shear wave velocity after the images were acquired

Fig. 2 Comparative pSWE and 2D-shear wave studies from the same patient. 44-years-old female with chronic hepatitis. **a** 2D-SWE per-formed on GE (LOGIQ E9) showed normal shear wave velocity indi-cated by homogenous blue colour. The dotted ROI circle was placed to calculate the velocity which is 0.8 m/s. **b** pSWE performed on Siemens (S3000 Acuson). A colour map was not produced using this technique instead the average shear wave velocity (0.77 m/s) within the rectangular ROI box was displayed in the left bottom corner on the screen. Patient had same day liver biopsy and showed to have Ishak fibrosis score of 0 from histological analysis

ROI box and subsequent separate analysis box can be placed within the ROI box, avoiding any reverberation artefact (Fig. 3). Additionally, for both pSWE and 2D-SWE, the transducer should be perpendicular to the liver capsule.

Using the median of 10 measurements as the stiff-ness value was recommended as standard practice when using the FibroScan™ machine and has subsequently been adopted as the required number of measurements in clinical practice by majority of pSWE studies, and has become the accepted requisite number of measurements supported by both the EFSUMB and WFUMB guidelines [4, 14]. However, recent evidence has suggested that fewer measurements may be acceptable when using pSWE [15]. For 2D-SWE, the availability of the colour stiffness map prior to selecting the analysis box reduces the data vari-ability allowing few measurements [16]. EFSUMB and WFSUMB both suggested that a minimum of three meas-urements be taken [4, 14] and recent meta-analysis from 34 2D-SWE studies showed fewer unreliable measurements in those studies which obtained more than three measure-ments [17]. All guidelines recommend the use of inter-quartile range over median (IQR/M), an indicator for data variability, to assess data quality when performing liver stiffness measurement using TE and pSWE techniques. Liver stiffness values with IQR/M of ≤30% are associ-ated with increased accuracy for staging liver fibrosis [15, 18–20] as well as has a better agreement among different elastography machines [21]. Reducing the number of liver stiffness measurements has also been shown to have little effect on diagnostic accuracy using measurements with IQR/M ≤ 30% [15]. However, IQR/M can only be obtained

once the study has been completed and more advanced stages of fibrosis can also influence the data variability, hence affecting the IQR/M. Newer systems have incorporated reliability indicators for each measurement displayed at the time of study, which allows the examiner assess the data reliability at the time of the examination [22–24].

Normal values of shear wave velocities and potential confounding factors

Current literature for liver stiffness measurement in healthy volunteers is summarized by Dong et al. [25]. Among the larger studies, the mean/median liver stiffness value using FibroScan™ ranges between 4.1 to 5.5 kPa with calculated highest upper 95% percentile of 8.7 kPa [26–32]. The mean or median shear wave velocity measurements using pSWE are available for most commercial systems VTQ™ [33–37], ElastPQ™ [38, 39], Samsung RS80A [40] and these measurements are between 1.03 to 1.19 m/s, with the calculated highest upper 95% percentile value of 1.69 m/s and mean/median value of 4.95 kPa to 5.5 kPa with 95% percentile value of 8.04 kPa [41–45].

Liver elastography measures tissue stiffness which can be increased in circumstances other than the presence of liver fibrosis. There are known confounding factors which include post prandial status [46], physical exercise [12], any liver disorders causing acute inflammation associated with a transaminase rise [47], right heart failure causing liver congestion [48], the Valsalva manoeuvre during the examination and biliary obstruction [49]. Age, gender and body mass index are not thought to influence the liver stiffness value. The impact of hepatic steatosis on liver stiffness is uncertain. Although steatosis has not been proven to affect liver stiffness values, it will attenuate the shear wave.

Performance of shear wave elastography

Staging of fibrosis in chronic liver disease

SWE has been widely used to assess the degree of liver fibrosis in the management of patients with chronic liver disease in the last 5 years. In many centres, it has gradually replaced the "gold standard" of liver biopsy. In comparison to liver biopsy, liver elastography is non-invasive, has high patient compliance, good intra- and interobserver reproducibility [17, 50–55], whereas a liver biopsy is invasive with significant mortality and mobility [56, 57]. A liver biopsy is prone to sampling errors and the histological analysis has a high observer variability [58, 59].

The European Association for the Study of the Liver (EASL-ALEH) recommend TE as part of the non-invasive tests for evaluating severity and prognosis of liver disease by determining the stage of liver fibrosis [60]. In the United Kingdom, the National Health Service Institute for Health and Care Excellence (NICE) have also recommended the use of VTQ™ (pSWE, Siemens Healthineers, Germany) to assess liver fibrosis in patients with viral hepatitis B and C [61]. A number of meta-analyses have shown good to excellent diagnostic accuracy using TE in determining significant and severe liver fibrosis when the results were correlated with pathological classification of liver fibrosis with Area Under the Curve Receiver Operating Characteristic (AUROC) of 0.82–0.88 for significant fibrosis and 0.91–0.93 for severe fibrosis [62–64]. Similar AUROC values for significant fibrosis and severe fibrosis using pSWE (VTQ™) (0.88—significant fibrosis; 0.91—severe fibrosis) [65] and 2D-SWE AUROC (0.91—significant fibrosis; 0.95—severe fibrosis) [66] were reported. Both pSWE and 2D-SWE techniques have persistently demonstrated a higher technical success rate compared with TE [67, 68]. This is likely due to the ability to visualize the liver with the B-mode ultrasound component and place a region of interest within the liver, avoiding vascular/biliary structures, at the optimal depth during the pSWE and 2D-SWE examinations. Higher diagnostic accuracy has been reported for 2D-SWE compared to TE for all aetiologies of liver disease [69]. There are very few studies which have compared the diagnostic performance between 2D-SWE and pSWE; one early study showed a higher diagnostic performance using 2D-SWE in predicting significant fibrosis than with pSWE (VTQ™) [70] and later studies have showed similar performances [71, 72].

According to the EFSUMB guidelines, the optimal cut-off values for predicting significant fibrosis and cirrhosis in the presence of viral hepatitis C, for VTQ™ is 1.21 m/s–1.34 m/s and 1.55 m/s and 2.00 m/s. In the presence of viral hepatitis B, a meta-analysis has indicated that the optimal cut-off for predicting significant fibrosis and cirrhosis is 1.35 m/s and 1.87 m/s respectively [73]. The optimal cut-off measurement for a mixed aetiology is reported in a meta-analysis to be 1.30 ± 0.07 m/s for predicting significant fibrosis and 1.80 ± 0.16 m/s for cirrhosis [74].

Measurement variation

More advanced stages of fibrosis will result in higher shear wave velocities, and this has been demonstrated in numerous studies. Whist these shear wave velocities differ significantly between the METAVIR classification categories of F1 and F4 liver fibrosis, the range of shear wave velocities can overlap significantly among the early and intermediate stages of fibrosis (F1 to F3). It has been also been observed that individual cut-off values for different fibrosis stages may also vary depending on disease aetiology and significantly, machine manufacturer, as absolute shear wave

velocities measurements are not transferable between different machines [21, 52, 75–77]. This is an issue associated with the technique of measurement and calculation with each manufacturer processing the data obtained differently. This limitation may be overcome by using the same machine for all studies, but this may not be practicable. WFUMB has recommended applying a 'rule of 5' when interpreting liver stiffness values and managing patients; measurement < 5 kPa is normal, value between 5 and 10 kPa rules out compensated advanced chronic liver disease in the absence of known clinical signs, values between 10 and 15 kPa rules out advanced compensated chronic liver disease, values between 15 and 20 kPa highly suggests compensated advanced chronic liver disease and a value exceeding 20 kPa is in keeping with clinically significant portal hypertension [4]. This emphasizes the importance of interpreting liver stiffness measurement by liver specialists in conjunction with patient's other clinical data rather than being used as a screening tool in the general population [60].

Anti-viral therapy

There are increasing numbers of hepatitis C patients with a sustained virological response when treated with the new generation of anti-viral therapy [78]. Although histology regression of fibrosis has been demonstrated [79], the role and timing of liver elastography in assessing regression of liver fibrosis is yet to be established. This is because the established cut-off values may not be applicable following eradication of viral hepatitis and it may be difficult to differentiate the reduction of liver stiffness as being due to reduction of inflammation or regression of fibrosis. Abrupt reduction in liver stiffness values assessed have been reported immediately after anti-viral treatment [80, 81].

Non-alcoholic fatty liver disease

NAFLD is increasingly prevalent and is becoming the most common cause of chronic liver disease worldwide [82, 83] with non-alcoholic steatohepatitis (NASH) becoming the main indication for liver transplantation in the United States [84]. Liver fibrosis has been reported to be the strongest predictor for long term disease specific mortality [85]. The EASL-ALEH clinical guidelines recommend non-invasive screening for liver fibrosis in NAFLD patients [60] with liver biopsy reserved for patients at high risk of advanced fibrosis if the non-invasive tests were unable to exclude advanced fibrosis [86]. Diagnostic performance of using TE, pSWE and 2D-SWE have all been reported in the literature. A recent meta-analysis reported cut-off values for severe fibrosis ranging from 7.6 to 9 kPa using TE with sensitivity between 83 and 89% and specificity between 77 and 78% [87]. Unreliable liver stiffness values and increased technical failure rate in NAFLD patients appears to be associated with obesity and use of M transducer on the Fibro-Scan™ machine, both of which increases the false positive rate, using the XL transducer can overcome these issues [88]. Fewer studies are available for pSWE and 2D-SWE [89–91]. A recent meta-analysis reported good and comparable diagnostic performance with AUROC between 0.86–0.95 and 0.85–0.94 for TE and pSWE respectively [68]. A single meta-analysis has reported a superior diagnostic accuracy using 2D-SWE than TE [87].

Alcoholic liver disease

For patients with alcoholic liver disease, there is no consensus in terms of the optimum cut-off values for significant fibrosis, severe fibrosis and cirrhosis due to a wide range of cut-off values reported from TE studies [92–96]. There are a limited number of studies using pSWE and 2-SWE. Currently, WFUMB recommends the use of shear wave elastography (including TE, pSWE, 2D-SWE) in patients with alcoholic liver disease to rule out advanced disease [4], while EFSUMB only recommends the use of TE for this indication [14]. Significantly reduced liver stiffness values have been reported in patients who have stopped consuming alcohol and falsely elevated values are seen in patients with acute alcohol intoxication with increased transaminases, bilirubin or gamma-glutamyl transferase. It is suggested that the best time to assess liver fibrosis is after a period of abstinence [97].

Assessment of portal hypertension

Patients with significant and severe portal hypertension are at increased risk of developing varices and consequently acute variceal bleeding. The gold standard of assessing the presence and severity portal hypertension is through an invasive angiographic technique; venous pressure gradient (HVPG) measurement with a cut-off value of HVPG ≥ 10 mmHg indicating clinical significant portal hypertension and a HVPG ≥ 12 mmHg indicating the potential for variceal bleeding [98, 99]. SWE has also been used as a non-invasive tool for assessing the severity of portal hypertension in patients with chronic liver disease. A meta-analysis has shown consistent evidence supporting the use of a liver stiffness value as a biomarker for clinically significant portal hypertension, although the optimal cut-off value calculated from different studies varies from 15 to 25 kPa [100]. A further meta-analysis showed 2D-SWE values of 14 kPa or less can rule out clinically significant portal hypertension in cirrhotic patients with a reported AUROC value of 0.88 and sensitivity value of 91%. However, this does not predict severe portal hypertension with the presence of varices needing treatment [101]. The current evidence suggests that

liver stiffness values show a good correlation with HVPG up to 12 mmHg but cannot replace invasive assessment for assessing the severity and progression of the portal hypertension, primarily as the SWE values are less dependent on intrahepatic resistance with the development of fibrosis [60]. According to the Baveno VI consensus, patients with liver stiffness of < 20 kPa and platelet count of $> 150{,}000$ can avoid screening endoscopy for esophageal varices [102].

Artificial intelligence

The use of artificial intelligence (machine learning) in analysing medical images has experienced an exponential growth in recent years due to the arrival of deep learning methods using convolutional neural networks (CNNs) [103] and its superior accuracy compared to traditional supervisor classification methods [104]. Most recently, Wang et al. showed superior diagnostic performance in predicting severe liver fibrosis (F $\geq$ 3) and cirrhosis (F4) in patients with chronic hepatitis B by analysing images from 2D-SWE studies using deep learning radiomics compared to 2D-shear wave velocity measurements [105]. Gatos et al. also demonstrated that by identifying areas of high and lower temporal stability from 2D-SWE images by means of deep learning algorithm, the diagnostic accuracy and inter observer variability are better when using areas of high temporal stability (reliable areas) than that from lower temporal stability (unreliable areas) [106].

Conclusion

Ultrasound-based elastography offers a cost-effective, noninvasive and accurate method of assessing the severity of diffuse liver disease. Currently, it has superior accuracy in predicting cirrhosis rather than significant fibrosis. Its high negative predictive value should be incorporated into the decision-making process in managing patients with chronic liver disease. Individual optimal cut-off values of fibrosis stages for different aetiologies are yet to be validated in large prospective studies.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

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