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REVIEW

# Clinical applications, limitations and future role of transient elastography in the management of liver disease

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## Abstract

Transient elastography (TE) is a reliable tool for the non-invasive assessment of liver fibrosis in routine clinical practice. TE is currently approved for use in Europe, Asia and the United States. The widespread adoption of this technology is certain to increase the use of TE worldwide. Although TE has been well validated in chronic viral hepatitis, its clinical role in other liver diseases remains less clear. The advent of new treatment for chronic hepatitis C and emerging prevalence of non-alcoholic steatohepatitis raises new questions on the role of TE in current clinical practice. This review aims to examine the clinical applications, limitations and future role of TE in current clinical practice in light of the changing epidemiology of liver diseases and new clinical management paradigms. In current clinical practice, TE is the most accurate non-invasive method for diagnosis of liver cirrhosis. TE is useful to rule out fibrosis and cirrhosis but does not have sufficient accuracy to discern between various stages of fibrosis. The clinical role of TE has evolved from cross-sectional point-in-time assessment of fibrosis and cirrhosis to the more relevant role of prediction of vital clinical end-points. This provides clinicians with the ability to modify treatment strategies based on the information provided by TE. TE has evolved over the past decade to become an essential tool to assist the clinician in the management of chronic liver disease.

**Key words:** Liver stiffness; Transient elastography; Non-invasive; Fibrosis; Chronic



**Core tip:** Transient elastography (TE) is a reliable tool for the non-invasive assessment of liver fibrosis in routine clinical practice. Although TE has been well validated in chronic viral hepatitis, its clinical role in other liver diseases remains less clear. The advent of new treatment for chronic hepatitis C and emerging prevalence of non-alcoholic steatohepatitis raises new questions on the role of TE in current clinical practice. This review aims to examine the clinical applications,

limitations and future role of TE in current clinical practice in light of the changing epidemiology of liver diseases and new clinical management paradigms.

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## INTRODUCTION

Liver fibrosis is the common end-point of a variety of chronic liver diseases. The progression of liver fibrosis leads to cirrhosis, decompensation, liver failure, hepatocellular carcinoma (HCC) and death[1]. Accurate diagnosis of liver fibrosis and cirrhosis is essential for prognostication of liver disease and for timely intervention to prevent negative outcome. Liver biopsy was the traditional gold standard for diagnosis of fibrosis, but significant progress has been made in the field of non-invasive assessment of liver fibrosis over the past decade such that the role of liver biopsy has been diminishing in clinical practice. Non-invasive markers of fibrosis include serum markers which assess the biochemical properties of fibrosis and elastography devices which assess the physical stiffness of the fibrotic liver. Transient elastography (TE) measured by Fibroscan® (Echosens, France) was the first of such elastography devices, followed by magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) and shear wave elastography (SWE). In current clinical practice, TE is the most widely used elastography device for non-invasive assessment of liver fibrosis and is popular in Europe, Asia and recently North America as well.

TE works by measuring shear wave speed through the liver[2]. A handheld probe is placed in the intercostal space of the patient over the right lobe of the liver[3]. A vibration pulse of mild amplitude and low frequency is transmitted by the transducer. This induces a shear wave that propagates through the liver. Pulse-echo ultrasonic acquisitions are simultaneously performed by the machine to follow the shear wave and to measure its velocity. The velocity of the returning shear waves is measured at a depth of 25-65 mm when using the standard M probe and 35-75 mm with the XL probe. This provides an indication of the stiffness of the liver, which is expressed in kPa. The stiffer the liver, the faster the shear wave and hence the higher the liver stiffness measurement (LSM) value. At least 10 successful measurements are required for a valid assessment. The TE result is reported as the median value of at least 10 successful LSMs.

## LIMITATIONS OF TE

Before we review the use of TE in clinical practice, it is important to be familiar with the limitations of this new technology. Although TE has been proposed as a non-invasive tool to measure liver fibrosis, TE actually measures the the shear wave speed through the liver which reflects liver stiffness and not actual amount of fibrosis in the liver. Hence, conditions which increase the stiffness of the liver independent of fibrosis will result in an increased LSM and will result in a falsely high estimate of liver fibrosis.

### *Acute hepatitis*

TE has been demonstrated to be unreliable in acute hepatitis, with LSM values increasing 1.3 to 3 fold during alanine transaminase (ALT) flares[4,5]. This can lead to inaccurate diagnosis of cirrhosis in patients with acute transaminitis. A clear correlation between aminotransferases and LSM has been described, with LSM values falling to normal range after resolution of the acute liver injury[6]. It is thus advised that TE be avoided in situations where there is acute hepatitis as the LSM result is likely to overestimate the degree of fibrosis. The LSM should be repeated when or delayed till recovery from the acute liver injury when the ALT levels return to the baseline. It has been suggested that caution should be applied in the interpretation of LSM values when the ALT level is above 100 IU/L. This poses a clinical dilemma in conditions where there is constant fluctuation of transaminitis, for example in chronic hepatitis B (CHB). Initial validation studies of LSM were largely performed in patients with chronic hepatitis C (CHC) and did not report any association between LSM and ALT[7]. However studies in patients with CHB reported a significant correlation between ALT and LSM[8]. From a clinical perspective, it is not feasible to discount the LSM in every CHB patient who has an ALT level > 100 IU/L since many CHB patients would be expected to have fluctuations in ALT. This has led to proposals to use different LSM cut-off values and algorithms for fibrosis estimation for patients with normal and elevated ALT[9]. A large multicentre study recently demonstrated that ALT and LSM maintain a weak linear relationship for each fibrosis stage up to an ALT of 300 IU/L and proposed using probability-based interpretation of LSM using the LiFA-HBV score[10]. This new score helps the clinician to assess the probability of severity of fibrosis based on the LSM and ALT. For example, a patient with an LSM of 18.4 kPa and a normal ALT of 35 IU/L would have a 0.97 probability of F2 fibrosis, a 0.89 probability of F3 fibrosis and a 0.73 probability of cirrhosis. Another patient with the same LSM of 18.4 kPa but an elevated ALT of 350 IU/L would have a 0.97 probability of F2 fibrosis, 0.77 probability of F3 fibrosis but only 0.35 probability of cirrhosis. This provides the clinician with a practical and useful way

of interpreting LSM in patients with elevated ALT in order to make appropriate clinical decisions. However, the LiFA-HBV score was developed based on untreated CHB patients and requires further validation in other liver diseases.

### Hepatic congestion

LSM values has been shown to increase significantly after a liquid meal, suggesting that TE should be performed after at least a 3 h fast in order to ensure accuracy of fibrosis assessment[11,12]. Liver stiffness is affected by the central venous pressure[13,14] and has been used as a potential non-invasive measure of decompensated chronic heart failure[15] and in congenital heart disease[16]. It is thus important for clinicians to be aware that TE is not suitable for assessment of liver fibrosis in patients in cardiac failure and those with tricuspid regurgitation as it will lead to an overestimation in the severity of liver fibrosis. This poses a clinical challenge in the assessment of patients with cardiac causes of fibrosis, *e.g.*, those with chronic congestive hepatopathy as a result of Fontan procedure for complex congenital heart disease[17]. TE has been reported to be useful for identifying Fontan patients with significant liver fibrosis and cirrhosis[18,19]. However in the absence of biopsy confirmation, LSM cannot be considered to be a reliable predictor for liver cirrhosis as an elevated liver stiffness value cannot differentiate between hepatic congestion and hepatic fibrosis.

### Cholestasis

Extrahepatic cholestasis leads to increased liver stiffness values and results in false estimation of severity of fibrosis. Studies in patients with extrahepatic biliary obstruction either due to neoplasm or choledocholithiasis report elevated LSM readings which declined significantly on repeat TE after biliary drainage[20-23]. It has been suggested that TE should be avoided in patients with significant hyperbilirubinemia (bilirubin > 100 $\geqslant$ μmol/L) and should be repeated after biliary drainage when the bilirubin levels return to baseline[20,23].

### Operator experience

TE has been described to be an operator-independent procedure with a high inter-observer agreement of up to 98%[24]. However a large review of 13369 TE examinations over 5 years demonstrated LSM failure in 3.1% and unreliable LSM in 15.8%. Both were associated with two main factors: Elevated body mass index (BMI) > 30 kg/m$^2$ and operator experience of less than 500 examinations[25]. In a separate French study of TE in 935 patients, the odds ratio (OR) for successful LSM were significantly higher for operators with prior experience of 50-99 measurements and even higher with > 100 previous measurements[26]. Poor operator technique may result in a higher variability of LSMs, which is reflected by a higher interquartile range (IQR). LSM measurements with an IQR greater than 30% of the median value (IQR/M > 0.3) are considered to be invalid and should be either repeated or discarded. In a study examining factors affecting accuracy of TE in patients with CHC fibrosis, an IQR/M $\geqslant$ 0.21 was associated with an increased likelihood of inaccurate TE assessment, with an OR of 2.23[27]. The authors suggest that TE measurements with IQR/M $\geqslant$ 0.21 should be repeated, and if the repeat LSM has a consistent IQR/M $\geqslant$ 0.21, the assessment should be discarded and alternative methods to assess liver fibrosis should be explored. One of the most important factors related to operator technique is the maintenance of perpendicularity of the probe to the liver surface. Correct positioning of the probe is also important to achieve reliable LSM readings[28]. The available data suggests that while a minimal experience of 50 prior measurements may be sufficient for an operator to perform TE, the reliability of LSM measurements is increased in experienced operators with > 500 previous examinations[29].

### Obesity

Early studies in TE using the standard M probe encountered a high rate of TE failure between 5%-22% in obese patients with high BMI (> 30 kg/m$^2$) and increased waist circumference[24,25]. This has been attributed to the interference with the transmission of shear waves and ultrasound waves through the liver parenchyma by thick subcutaneous adipose tissue[30]. However, further studies established that the thoracic fatty belt and not BMI per se was the main determinant of TE failures in obese individuals[31]. Subsequent studies established that the primary factor that was responsible for the failure to obtain a LSM result in obese patients was the distance between the skin and the liver capsule. Patients with a skin-capsule distance (SCD) > 2.6 cm due to increased subcutaneous thoracic fat were more likely to have unsuccessful TE examinations using the M probe[32]. This has led to the development of the XL probe, which differs from the M probe in the following features: a lower ultrasound frequency of 3.5 MHz compared to 5 MHz, a greater transducer focal length of 50 mm *vs* 35 mm, a larger probe tip diameter of 12 mm *vs* 9 mm, higher vibration amplitude of 3 mm *vs* 2 mm and measurement depths of 35-75 mm *vs* 25-65 mm. The XL probe is able to provide a valid TE result in approximately 60% of M probe failures[33]. XL probe failures occur when the SCD is > 3.4 cm, which exceeds the measurement depth of the XL probe. Such patients should undergo alternative assessments for liver fibrosis such as MRE which is not affected by subcutaneous thoracic fat.

### Optimal cut-off levels for diagnosis of fibrosis and cirrhosis in different etiologies of liver disease

One of the difficulties in using TE in routine clinical

**Table 1 Optimal cut-off values for liver stiffness measurement in different etiologies of chronic liver disease**

| | Optimal cut-off LSM for F2 | Optimal cut-off LSM for F3 | Optimal cut-off for LSM F4 | Ref. |
|---|---|---|---|---|
| Chronic hepatitis C | 7.6 (5.1-10.1) | 10.9 (8.0-15.4) | 15.3 (11.9-26.5) | [33] |
| Chronic hepatitis B | 7.0 (6.9-7.2) | 8.2 (7.3-9.0) | 11.3 (9.0-13.4) | [33] |
| Alcoholic liver disease | 8.9 (2.8-46.4) | 10.3 (7.7-20.8) | 18.4 (12.2-75.0) | [66] |
| Non-alcoholic fatty liver disease | 7.0 (6.7-7.8) | 8.7 (7.1-10.4) | 10.3 (10.3-22.3) | [35-37] |
| Cholestatic liver disease | 7.3 | 9.8 | 17.3 | [54] |

LSM: Liver stiffness measurement.

practice is the variability of optimal cut-off levels for the diagnosis of fibrosis and cirrhosis in different etiologies of liver disease. In a meta-analysis of 40 studies evaluating the diagnostic accuracy of TE in various chronic liver disease[34], the optimal cut-off LSMs for CHC are 7.6 kPa for significant fibrosis and 15.3 kPa for cirrhosis (Table 1). Cut-off levels in CHB are similar although some studies demonstrate a slightly lower LSM cut-off for cirrhosis in CHB compared to CHC[35,36]. TE has been shown to be useful for detection of fibrosis and cirrhosis in non-alcoholic fatty liver disease (NAFLD), but the reported optimal cut-off levels for diagnosis of cirrhosis vary from 10.3 kPa to 17.5 kPa[37-39]. In alcoholic liver disease and cholestatic liver disease, the optimal cut-off levels for diagnosis of cirrhosis are significantly higher than viral hepatitis or NASH. Given the variability of cut-off LSMs, LSM results should be interpreted by based on the underlying etiology of liver disease. However, this poses challenges when patients have concomitant liver disease, *e.g.*, CHC and alcoholic liver disease or CHB and NASH. In such situations, most clinicians intuitively use the lower cut-off value to determine the fibrosis stage. However, there have been no studies to date that specifically address this clinical predicament.

One of the underlying reasons for the variability of cut-off levels is that although TE measures amount of fibrosis tissue in the liver, it does not grade the severity of the fibrosis. The METAVIR classification, which is the fibrosis staging system used in most biopsy-paired TE studies, grades severity of fibrosis based on the pattern of fibrosis distribution (*i.e.*, portal fibrosis *vs* portal-central bridging). In contrast, TE simply measures the stiffness of the liver which reflects overall amount of fibrosis tissue in the liver. TE cannot assess the distribution or pattern of fibrosis. This may in part explain the variability of cut-off levels in different diseases. Another contributing factor is that a majority of biopsy-paired validation studies for TE were performed using the METAVIR scoring system as the comparator. While this is relevant for chronic viral hepatitis since the METAVIR system is accurate for staging severity of portal-based fibrosis, it is less relevant for NASH and alcoholic liver disease where the distribution of fibrosis is not predominantly portal-based but pericellular or perivenular, respectively. In a study of accuracy of LSM for the diagnosis of cirrhosis in 1257 patients with various chronic liver disease, Ganne-Carrié *et al*[40] observed that false-positive LSM results were mainly observed in patients with extensive fibrosis. This could reflect a situation where either the liver biopsy has under-staged cirrhosis due to sampling error or there is extensive fibrosis (reflecting a large amount fibrous tissue) but without the nodular architecture required for a pathological diagnosis of cirrhosis.

Differences in the optimal cut-off values reported in different studies can also result from statistical bias. The identification of a specific cut-off value to diagnose a particular fibrosis grade is dependent on the choice of sensitivity and specificity parameters, which in turn depend on the indication for the test and the prevalence of the condition in the study population. For purposes of screening (*e.g.*, diagnosis of fibrosis in NAFLD patients), a lower LSM cut-off level would be more clinically applicable so as not to miss subjects who may require treatment. However, this would reduce the specificity of the test and result in more false-positive tests. In contrast, in clinical situations where accurate identification is important, a LSM cut-off level which provides a high specificity is more relevant than sensitivity. For example, accurate identification of patients with cirrhosis in viral hepatitis is important as these subjects would require antiviral treatment, endoscopic variceal screening and routine surveillance for liver cancer. Some authors have proposed the use of dual cut-off LSMs to rule in or rule out fibrosis and cirrhosis in clinical practice[41].

Cut-off values identified for one population may not be applicable to another which has a different prevalence of disease. For this reason, the performance of TE is more accurate for the identification of more advanced degrees of fibrosis compared to mild fibrosis in biopsy-paired studies because there is an inherent bias to biopsy patients in whom severe fibrosis is clinically more likely. In clinical practice, the use of a specific LSM cut-off value to determine fibrosis stage is less reliable, especially when the LSM value is close to the cut-off value or when there are confounding factors present like necroinflammation, congestion or steatosis. The LSM result should be interpreted in a range or continuum as this provides more reliable clinical interpretation of this non-invasive marker. For example, patients with LSM values ranging from 2.5 to 7 kPa are unlikely to have significant fibrosis, whereas patients with LSM > 13 kPa are likely to have

cirrhosis[42]. A patient with LSM of 25 kPa is more likely to have definite cirrhosis as compared to a patient with an LSM of 13.5 kPa. Hence, the use of probability-based interpretation of LSM results promise to be the most useful way to interpret LSM in routine clinical practice[10].

### *Reliability criteria*

Initial studies in TE defined reliable results as those with at least 10 validated measurements, a success rate of at least 60% and an IQR/M ratio less than 0.3[7]. These criteria were based on the manufacturer's recommendations. However, the impact of these un-reliable TE measurements on accuracy for diagnosis for fibrosis and cirrhosis was not known. Boursier *et al*[43] evaluated the relevance of the recommended reliability criteria in a large multicentre cohort with the aim of improving reliability by using diagnostic accuracy as the primary outcome. They demonstrated that TE success rate and $\geqslant$ 10 valid measurements had no significant influence on reliability for accurate fibrosis staging. The reliability of LSM was shown to be due to the IQR/M according to the liver stiffness median level, which defined three reliability categories: Very reliable (IQR/M $\leqslant$ 0.10), reliable (IQR/M between 0.10 and 0.30 or IQR/M > 0.30 with median LSM < 7.1 kPa) and poorly reliable (IQR/M > 0.30 with median LSM $\geqslant$ 7.1 kPa).

## CLINICAL APPLICATIONS OF TE IN CURRENT PRACTICE

### *Non-invasive diagnosis of fibrosis and cirrhosis in chronic liver disease*

**CHC:** The primary role of TE is for the non-invasive diagnosis of liver fibrosis with the aim of reducing the need for liver biopsy in the clinical management of chronic liver disease. TE was first developed for and extensively validated in patients with CHC[7,44]. Numerous meta-analyses have demonstrated that TE has a high diagnostic accuracy for the diagnosis of CHC cirrhosis with a mean AUROC of 0.94[45,46]. Castéra *et al*[47] established TE as the most accurate non-invasive method for detection of early cirrhosis when compared with other available tests and algorithms. In this study involving 298 CHC patients, the AUROC of TE for detection of cirrhosis was 0.96 compared to 0.82 for Fibrotest®, 0.80 for Lok index and APRI, 0.79 for platelet count, 0.73 for prothrombin index and 0.61 for AST/ALT ratio ($P$ < 0.0001). A subsequent larger study of 1839 French patients with CHC confirmed a similar significant superiority of TE over serum markers in excluding cirrhosis[48]. The performance of TE has also been shown to be equally accurate in special populations of CHC patients. These include patients with HCV/HIV co-infection[49,50] and post-transplant HCV[51,52]. The introduction of TE has resulted in a significant reduction in the numbers of liver biopsy in Europe[53].

The recent introduction of highly effective direct antiviral treatment (DAA) for CHC has provided cure rates exceeding 95% with minimal side-effects. With the availability of DAA, all CHC patients should be considered for treatment irrespective of severity of fibrosis since cure is possible. With this paradigm shift in CHC management, the role of non-invasive markers for fibrosis becomes diminished. However, the high cost of such treatment has necessitated prioritization for CHC treatment based on severity of fibrosis. Hence for present day clinicians, TE plays a role to assist in stratifying patients for CHC treatment (Table 2). Based on the latest EASL guidelines, DAA should be prioritized for CHC patients with cirrhosis and advanced fibrosis (F3 and F4), justified in those with significant fibrosis (F2) and individualized in those with no or mild fibrosis (F1 and F0) in whom risk of decompensated cirrhosis and HCC remains low[54].

**CHB:** In the management of patients with CHB, it is most important to distinguish those with inactive disease from those with active hepatitis, as the latter group of patients is more likely to progress to advanced fibrosis and cirrhosis. Even among patients with persistently normal transaminases, a subgroup will present with higher degree of fibrosis and are more likely to have adverse long-term outcomes, particularly those with greater viraemia[55,56]. The main role of TE in CHB is to differentiate patients with significant fibrosis from those with inactive disease without fibrosis. Maimone *et al*[57] demonstrated that the LSM in patients with inactive CHB was significantly lower than those with e-antigen negative CHB. In another study by Fung *et al*[58], TE demonstrated excellent diagnostic accuracy across the entire spectrum of liver fibrosis with good negative predictive value, although caution needs to be exercised when encountering patients with elevated transaminases. Interpretation of LSM is sometimes challenging due to the confounding effect of ALT, but several strategies can be used to circumvent this problem. One is to use different LSM cut-off levels for those with normal and elevated ALT[9] and the other is to use probability-based scores that correct for the ALT level[10]. In routine clinical practice, TE can be used to select patients with higher risk of disease progression and targeted for closer surveillance and consideration of early antiviral therapy.

**NAFLD:** NAFLD is one of the most common chronic liver diseases worldwide, with increasing disease prevalence in parallel with the burgeoning obesity and metabolic syndrome epidemic[59]. NAFLD is a spectrum of disease, ranging in severity from simple steatosis, which is considered relatively benign, to non-alcoholic steatohepatitis (NASH), the more aggressive, severe end of the spectrum. NASH can potentially progress to cirrhosis and accompanying complications such as HCC[60]. Accurate staging of liver fibrosis is important

**Table 2 What the clinician needs to know about transient elastography (Fibroscan®)**

| | | |
|---|---|---|
| 1 Clinical indications for TE | | |
| Liver disease | Indications for TE | Potential clinical applications |
| Chronic liver disease | To assess for severity of fibrosis | Assist in treatment decisions in CHC and CHB<br>Selection of patients for treatment trials<br>Decision to continue or stop MTX |
| | To diagnose early cirrhosis | Commence variceal screening and HCC surveillance, monitor for decompensation |
| | Longitudinal assessment of fibrosis | Assess for progression of fibrosis in untreated patients and for regression of fibrosis/cirrhosis in treated patients |
| Patients with NAFLD | Assess severity of fibrosis and steatosis (with Fibroscan-CAP) | Aggressive control of risk factors<br>Selection of patients for treatment trials<br>Selection of patients for liver biopsy |
| Post-liver transplant | Assess for fibrosis in recurrent CHC post liver transplant | Avoid protocol liver biopsies for diagnosis of fibrosis |
| Non-cirrhotic portal hypertension | Exclude cirrhosis | Assists in differentiating cirrhotic *vs* non-cirrhotic portal hypertension |
| Patients with cirrhosis | Predict significant portal hypertension and risk of liver-related events | Stratify frequency of follow-up in low-risk *vs* high-risk cirrhotics |
| | Predict absence of varices | Avoid/delay endoscopy screening in cirrhotics at low risk for varices |
| 2 Conditions that affect accuracy of TE | | |
| Condition | How it affects the TE result | What the clinician should do |
| Post-meal | LSMs are elevated after meals due to increased hepatic venous flow | Patients should fast for at least 3 h before TE measurement |
| Elevated ALT | LSMs are elevated due to hepatic inflammation | Repeat or delay TE till after ALT has returned to baseline/normal levels<br>Use ALT-based LSM cut-off values to interpret LSM result<br>Use probability-based LSM interpretation scores which account for ALT |
| Cardiac failure | LSMs are elevated due to hepatic congestion in right heart failure | Repeat or delay TE until after patient's heart failure is treated |
| Cholestasis | LSMs are elevated due to increased stiffness from biliary dilatation | Repeat or delay TE until after biliary obstruction is resolved |
| Operator experience | Operator inexperience may lead to higher rate of unsuccessful or invalid LSM results | TE should be performed by operators with prior experience of at least 50-100 examinations |
| Obesity | Higher rate of unsuccessful LSMs due to increased SCD because of increased subcutaneous fat | Use XL probe if SCD > 3.4 cm (with the current Fibroscan 502 Touch®, the machine will automatically advise when the XL probe should be used)<br>If LSM is unsuccessful with XL probe, use alternative non-invasive test |
| Ascites | High rate of unsuccessful LSM due to interruption of shear waves by ascites | Use alternative non-invasive test |
| Pregnancy, cardiac pacemaker, AICD | Safety of TE in these conditions have not been assessed | TE contraindicated |

TE: Transient elastography; CHC: Chronic hepatitis C; CHB: Chronic hepatitis B; MTX: Methotrexate; HCC: Hepatocellular carcinoma; CAP: Controlled attenuation parameter; NAFLD: Non-alcoholic fatty liver disease; LSM: Liver stiffness measurement; ALT: Alanine transaminase; SCD: Skin-capsule distance; AICD: Activation-induced cell death.

in the management algorithm of NAFLD for aiding treatment decisions and prognostication to monitoring disease progression or treatment response. As such, there have been a myriad of studies exploring the use of TE in patients with NAFLD, with data derived from both Asian and Western series in addition to adult and paediatric cohorts[61-66]. Based on these studies, variable LSM cut-off values for each stage of fibrosis have been reported, with readings of 6.6-7.8, 7.1-10.4 and 10.3-22.3 kPa corresponding to stage F2, F3 and F4, respectively[67]. A recent meta-analysis on the utility of TE in the context of NAFLD included 9 studies consisting of 1047 NAFLD patients[39]. The analysis suggested excellent accuracy in diagnosing F3 or higher (85% sensitivity, 82% specificity) and F4 (92% sensitivity, 92% specificity) while performance was moderate for stage F2 or higher (79% sensitivity, 75% specificity).

**Alcoholic liver disease:** A recent Cochrane Database review examined the diagnostic accuracy of TE for diagnosis and staging of liver fibrosis in patients with alcoholic liver disease[68]. Five retrospective and nine prospective cohort studies with a total of 834 subjects were reviewed. The authors concluded that TE may be used to rule out liver cirrhosis in patients with alcoholic liver disease when the pre-test probability is about 51% (range 15%-79%) using a cut-off value of 12.5 kPa. However the authors cautioned that the optimal cut-off values for assessing fibrosis cannot be established due to the wide range of cut-off values used in individual studies. In a recent study comparing different non-invasive modalities for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease, TE performed better than FibroTest, APRI, Forns and FIB-4 with an optimal LSM of 10.3 kPa for F3 and 18.0 kPa for F4 disease[69,70].

**Cholestatic liver diseases:** TE is a reliable non-invasive means for assessing fibrosis stages in cho-

lestatic liver diseases such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis[71-74]. Optimal stiffness cutoff values of 7.3, 9.8, and 17.3 kPa for F ⩾ 2, F ⩾ 3 and F ⩾ 4 respectively have been proposed[71]. TE has been shown to be significantly superior to biochemical markers such as aspartate aminotransferase (AST)/platelet ratio, FIB-4, hyaluronic acid, AST/alanine aminotransferase ratio, and Mayo score in assessing fibrosis stages in PBC. Furthermore, it has also been shown that serial TE can provide prognostic information, as a 2.1 kPa-per-year increase is associated with an 8.4 fold increased risk of liver decompensations, liver transplantations, or deaths in patients with PBC[72].

**Autoimmune hepatitis:** The utility of TE in autoimmune hepatitis (AIH) is less well validated. There are case reports that described markedly increased liver stiffness in acute AIH. However, liver stiffness normalised after 4 mo of therapy suggesting that liver stiffness measurement can be greatly influenced by florid inflammatory liver process in AIH[75]. Another small case series supported the use of TE in assessing fibrosis in non-viral chronic liver diseases including AIH[73]. Optimal TE cut-off value for AIH has not been established. Therefore, care needs to be taken when performing TE on AIH patients, bearing in mind that uncontrolled inflammation from AIH will increase liver stiffness.

**Post liver transplant:** Several studies have evaluated the role of TE as a non-invasive tool for the detection of hepatic fibrosis due to recurrent hepatitis C following living donor and deceased donor liver transplantation[76-79]. All studies confirmed the excellent correlation of LSM to fibrosis on histology. In addition, Carrión *et al*[76] also showed that TE is an excellent tool to diagnose portal hypertension among patients with advanced fibrosis, cirrhosis and fibrosing cholestatic hepatitis. TE was also shown to be superior to serum markers[77] and other more complex scoring systems for the diagnosis of advanced fibrosis and cirrhosis in this group of liver transplant recipients[78]. These studies suggest that in patients with very low liver stiffness values, liver biopsy may safely be avoided. However, the main drawback of TE is the interpretation of results which correspond to the intermediate stages of fibrosis, where liver biopsy is still mandatory for accurate staging of liver fibrosis[79].

**Other liver diseases:** The availability of reliable non-invasive tools to diagnose liver fibrosis is of tremendous clinical relevance for patients on long-term treatment with methotrexate (MTX) as it helps to avoid routine liver biopsy for assessment of MTX toxicity. Despite a lack of high-quality, prospective studies providing biopsy-paired correlation of the accuracy of TE in this population, the existing literature suggests that TE is an effective non-invasive tool for monitoring MTX toxicity in patients with inflammatory bowel disease, rheumatoid arthritis and psoriasis[80-84]. The prevalence of abnormal LSM values > 7.1 kPa was generally low in this patient population and LSM values are not correlated with the cumulative MTX dose[85]. A recent review from the International Society of Dermatology states that both TE and MRE have outstanding efficacy in detection of liver fibrosis and can help the physician in the decision to use a therapeutic alternative to MTX[86].

In patients with hemochromatosis, an algorithm using serum ferritin levels together with TE was shown to accurately classify the presence of severe fibrosis in 61% of patients, thus avoiding liver biopsy in this group[87]. Together with other studies on patients with hemochromatosis, the evidence suggests a role for TE although more longitudinal prospective studies are required to clearly establish the clinical role of TE in hemochromatosis[88,89].

TE plays a role in the clinical evaluation of individuals with non-cirrhotic portal hypertension[90]. The primary role of TE in this setting is to exclude cirrhosis in patients who present with clinical features suggesting cirrhosis such as splenomegaly, esophageal varices and thrombocytopenia. Compared to cirrhotics, patients with non-cirrhotic portal hypertension have much lower liver stiffness values in the range of 8-9 kPa, which is clearly not compatible with the diagnosis of cirrhosis[91,92].

In summary, TE is the most accurate non-invasive test for the diagnosis of cirrhosis with a high negative predictive value to exclude liver cirrhosis[93]. One important use of TE in clinical practice is to exclude cirrhosis in patients with chronic liver disease, thus avoiding the need for patients to undergo invasive and expensive investigations such as screening gastroscopy for varices and routine HCC surveillance. This translates to a greater cost-effective management for this group of patients. The performance of TE is only moderate for the non-invasive diagnosis of fibrosis and it cannot reliably replace liver biopsy to diagnose milder stages of fibrosis.

### *Longitudinal assessment of fibrosis regression*

All the preceding applications of TE were based on a single, point-in-time TE assessment. Intuitively, serial TE measurements should allow one to assess the progression of fibrosis over time or the regression of fibrosis after successful treatment of the underlying liver disease. This has been shown to be possible in chronic viral hepatitis. Vergniol *et al*[94] showed that there was a significant reduction of TE readings in CHC patients successfully treated with pegylated interferon and ribavirin. Regression of fibrosis in CHB patients on antiviral treatment is associated with good outcomes[95-97]. Several short and long-term studies have shown that LSM values consistently decrease over

time during continuous antiviral treatment[98-100]. This decrease in liver stiffness is not restricted to patients with milder degree of fibrosis. Kim *et al*[101] reported that a higher liver stiffness value was the only significant factor associated with a decline in liver stiffness value during prolonged antiviral therapy. However, it is known that liver stiffness measurement by TE is increased by elevation of aminotransferases[102]. In a study by Lim *et al*[103], the decrease in liver stiffness value during antiviral therapy was correlated to decrease in liver inflammation on histology but not fibrosis, while contradicting findings were reported by Wong *et al*[104]. Therefore, it remains unclear based on available evidence if a decrease in LSM in treated CHB reflects a regression of liver fibrosis or a decrease in hepatic necroinflammation as a result of viral suppression. In current clinical practice, an emerging role for TE is for the longitudinal monitoring for regression of cirrhosis and fibrosis in patients on antiviral therapy. This role is likely to expand with recent advances in antifibrotic treatment.

### Non-invasive prediction of significant portal hypertension

In patients with compensated liver cirrhosis, the presence of clinically significant portal hypertension predicts clinical decompensation and poor outcomes[105]. One area of interest in TE is the correlation between LSM and hepatic venous pressure gradient (HVPG). Five studies have evaluated the diagnostic accuracy of TE for diagnosis of clinically significant portal hypertension (defined as HVPG $\geqslant$ 10 mmHg)[106-110]. A recent meta-analysis[111] evaluating 18 studies involving 3644 patients with chronic liver disease showed that TE was a good screening tool for detecting significant portal hypertension with 81% probability of correctly detecting significant portal hypertension when the pre-test probability was 50%. Cut-off LSM values ranged from 13.6 to 34.9 kPa with summary sensitivity of 0.90 and 0.79, with PPV of 0.88 and NPV of 0.88. Bureau *et al*[108] reported that a LSM of 21 kPa accurately predicted significant portal hypertension in 92% of patients undergoing paired HVPG and TE with an OR of 120 for HVPG $\geqslant$ 10 mmHg. However, Vizzutti *et al*[106] demonstrated that while a strong correlation existed between LSM and HVPG up to a HVPG of 12 mmHg, the correlation was poor at HVPG values beyond 12 mmHg. As such, although there may be a potential role of LSM for screening for presence of significant portal hypertension, it cannot replace HVPG for the quantitative assessment of portal pressures.

### Prediction of liver-related clinical outcomes

While earlier studies exploring the role of TE in clinical practice focused on cross-sectional studies, there is a wealth of convincing literature which demonstrates that TE has a prognostic role for prediction of important clinical end-points related to progression of fibrosis and cirrhosis[112-114]. In our opinion, this has greater clinical significance compared to point-in-time assessment of cirrhosis. Foucher *et al*[115] were the first to demonstrate that progressively higher LSM values were correlated with clinical decompensation events such as ascites, HCC and variceal bleeding. In this study of 711 CHC patients, various LSM cut-offs had NPV exceeding 90% for different associations, *e.g*., 27.5 kPa for large esophageal varices, 37.5 kPa for Child-Pugh B or C, 49.1 kPa for past history of ascites, 53.7 kPa for HCC and 62.7 kPa for esophageal variceal bleeding.

A significant correlation was shown between TE and presence of esophageal varices[116,117]. In a meta-analysis of 12 studies examining the accuracy of TE for detection of esophageal varices[111], there was a wide range of cut-off LSM values from 15.1 to 28.0 kPa, with a summary sensitivity of 0.87 but poor specificity of 0.53. In a setting of a low pre-test index of suspicion, the probability of a correct diagnosis following a "correct" LSM measurement was less than 70%. Recently Kim *et al*[118] developed a liver stiffness measurement based prediction model which included spleen diameter to platelet ratio, to enable identification of patients with very low likelihood of high risk esophageal varices with a negative predictive value of 94.0%. However, this was a single-centre study where external validation is necessary before the prediction model may be widely used. At present, TE is not sufficiently reliable to replace endoscopy for assessment of esophageal varices in routine clinical practice[119].

Importantly, TE has the potential to predict clinical liver-related events. A prospective study by Robic *et al*[120], demonstrated that a LSM > 21.1 kPa proved as effective as HVPG to predict clinical decompensation and liver-related events (ascites, variceal bleeding, HCC, HE and death). A Japanese study demonstrated in a large 3-year study of 866 CHC patients that a TE value of > 10 kPa carried a significantly higher risk of developing HCC[121]. This finding is not surprising as a TE value of 10 kPa really denotes that a patient has significant fibrosis which is a known association with HCC. Kim *et al*[122] correlated liver stiffness values according to histological sub-classifications of cirrhosis according to Laennec system, and showed that the proportion of liver-related events increased according to the baseline histological sub-classification and LSM prior to starting antiviral therapy. In another study by Lee *et al*[123], TE was shown to be a useful tool to predict liver-related events among CHB patients with complete viral suppression, where patients with LSM > 13.0 kPa had a hazard ratio of 12.0 for any cirrhosis-related decompensation, HCC and liver-related mortality as compared to patients with liver stiffness < 8.0 kPa. These two studies suggest that baseline as well as dynamic change in the liver stiffness value among patients on antiviral therapy can risk stratify

patients into those at higher risk of decompensation and mortality, even among those with complete viral suppression. Serial TE in cirrhotic patients may be clinically relevant as increases in serial LSM has been shown to predict clinical outcomes including decompensation, need for liver transplant and death[72].

### *Assessment of hepatic steatosis*

The rising prevalence of NAFLD worldwide is becoming an increasing problem in tandem with rising rates of obesity and metabolic syndrome. This raises the need to screen, diagnose and quantify hepatic steatosis in the large population at risk. TE has been shown to be useful for the non-invasive prediction of fibrosis in NAFLD patients and helps to select patients at high risk for progression to cirrhosis and HCC. The introduction and widespread adoption of the XL probe has resolved issues with TE failure in obese NAFLD patients. Apart from fibrosis assessment, the recent introduction of the novel controlled attenuation parameter (CAP) function allows for the non-invasive measurement of hepatic steatosis[124]. CAP measures ultrasound attenuation to quantify hepatic steatosis using the M probe and is expressed in dB/m. Studies have shown that CAP is able to detect more than 5% hepatic steatosis which intuitively is more sensitive than conventional ultrasound which can only detect more than 30% steatosis. In addition, CAP provides comparable accuracy in detection and quantification of hepatic steatosis across a range of liver disease etiologies[125,126]. Further studies are required to explore the robustness and validity of CAP in the study of liver disease. Interestingly, the combination of TE and CAP can simultaneously evaluate hepatic fibrosis and steatosis in a single examination. However, clinicians need to be mindful that this combination of TE and CAP can only predict for fibrosis and steatosis but cannot assess lobular inflammation and balloon degeneration. Hence the reliability of TE to predict clinical progression in NAFLD is limited considering that balloon degeneration is the most important histological feature that predicts disease progression. As such, in contrast to viral hepatitis, TE is unlikely to replace liver biopsy for NAFLD. Currently, the main clinical role for TE in NAFLD is for population screening to detect those with significant steatosis and fibrosis who would benefit from specialty care or treatment. Confirmation of NASH and assessment of severity will still require liver biopsy.

## COMPARISON BETWEEN TE AND OTHER NON-INVASIVE MARKERS OF FIBROSIS

### *TE vs serum markers*

There have been numerous studies comparing the performance of TE against serum markers for the non-invasive diagnosis of liver fibrosis. Overall, the diagnostic accuracy of TE and serum markers are comparable for the diagnosis of significant fibrosis but TE has improved accuracy for the diagnosis of cirrhosis[127]. A large multi-center prospective study comparing TE to serum markers (FIBROSTIC study) of 1307 patients with chronic viral hepatitis concluded that the accuracy of TE was significantly higher than serum markers for predicting cirrhosis. However, all non-invasive markers including TE had only moderate accuracy for predicting significant fibrosis[48]. In another multicentre study, TE was compared against nine serum markers for the diagnosis of fibrosis and cirrhosis in untreated CHC patients. FibroTest, FibroMeter, Hepascore and TE had similar superior performance compared to the other tests[128]. Overall performance of TE was reduced because 22% had uninterpretable results using the M probe. The advantage of serum markers is that it is easily available, inexpensive and does not require specialized equipment and training. However, serum markers can be confounded by biochemical abnormalities (*e.g.*, transaminitis, hemolysis, *etc*.) and do not provide a reflection of the physical degree of fibrosis in the liver. TE provides a more reliable assessment of liver fibrosis but is limited by invalid measurements in obese individuals or those with ascites (Table 3).

### *Combining TE and serum markers*

Combination of serum markers with TE can improve the accuracy of fibrosis staging. TE may falsely record high fibrosis scores due to increased stiffness of an inflamed liver. To overcome this weakness, a simple serum marker such as ALT can be used to improve its accuracy. ALT based algorithms for TE measurement of liver fibrosis has been proposed for CHB[9,10]. In addition, it has been demonstrated that spleen diameter and platelet ratio can also be used in combination with TE to improve accuracy[129]. Other markers such as haptoglobin, apolipoprotein A1, and $\alpha$2-macroglobulin levels have been used in combination with TE to establish a prediction model, called the HALF index, for better estimation of fibrosis staging[130]. Combination of serum markers with TE has been shown to improve the accuracy of detecting fibrosis and cirrhosis[7,128]. The latest clinical practice guidelines from the EASL and AASLD both recommend combination of TE and serum markers as the most efficient method of assessing liver fibrosis in making treatment decisions for patients with CHC[54,131]. Liver biopsy is reserved only in situations where there is discordance between the two non-invasive modalities.

### *TE vs MRE*

MRE uses a modified phase-contrast technique to visualise the propagation characteristics of acoustic shear waves generated by an acoustic driver placed over the liver[132]. Early studies have demonstrated that MRE indeed is a feasible alternative method to

**Table 3 Comparison of non-invasive modalities for assessment of fibrosis**

| Non-invasive test | Advantages | Disadvantages |
|---|---|---|
| Transient elastography | Easy to perform | Requires costly equipment |
| | Painless and comfortable | Unreliable in patients with severe obesity and ascites |
| | Can be done in clinic or office | Requires technical expertise |
| | Provides immediate results for clinician | Requires fasting |
| | Well-validated | Interpretation of LSM result dependent on etiology, ALT, *etc.* |
| | Can be performed reliably in obese patients with the use of XL probe | Only assesses part of the liver |
| | Readily available in most centres | |
| Serum markers | Easy to perform | Results can be confounded by biochemical abnormalities |
| | Inexpensive | Indirect reflection of liver fibrosis |
| | Does not require training or equipment | Does not assess liver stiffness directly |
| | Well-validated | Some tests are proprietary and are relatively costly |
| | Easily repeatable | |
| MRE | Multi-dimensional assessment | High cost |
| | Able to assess whole liver | Limited availability |
| | Operator independence | Cannot be performed in subjects with claustrophobia |
| | Can be performed in obese patients and those with ascites | Long examination time |
| | Can be integrated as part of a comprehensive MRI examination | Cannot be performed in livers with iron overload |
| ARFI/SWE | Higher success rate compared to TE (using M probe) | Requires special equipment and technical expertise |
| | Similar accuracy to TE | Operator-dependent |
| | Can be performed in obese patients and those with ascites | Not widely available |
| | Can assess whole liver | |
| | Can assess specific part of the liver (*i.e.*, region of interest) | |

TE: Transient elastography; MRE: Magnetic resonance elastography; ARFI: Acoustic radiation force impulse; SWE: Shear wave elastography; LSM: Liver stiffness measurement; ALT: Alanine transaminase; MRI: Magnetic resonance imaging.

assess liver elasticity[133-135]. Like TE, MRE has been shown to be repeatable and reproducible[136,137], has been validated against histological fibrosis in various chronic liver diseases including CHB, CHC and NAFLD[138-140] and has been shown to predict esophageal varices[141,142]. MRE is also falsely elevated by necroinflammation[143] but is not affected by steatosis[135].

In a study by Huwart *et al*[144] comparing the performance of TE and MRE in 141 patients with various liver diseases, MRE was shown to be superior to TE in predicting liver fibrosis stage. The better performance of MRE over TE was attributed to several reasons. In MRE, a multi-dimensional displacement vector is assessed as opposed to the 1-dimensional model of TE which improves the shear elastic parameter measured. Also, in MRE, a volume that includes several liver sections is analysed, in contrast to TE which analyses a single cylindrical liver sample of 20-40 mm. Hence, the volume analysed by MRE is far more representative of the liver parenchyma. However, in another study by Bohte *et al*[145], the diagnostic accuracies of TE and MRE for detecting METAVIR F > 2 and F > 3 in patients with CHB and CHC did not differ significantly.

Although there is no conclusive data on superiority of MRE over TE, there are several advantages of MRE over TE. Unlike TE, MRE has a freely oriented field of view without the need for an acoustic window and the latter is one of the important reasons for TE failure. MRE is operator independent and can be used in obese patients and patients with ascites. Perhaps most importantly, MRE can be integrated as part of a comprehensive liver MR imaging examination that can include a conventional diagnostic liver MRI in addition to MRE as well as protocols for assessment of steatosis. The disadvantages of MRE include the high cost, longer examination time, facility constraints and the inability to perform MRE in livers with iron overload due to signal-to-noise limitation. Importantly TE offers the convenience of a rapid bedside procedure which can be done in the clinic and can provide immediate results to the physician.

### *TE vs ARFI*

In the last few years, several non-invasive methods have been developed to evaluate liver fibrosis, including TE and ARFI elastography.

ARFI is performed with a Siemens AcusonS2000TM (Siemens AG, Erlangen, Germany) ultrasound system. The ultrasound probe automatically generates shearwaves which propagate into the tissue. The propagation speed increases with fibrosis severity, providing an estimation of the elasticity which is expressed in m/s[146]. Both TE and ARFI have been validated and advocated for assessment of liver fibrosis across a range of liver diseases. In a meta-analysis comparing diagnostic performance of ARFI and TE involving 13 studies and 1163 patients, failure rates were higher in TE compared to ARFI (6.6% *vs* 2.1%); caveat being that the TE evaluations were performed using M probe[146]. In terms of diagnostic accuracy, there were no significant differences between either modality to detect significant fibrosis or cirrhosis. For

detection of F2, sensitivity of 0.74 and specificity of 0.83 while sensitivity of 0.78 and specificity of 0.84 was reported for ARFI and TE, respectively. For detection of F4, sensitivity of 0.87 and specificity of 0.87 while sensitivity of 0.89 and specificity of 0.87 was reported for ARFI and TE, respectively.

## CONCLUSION

The role of TE in clinical practice has evolved over the past decade in tandem with changing trends in clinical management of chronic liver disease. The diagnostic accuracy of TE has been clearly defined for the diagnosis of cirrhosis. In current clinical practice, TE has replaced ultrasound and CT as the most accurate non-invasive method for diagnosis of liver cirrhosis. TE is useful to rule out fibrosis and cirrhosis but does not have sufficient accuracy to discern between various stages of fibrosis. This has led to the recommendation to use TE in combination with serum markers for clinical assessment of fibrosis in CHC. Importantly, the clinical role of TE has evolved from cross-sectional point-in-time assessment of fibrosis and cirrhosis to the more relevant role of prediction of vital clinical end-points. This provides clinicians with the ability to modify treatment strategies based on the information provided by TE. In addition, recent advances in development of antifibrotic therapy will increase the role of serial TE for longitudinal assessment of progression and regression of fibrosis. The availability of the combination of TE and CAP will provide the opportunity to screen at-risk populations with NAFLD for fibrosis and steatosis in a single convenient examination. TE has evolved over the past decade to become an essential tool to assist the clinician in management of chronic liver disease.

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