

## Transient elastography: Kill two birds with one stone?

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### Abstract

Assessment of liver fibrosis and steatosis is crucial in chronic liver diseases in order to determine the prognosis, the need of treatment, as well as monitor disease progression and response to treatment. Liver biopsy is limited by its invasiveness and patient acceptability. Transient elastography (TE, Fibroscan®) is a non-invasive tool with satisfactory accuracy and reproducibility to estimate liver fibrosis and steatosis. TE has been well validated in major liver diseases including chronic hepatitis B and C, non-alcoholic fatty liver disease, alcoholic liver disease, primary biliary cirrhosis, and primary sclerosing cholangitis. As alanine aminotransferase (ALT) is one of the major confounding factors of liver stiffness in chronic hepatitis B, an ALT-based algorithm has been developed and higher liver stiffness measurements (LSM) cutoff values for different stages of liver fibrosis should be used in patients with elevated ALT levels up to 5 times of the upper limit of normal. Otherwise falsely-high LSM results up to cirrhotic range may occur during ALT flare. TE is also useful in predicting patient prognosis such as development of hepatocellular carcinoma (HCC), portal hypertension, post-operative complications in HCC patients, and also survival. Unfortunately, failed acquisition of TE is common in obese patients. Furthermore,

obese patients may have higher LSM results even in the same stage of liver fibrosis. The new XL probe, a larger probe with lower ultrasound frequency and deeper penetration, increases the success rate of TE in obese patients. The median LSM value with XL probe was found to be lower than that by the conventional M probe, hence cutoff values approximately 1.2 to 1.3 kPa lower than those of M probe should be adopted. Recent studies revealed a novel ultrasonic controlled attenuation parameter (CAP) of the machine is a useful parameter to detect even low-grade steatosis noninvasively. CAP may also be used to quantify liver steatosis by applying different cutoff values. As both LSM and CAP results are instantly available at same measurement, this makes TE a very convenient tool to assess any patients who are suspected or confirmed to suffer from chronic liver diseases.

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**Key words:** Biopsy; Cirrhosis; Fibrosis; Hepatitis; Fatty liver; Steatosis of liver

**Core tip:** Transient elastography (TE, Fibroscan®) is a non-invasive tool with satisfactory accuracy to estimate liver fibrosis and steatosis. Liver stiffness measurement (LSM) with TE has been well validated to detect advanced fibrosis in most liver diseases. LSM is useful in predicting hepatocellular carcinoma (HCC), portal hypertension, post-operative complications in HCC patients, and survival. The new XL probe increases the success rate of TE in obese patients. A novel ultrasonic controlled attenuation parameter (CAP) of the machine is useful to detect steatosis noninvasively. Simultaneous LSM and CAP results make TE very convenient to assess any patients with suspected or confirmed liver diseases.

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## INTRODUCTION

Liver fibrosis is the natural wound-healing response to parenchymal injury in chronic liver diseases. Simple steatosis is a usually reversible and benign condition, but steatosis may be part of the more sinister condition in the setting of steatohepatitis where inflammation and hepatocyte changes co-exist<sup>[1-3]</sup>. Both liver fibrosis and steatohepatitis may eventually result in liver cirrhosis and its various complications. Sensitive detection and accurate staging of liver fibrosis and steatosis is now essentially indispensable in the decision process of treatment in chronic viral hepatitis as well as predicting disease prognosis<sup>[4,5]</sup>. It is also vital to monitor disease progression and response to treatment.

## LIVER BIOPSY: DRAWBACK OF THIS “GOLD STANDARD”

Liver biopsy has been the “gold standard” for assessing liver fibrosis and steatosis in the last few decades<sup>[6,7]</sup>. However, it has numerous limitations namely its invasive nature, risk of complications, patient discomfort, and sampling errors<sup>[8,9]</sup>. Complications associated with liver biopsy are rare but can be severe and even life threatening. Pain and hypotension are the predominant complications for which patients are hospitalized<sup>[10]</sup>. Clinically significant intraperitoneal hemorrhage is the rarest but most serious bleeding complication of percutaneous liver biopsy, which may happen more often in older age patients with cirrhosis or liver cancer<sup>[11]</sup>. Inadvertent puncture of gallbladder may lead to choleperitoneum<sup>[12]</sup>. The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10000 to 1 in 12000<sup>[13]</sup>. All these problems make it impractical to perform serial biopsies to assess disease progression in routine clinical practice<sup>[5]</sup>. The cost of liver biopsy is generally high as an in-patient bed, at least as day admission to hospital, is required. Including the charges of specialist doctor, nursing care and histologic examinations, it usually costs at the range of USD \$800 to USD \$1200 in Hong Kong.

The diagnostic accuracy of liver biopsy is limited by the sampling variability<sup>[14-16]</sup>. The average size of biopsy is 15 mm in length, which represents 1/50000 the size of the entire liver. There is significant variability in the histologic assessment of two readings of the same biopsy by the same pathologist, and between two pathologists, even among those who are highly specialized<sup>[8]</sup>. This variability is low for the diagnosis of cirrhosis (kappa coefficient of concordance  $\geq 0.80$ ), moderate for earlier fibrosis stages (kappa 0.70-0.80), but high for the activity grades (kappa 0.40-0.50)<sup>[8]</sup>. Fortunately, the variability is usually low for the diagnosis of steatosis (kappa coefficient of concordance  $\geq 0.80$ )<sup>[14]</sup>. Given the above limitations to the practice of liver biopsy, a noninvasive transient elastography has been proposed as an alternative tool.

## TRANSIENT ELASTOGRAPHY

### Working principles of liver stiffness measurement

Transient elastography (TE; Fibroscan<sup>®</sup>; Echosens, Paris, France) measures liver stiffness<sup>[17]</sup> in patients suffering from different chronic liver diseases<sup>[18]</sup>. An ultrasound transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency (50 Hz) are transmitted by the transducer, inducing a plastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisition is used to follow the propagation of the shear wave and to measure its velocity, which is directly related to tissue stiffness. The stiffer the tissue, the faster the shear wave propagates. TE measures liver stiffness in a volume that approximates a cylinder 1 cm in diameter and 4 cm in length, between 25 to 65 mm underneath the skin surface. This volume is at least 100 times bigger than a biopsy sample, and therefore should be more representative of the liver parenchyma<sup>[17]</sup>. Results of liver stiffness measurement (LSM) are expressed in kPa and correspond to the median of 10 validated measurements according to Sandrin *et al*<sup>[17]</sup>. According to the manufacturer, the examination is considered reliable if  $\geq 10$  valid measurements are acquired, the success rate (number of valid acquisitions divided by the number of attempts) is over 60%, and the ratio of the interquartile range to the median of 10 measurements (IQR/M) is  $\leq 0.3$ <sup>[17]</sup>.

### Working principles of controlled attenuation parameter

It is important to assess liver steatosis, not only because non-alcoholic fatty liver disease (NAFLD) is the commonest liver disease<sup>[19]</sup>, but also that steatosis often coexists in other chronic liver diseases likely chronic hepatitis C (CHC)<sup>[20]</sup>. A new physical parameter based on the properties of ultrasonic signals acquired by the machine has been recently developed to assess liver steatosis by applying the property that liver steatosis affects ultrasound propagation<sup>[21]</sup>. This controlled attenuation parameter (CAP), is measuring ultrasound attenuation (go and return path) at 3.5 MHz using signals acquired by the M probe of TE machine. Ultrasound attenuation is a physical property of the medium of propagation which corresponds to the loss of energy as ultrasound travels through the medium. Due to attenuation, the intensity of the emitted ultrasound decreases exponentially with depth<sup>[21]</sup>. At a given frequency, the ultrasound-attenuation coefficient ( $\alpha$ ) can be expressed in dB/m. The CAP is measured only on validated measurements according to the same criteria used for LSM, and on the same signals. This ensures that the operator obtains a liver ultrasonic attenuation simultaneously and in the same volume of liver parenchyma as the LSM. The final CAP value was the median of individual CAP values using the same valid measurements<sup>[22]</sup>.

### Practical issues

TE has the advantages of being painless, rapid (usually

**Table 1** Diagnostic performance and suggested cutoff values of liver stiffness measurement for the diagnosis of histologic cirrhosis (F4)

Ref.	Biopsies (n)	Prevalence of cirrhosis (F4)	Etiologies	Proposed cutoff values (kPa)	Sensitivity	Specificity	NPV	PPV	Positive LR	Negative LR	AUROC
Castéra <i>et al</i> <sup>[41]</sup> , 2005	183	25%	HCV	12.5	87%	91%	95%	77%	9.7	0.1	0.95
Fraquelli <i>et al</i> <sup>[23]</sup> , 2007	200	12%	All	11.9	91%	89%	98%	53%	8.3	0.1	0.9
Arena <i>et al</i> <sup>[24]</sup> , 2008	150	19.3%	HCV	14.8	94%	92%	98%	73%	11.3	0.07	0.99
Ziol <i>et al</i> <sup>[25]</sup> , 2005	251	19%	HCV	14.6	86%	96%	97%	78%	23.1	0.1	0.97
Chan <i>et al</i> <sup>[26]</sup> , 2009	161	25%	HBV	13.4	60%	93%	88%	75%	85	0.43	0.93
Marcellin <i>et al</i> <sup>[27]</sup> , 2009	173	8%	HBV	11	93%	87%	99%	38%	7	0.08	0.93
Wong <i>et al</i> <sup>[28]</sup> , 2010 <sup>1</sup>	238	23.5%	HBV	9.0 (normal ALT) 12.0 (elevated ALT)	54%	99%	67%	98%	3.3	0.7	0.88
de Lédinghen <i>et al</i> <sup>[29]</sup> , 2006	72	23.6%	HCV-HIV	11.8	100%	92.7%	82%	100%	13.7	0	0.97
Nobili <i>et al</i> <sup>[30]</sup> , 2008 <sup>1</sup>	52	5.8%	NAFLD	10.2	100%	100%	100%	100%	∞	0	1
Wong <i>et al</i> <sup>[31]</sup> , 2010	246	10.1%	NAFLD	10.3	92%	88%	99%	46%	7.5	0.09	0.95
Nahon <i>et al</i> <sup>[32]</sup> , 2008	174	53.7%	ALD	22.7	84%	83%	82%	85%	5.24	0.19	0.87
Corpechot <i>et al</i> <sup>[33]</sup> , 2006	95 (66 PBC, 29 PSC)	16%	PBC/PSC	17.3	93%	95%	99%	78%	18.6	0.1	0.96
Carrión <i>et al</i> <sup>[34]</sup> , 2006	124	11%	HCV-LT	12.5	100%	87%	100%	50%	7.7	0	0.98
Witters <i>et al</i> <sup>[36]</sup> , 2009	66	NA	Cystic fibrosis	6.5	100%	81%	NA	NA	NA	NA	0.92
Coco <i>et al</i> <sup>[75]</sup> , 2007	228	20.2%	HCV/HBV	14	78%	98%	82%	98%	39	0.2	0.96
Ganne-Carrié <i>et al</i> <sup>[106]</sup> , 2006	775	15.5%	All	14.6	79%	95%	96%	74%	15.8	0.1	0.95
Foucher <i>et al</i> <sup>[107]</sup> , 2006	354	13.3%	All	17.6	77%	97%	92%	91%	25.7	0.2	0.96
Gómez-Domínguez <i>et al</i> <sup>[108]</sup> , 2006	94	17%	All	16	89%	96%	98%	80%	22.3	0.1	0.94
Vergara <i>et al</i> <sup>[109]</sup> , 2007	169	38.5%	HCV-HIV	14.6	93%	88%	94%	86%	7.8	0.1	0.95
Rigamonti <i>et al</i> <sup>[110]</sup> , 2008	95	17%	HCV-LT	12	93%	93%	99%	74%	14	0.1	0.9
Yoneda <i>et al</i> <sup>[111]</sup> , 2007	67	7.5%	NAFLD	17	100%	98%	95%	64%	50	0	0.99

<sup>1</sup>Cut-off values proposed for advanced fibrosis (F3 or above). ALD: Alcoholic liver disease; ALT: Alanine aminotransferase; AUROC: Area under receiver operating characteristics curves; HBV: Hepatitis B virus infection; HCV: Hepatitis C virus infection; HCV-HIV: Hepatitis B virus and human immunodeficiency virus co-infection; HCV-LT: Hepatitis C virus infection recurrence after liver transplantation; LR: Likelihood ratio; NAFLD: Non-alcoholic fatty liver disease; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis; NPV: Negative predictive value; PPV: Positive predictive value; NA: Not available.

less than 5 min) and easy to perform at the bedside or in the outpatient clinic. The examination is performed on a non-fasting patient lying supine with the right arm placed behind the head to facilitate access to the right upper quadrant of the abdomen. The tip of the probe transducer is placed on the skin between the rib bones at the level of the right lobe of the liver where liver biopsy would be performed. Once the measurement area has been located, the operator presses the button on the probe to start an acquisition. The software determines whether each measurement is successful or not. The cost of a TE examination ranges from USD \$100 to USD \$150 in Hong Kong, which is much lower than a liver biopsy examination. It is obvious that TE is a user- and patient-friendly, but it would be even more important to be an accurate tool to assess liver fibrosis and steatosis.

## ACCURACY OF TE

### Liver stiffness measurement

Reproducibility of TE is an important feature for its widespread clinical application. The reproducibility of LSM was excellent for both inter-observer and intra-observer agreement, with intraclass correlation coefficients (ICC) of 0.98<sup>[23]</sup>. However, interobserver agreement was significantly reduced in patients with lower degrees of liver fibrosis (ICC for F0-1 and F2 were 0.60 and 0.99 respectively), with liver steatosis (ICC for steatosis <

25% and 25% of hepatocytes 0.98 and 0.90 respectively), and with increased body mass index (ICC for body mass index  $\geq 25$  kg/m<sup>2</sup> and < 25 kg/m<sup>2</sup> were 0.98 and 0.94 respectively).

Using TE to assess liver fibrosis has been widely validated in different liver diseases, including CHC<sup>[4,24,25]</sup>, chronic hepatitis B (CHB)<sup>[26-28]</sup>, co-infection with HIV<sup>[29]</sup>, NAFLD<sup>[30,31]</sup>, alcoholic liver disease<sup>[32]</sup>, primary biliary cirrhosis, primary sclerosing cholangitis (PSC)<sup>[33]</sup>, post-liver transplantation setting<sup>[34]</sup>, and in cystic fibrosis<sup>[35,36]</sup>. In these studies, TE was valid with liver histology being the gold standard. In general, all these studies confirm that TE has good overall accuracy to diagnose advanced fibrosis and cirrhosis (though some uncommon diseases like PSC and cystic fibrosis are under-represented by small numbers of patients), independent of the underlying etiology<sup>[37,38]</sup>. The remaining controversy is the optimal cutoff values to diagnose advanced fibrosis and cirrhosis, which differ according to particular etiologies. This has significant implication when a clinician interprets TE results. The suggested diagnostic performance and cutoff values for histologic cirrhosis (F4) based on published studies are summarized in Table 1.

### Controlled attenuation parameter

In a retrospective study of 115 patients of mixed etiologies of chronic liver diseases, CAP was found efficient to detect low grade steatosis (> 10%), with a sensitivity of

Table 2 Diagnostic performance and suggested cutoff values of controlled attenuation parameter for the diagnosis of liver steatosis

Ref.	Biopsies (n)	Study design	Etiologies	AUROC S1 (11%)	AUROC S2 (34%)	AUROC S3 (67%)	Cutoff values for S1 (dB/m)	Sen	Spe	NPV	PPV	Cutoff values for S2 (dB/m)	Sen	Spe	NPV	PPV	Cutoff values for S3 (dB/m)	Sen	Spe	NPV	PPV
Sasso <i>et al</i> <sup>[21]</sup> , 2010	115	Retrospective	All	0.91	0.95	0.89	238	91 %	81 %	87 %	87 %	259	89 %	86 %	92 %	80 %	292	100 %	78 %	100 %	28 %
de Ledinghen <i>et al</i> <sup>[39]</sup> , 2012	112	Prospective	All	0.84	0.86	0.93	215					252					296				
Myers <i>et al</i> <sup>[40]</sup> , 2012	153	Prospective	All	0.81			283	76 %	79 %	64 %	87 %										
Beaugrand <i>et al</i> <sup>[41]</sup> , 2010	74	Retrospective	ALD	0.81	0.87	0.82															
Beaugrand <i>et al</i> <sup>[42]</sup> , 2010	96	Retrospective	ALD/ NAFLD	0.86	0.87	0.77															
Cardoso <i>et al</i> <sup>[43]</sup> , 2010	133	Retrospective	CHB	0.82	0.81	-															
Sasso <i>et al</i> <sup>[44]</sup> , 2012	615	Retrospective	CHC	0.8	0.86	0.88															

ALD: Alcoholic liver disease; AUROC: Area under receiver operating characteristics curves; NPV: Negative predictive value; PPV: Positive predictive value; Sen: Sensitivity; Spe: Specificity; NAFLD: Non-alcoholic fatty liver disease; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C.

91% and specificity of 81% at a cutoff value of 238 dB/m<sup>[21]</sup>. The accuracy of CAP was confirmed in two prospective studies of mixed etiologies<sup>[39,40]</sup>, as well as in individual etiology, including CHB, CHC, NAFLD and alcoholic liver disease<sup>[41-44]</sup>. The suggested diagnostic performance and cutoff values for different degrees of steatosis are summarized in Table 2. As a well-validated tool, TE is also well-investigated in different aspects of clinical applications.

### CLINICAL APPLICATIONS OF TE

#### Pre-treatment assessment of liver fibrosis

The severity of liver fibrosis is the key factor of timing and choice of therapy. This is particularly relevant in chronic viral hepatitis. Current international guidelines recommend antiviral therapy for CHB patients with significant liver fibrosis<sup>[45-47]</sup>. As TE has been repeatedly shown to have satisfactory accuracy to exclude and diagnose advanced fibrosis and cirrhosis as mentioned above, more than half of the patients might reach treatment decision without the need for confirmatory liver biopsies<sup>[20]</sup>. TE is also found to be more cost-effective than liver biopsy<sup>[48]</sup>. TE has been incorporated in the international guidelines of CHB and CHC<sup>[45,46]</sup>. TE, together with other non-invasive parameters, can also be used as the screening tool for cirrhosis in asymptomatic people<sup>[49,51]</sup>, as well as the diagnostic and/or prognostic tool of NAFLD, such that the need of liver biopsy can be reduced<sup>[52,53]</sup>.

#### Follow-up assessment of liver fibrosis

A few longitudinal studies have been reported that patients responding to treatment had low or decreased liver stiffness<sup>[54]</sup>. In fact, both reduction in fibrosis and necroinflammation might contribute to the decrease in liver stiffness<sup>[55]</sup>. In a prospective study of 71 CHB patients on antiviral therapy, paired liver biopsy and TE were both performed at baseline and at 1 year of treatment<sup>[56]</sup>. Although TE remained accurate in distinguishing patients with insignificant disease from those with advanced fibrosis or cirrhosis at both time points, the absolute change in liver stiffness correlated poorly with the change in histological fibrosis stage, and resolution of advanced fibrosis could only be assumed with significantly decreased liver stiffness to 5.0 kPa or less after antiviral treatment<sup>[56]</sup>.

#### Predict portal hypertension and variceal bleeding

TE is found useful to identify cirrhotic patients with higher risk of portal hypertension, and cutoff values of 17.6 kPa and 21.0 kPa having sensitivity  $\geq 90\%$  in order to detect patients with hepatic venous pressure gradient (HVPG) above 10-12 mmHg<sup>[57,58]</sup>. Presence of varices could be excluded with a liver stiffness below 12.5-19.8 kPa<sup>[59,60]</sup>. Unfortunately, these suggested cutoff values overlap with those for detecting histologic cirrhosis in most chronic liver diseases. Hence there seems no significant new information pro-



**Table 3** Liver stiffness measurement and the risk of hepatocellular carcinoma in chronic hepatitis B or C patients

Chronic hepatitis B patients		Chronic hepatitis C patients	
LSM (kPa)	HR of HCC	LSM (kPa)	HR of HCC
≤ 10.0	Referent	≤ 8.0	Referent
10.1-15.0	17	8.1-13.0	3.1
15.1-20.0	21	13.1-18.0	4.7
20.1-25.0	26	18.1-23.0	5.6
> 25.0	46	> 23.0	6.6

LSM: Liver stiffness measurement; HCC: Hepatocellular carcinoma.

vided by TE regarding screening endoscopy for varices among cirrhotic patients.

### Predict hepatocellular carcinoma

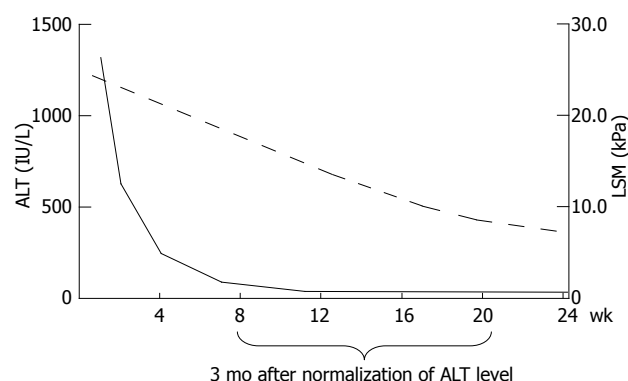
TE is also useful to predict the risk other liver-related complications and death. A dose-response relationship between LSM and risk of hepatocellular carcinoma (HCC) was found in both CHB and CHC patients (Table 3). Taking patients with LSM ≤ 10.0 kPa as reference, the hazard ratios of developing HCC were 17, 21, 26, and 46 in patients with LSM at 10.1-15.0, 15.1-20.0, 20.1-25.0 and above 25.0 kPa respectively, in a prospective cohort of 866 CHC patients<sup>[61]</sup>. Patients with LSM ≤ 8.0 kPa acted as the control group, the hazard ratios of developing HCC were 3.1, 4.7, 5.6 and 6.6 in patients with LSM at 8.1-13.0, 13.1-18.0, 18.1-23.0 and above 23.0 kPa respectively in another cohort of 1130 CHB patients<sup>[62]</sup>. LSM, as well as FibroTest, can also predict 5-year survival of patients with CHC; the prognostic values of LSM remained even after adjustments for treatment response, patient age, and degree of necroinflammation<sup>[63]</sup>.

### Predict post-operative outcomes

LSM is also an important prognostic tool in patients confirmed to have HCC. A prospective study of 105 HCC patients demonstrated that a LSM cutoff of 12.0 kPa had the sensitivity of 86% and specificity of 72% in predication of major post-operative complications<sup>[64]</sup>. This cutoff might also identify patients with more severe operative blood loss and higher transfusion rate<sup>[64]</sup>. Another study of 133 HCC patients revealed that patients of LSM ≥ 13.4 kPa had a nearly 2-fold increase in the risk of HCC recurrence compared to those with LSM < 13.4 kPa<sup>[65]</sup>.

### Assessment of liver steatosis

Liver steatosis is a common histological feature in the general population and in patients with chronic liver disease. Its prevalence is high: almost 30% in the general population<sup>[66,67]</sup>, 50% in patients with CHC<sup>[68]</sup>, above 80% in severely obese patients<sup>[69]</sup>. Liver steatosis plays a pivotal role in CHC, as metabolically (instead of virally) induced steatosis is associated with a lower response rate to antiviral treatment<sup>[70]</sup> and liver fibrosis progression<sup>[71]</sup>. Steatosis may also increase the risk of HCC<sup>[72]</sup>. Detection of liver steatosis is also important to the potential donors for liver transplantation, as their extent of steatosis is directly re-



**Figure 1** Falsely elevated liver stiffness measurement results in a patient with grossly elevated alanine aminotransferase levels. Liver stiffness measurement (LSM) values decreased considerably after the resolution of acute hepatitis. Modified from Wong *et al*<sup>[65]</sup>. ALT: Alanine aminotransferase.

lated to primary non-functioning of the graft, which may result in mortality or the need for re-transplantation<sup>[73]</sup>. Liver steatosis is also a risk factor for post-operative complications and mortality after liver resection<sup>[74]</sup>.

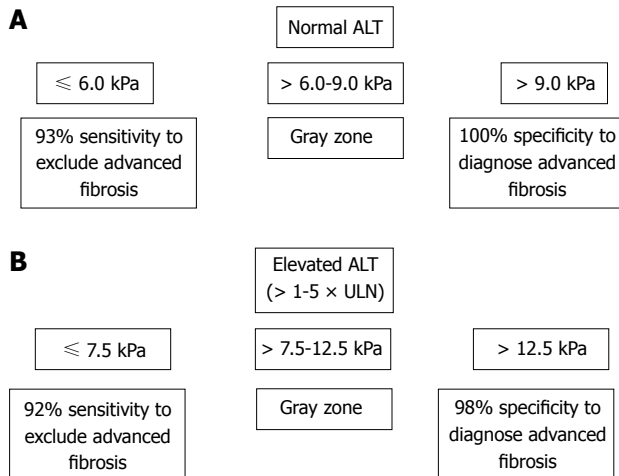
There have been enough data to prove TE is accurate and applicable in different clinical settings. How this tool also has a few shortcomings that any user should keep in mind.

## LIMITATIONS OF TE

### Factors affecting accuracy of measurements

Not only liver fibrosis but also other factors contribute to the liver stiffness. LSM has been consistently found to be falsely elevated in acute hepatitis manifested as alanine aminotransferase (ALT) flares<sup>[75,76]</sup>. Severe hepatic necroinflammation may lead to LSM values well within the cirrhotic range even in the absence of fibrosis on histology<sup>[55,77,78]</sup>. In this setting, LSM tends to decrease considerably after the resolution of acute hepatitis. Therefore, applying TE in this scenario can be misleading and not recommended until at least 3 mo after normalization or at least stabilization of ALT levels below 5 times the upper limit of normal<sup>[26,76]</sup> (Figure 1). An ALT-based algorithm has been developed and higher LSM cutoff values for different stages of liver fibrosis should be used in patients with elevated ALT levels (Figure 2). This also leads to another advantage of liver biopsy over TE that at this stage the necroinflammatory score is only available in histologic assessment.

Extrahepatic cholestasis<sup>[79]</sup>, hepatic congestion<sup>[80,81]</sup>, hepatic amyloidosis<sup>[82]</sup> and recent food intake (within 60 min)<sup>[83]</sup> were also found associated with a falsely high LSM values. Fortunately, the degree of liver steatosis does not appear to affect LSM results, therefore TE remains an accurate tool for fibrosis assessment in CHC and NAFLD<sup>[24,31]</sup>. A recent study found that the correlation between LSM and fibrosis stage was less strong in CHB and NAFLD than in CHC patients<sup>[84]</sup>. Our recent study showed that NAFLD patients with BMI 30 kg/m<sup>2</sup>, the lowest limit of an abnormal BMI in NAFLD, would have



**Figure 2** An alanine aminotransferase-based algorithm. A: Normal alanine aminotransferase (ALT); B: Elevated ALT levels up to 5 times of upper limit of normal (ULN) to exclude or establish advanced liver fibrosis for chronic hepatitis B patients. Modified from Chan *et al*<sup>[26]</sup>.

higher LSM values by M probe even in the same fibrosis stage<sup>[85]</sup>. This provocative finding may lead to concern about the M probe accuracy in obese patients. The emergence of XL probe is a possible solution to this issue.

#### Factors affecting success rate of measurements

It has been noted that unreliable and failed LSM occur at about 3% and 11.6% to 18.4% in all TE examinations, respectively, and they are independently associated body mass index (BMI) > 30 kg/m<sup>2</sup> in both Caucasians and Chinese<sup>[86,87]</sup>. The success rate of LSM with M probe would be as low as 75%<sup>[31]</sup> in NAFLD patients with BMI > 30 kg/m<sup>2</sup>. The low LSM success rate among obese patients is likely related to the thick subcutaneous fat, which hinders the transmission of shear waves and ultrasound waves through the liver parenchyma<sup>[87]</sup>. Patients with extreme very high and very low BMI were recently found to have higher LSM values in an Indian population<sup>[88]</sup>. Subjects with narrow intercostal space, high riding liver, hyperinflated lungs, ascites or free peritoneal fluid<sup>[87]</sup> may also have lower success rate or failed acquisition of LSM.

A recent study challenged the validity of the reliability criteria suggested by the manufacturer of 1165 patients with chronic liver diseases who underwent LSM within 3 mo of liver biopsy. The investigators found the number of successful acquisitions, and its success rate having no influence on the diagnostic accuracy<sup>[89]</sup>. Furthermore, LSM remained reliable even if the ratio of the interquartile range to the median of 10 measurements (IQR/M) > 0.30, provided that the median LSM < 7.1 kPa. These new findings implied that LSM results were more reliable than what was previously described.

#### Validity and availability of controlled attenuation parameter

Only a few studies on CAP have been published so far, and a few of them were only in abstract form. Hence

**Table 4** The characteristic of the new S and XL probes comparing to M probe

Probe	Frequency of ultrasound (MHz)	Depth (mm)
S	5	15-40
M	3.5	25-65
XL	2.5	35-75

CAP needs further validation in larger populations. Furthermore, CAP is not yet available in the measurements with the XL probe, which is designed for overweight and obese patients who are particularly at risk of liver steatosis<sup>[69]</sup>. Therefore, further development and calibration of CAP in XL probe is warranted.

## COMBINING TE WITH SERUM MARKERS

In general, serum markers have modest accuracy to diagnose advanced liver fibrosis<sup>[90,91]</sup>. TE has certain advantages over serum markers, as TE provides a more direct measurement of fibrosis, is less affected by inter-current health disorders, and is theoretically applicable to all chronic liver diseases. On the other hand, the diagnostic performance was particularly affected in patients with elevated serum ALT levels<sup>[55]</sup>. Hence a second non-invasive test independent of the serum ALT or AST levels may be a good supplementary test for LSM. Among various serum test formulae, Forns index<sup>[92]</sup> and Hui index<sup>[90]</sup> are composed of clinical parameters other than ALT or AST levels. We demonstrated that a combined LSM-Forns algorithm improved the accuracy to predict advanced liver fibrosis in 238 CHB patients<sup>[28]</sup>. In this combined algorithm, low LSM or low Forns index could be used to exclude advanced fibrosis with a high sensitivity of 95%. To confirm advanced fibrosis, agreement between high LSM and high Forns index could improve the specificity up to 99% to 100%<sup>[28]</sup>.

The combination of TE and FibroTest was found to have the best diagnostic performance compared to either test alone in patients with CHC<sup>[4]</sup>. When TE and FibroTest matched (present in 70%-80% of cases), results were also concordant, respectively in 84%, 95% and 94% of patients with liver fibrosis ≥ F2, ≥ F3 and F = 4<sup>[4]</sup>. The combination of LSM and FibroTest allowed exclusion of significant fibrosis (≥ F2) in nearly 80% of 100 CHB patients in inactive carrier stage.

## OTHER PROBES OF TE

The development of S and XL probes aim to cater for different population groups of various body-build types (Table 4). S probe contains a higher frequency ultrasonic transducer and shallower measurements below the skin surface, which suit pediatric subjects and those with small body build<sup>[93]</sup>. XL probe contains a lower frequency and a more sensitive transducer, a deeper focal length, larger vibration amplitude and a higher depth of measurements below the skin surface<sup>[94]</sup>. This probe serves obese sub-

jects with “XL” body builds. Data concerning the validations of these new probes are emerging.

With the XL probe, LSM could be successfully performed in more obese patients compared to the M probe<sup>[95]</sup>. In our validation study involving 286 patients, LSM using XL probe documented reliable results in 92% of patients, compared to 80% using M probe (64). In another study of 193 NAFLD patients, a cutoff value had reasonable sensitivity (78%), specificity (78%), positive predictive value (60%), and good negative predictive value (89%) for F3 or greater disease<sup>[96]</sup>. However, the median LSM by the XL probe was consistently found to be approximately 1.0 to 1.2 kPa lower than that of the M probe at the same stage of liver fibrosis in all of the histologic reports<sup>[95,96]</sup>. A recent exploratory study of 517 overweight patients having different etiologies, XL cutoff values of 4.8 kPa and 10.7 kPa, 6.0 kPa and 12.0 kPa with the M probe<sup>[85]</sup>, for patients with BMI > 25-30 kg/m<sup>2</sup>. Patients with BMI > 30 kg/m<sup>2</sup> might use M probe cut-offs for the XL probe. More studies are warranted to delineate the proper cutoff values of LSM using the XL probe in various etiologies.

## SPLEEN STIFFNESS: MEASURES PORTAL HYPERTENSION NON-INVASIVELY

Recent enthusiasm on spleen stiffness measurement (SSM) leads us to the non-invasive evaluation of portal hypertension, which is conventionally assessed by HVPG *via* hepatic angiogram<sup>[97]</sup>. SSM was recently found accurate to predict portal hypertension and esophageal varices<sup>[98,99]</sup>. The clinical role of SSM will be explored more in the near future.

## NEW IMAGING TECHNOLOGIES

Acoustic radiation force impulse (ARFI) is another new imaging technology based on the shear acoustic waves remotely induced by the radiation force of a focused ultrasonic beam<sup>[100]</sup>. ARFI may be even more accurate than TE for both significant and severe classes of liver fibrosis in CHC patients<sup>[101]</sup>. ARFI was also used for SSM in CHB and CHC patients<sup>[102]</sup>. Another technique called real-time tissue elastography (RTE) is incorporated into B-mode ultrasonography machine<sup>[103]</sup>. RTE is also found accurate to diagnose liver fibrosis and portal hypertension<sup>[104,105]</sup>. All these new technologies are also promising and should be further validated in the near future.

## CONCLUSION

TE is a non-invasive, accurate and reproducible test of advanced liver fibrosis, cirrhosis and steatosis. This tool has been validated in a wide spectrum of liver diseases. TE is also useful to predict patient outcomes. Further studies should explore the appropriate cutoff values of newer XL and S probes, and exploring the prognostic role of CAP.

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