MINI REVIEW

Transient Elastography (Fibroscan®): A New Look of Liver Fibrosis and Beyond

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ABSTRACT

It is now indispensable to assess the severity of liver fibrosis in essentially all 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 noninvasive tool with satisfactory accuracy and reproducibility to estimate liver fibrosis. TE has been well validated in all major liver diseases namely chronic hepatitis B (CHB) and C, nonalcoholic fatty liver disease (NAFLD), 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 CHB, 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. Falsely high LSM results well within cirrhotic range may occur during ALT flare, such that TE should not be used in patients with serum ALT level above five times of the upper limit of normal. TE is also useful in predicting patient prognosis such as development of hepatocellular carcinoma (HCC), portal hypertension, postoperative complications in HCC patients, and also survival. Unfortunately, failed acquisition of TE is common in obese patients. 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 lower LSM cutoff values may be warranted. On the other hand, a novel ultrasonic controlled attenuation parameter (CAP) of the machine is currently under the evaluation and it is a potentially useful parameter as a noninvasive and objective method to detect and quantify hepatic steatosis.

Abbreviations: ALT: Alanine aminotransferase; BMI: Body mass index; CAP: Controlled attenuation parameter; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; kPa: Kilopascal; LSM: Liver stiffness measurement; NAFLD: Nonalcoholic fatty liver disease; TE: Transient elastography.

Keywords: Cirrhosis, Hepatitis, Fatty liver, Histology, Liver biopsy, Liver stiffness measurement.

INTRODUCTION

Liver fibrosis is the natural wound-healing response to parenchymal injury in chronic liver diseases. It may eventually result in liver cirrhosis and its various complications. Accurate staging of liver fibrosis is now essentially indispensable in the decision process of treatment in chronic viral hepatitis and/or predicting disease prognosis.[1-4] It is also important to monitor disease progression and response to treatment.

'Gold Standard' Assessment of Liver Fibrosis—Liver Biopsy

Liver biopsy has been the 'gold standard' for assessing liver fibrosis in the last few decades.[5] However, it has numerous limitations namely invasive nature, risk of complications, patient discomfort, sampling errors and so on.[6] 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.[7] Clinically significant intraperitoneal hemorrhage is the rare but most serious bleeding complication of percutaneous liver biopsy; it usually becomes apparent within the first 2 to 3 hours after the procedure.[8] Risk factors for hemorrhage after liver biopsy are older age, more than three passes with the needle during biopsy, and the presence of cirrhosis or liver cancer.[8] The mortality rate among patients after percutaneous liver biopsy is approximately 1 in 10,000 to 1 in 12,000.[9] Mortality is highest among patients who undergo biopsies of malignant lesions. Cirrhosis is another risk factor for fatal bleeding after liver biopsy.

The diagnostic accuracy of liver biopsy is limited by the sampling variability. The average size of biopsy is 15 mm in length, which represents 1/50,000 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.[6] This variability is low for the diagnosis of cirrhosis (kappa coefficient of concordance higher than 0.80), moderate for earlier fibrosis stages (kappa between 0.70 and 0.80), but high for the activity grades (kappa between 0.40 and 0.50).[6]

Transient Elastography: How Does it Work?

The development of transient elastography (TE; Fibroscan®; Echosens, Paris, France) is one of the major breakthroughs in the field of noninvasive assessment of liver fibrosis. It is a novel noninvasive method that has been proposed for assessment of liver fibrosis by measuring liver stiffness.[10] Liver stiffness measurement (LSM) with TE has been widely

studied in patients suffering from different chronic liver diseases.[11]

TE works in this way. 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. Pulseecho 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 elastic modulus E expressed as $E = 3\rho V^2$, where V is the shear velocity and ρ is the mass density, which is constant for tissues). The stiffer the tissue, the faster the shear wave propagates (Fig. 1). TE measures liver stiffness in a volume that approximates a cylinder 1 cm in diameter and 4 cm in length, between 25 and 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.[10]

TE has the advantages of being painless, rapid (usually less than 5 minutes) and easy to perform at the bedside or in the outpatient clinic. The examination is performed on a nonfasting 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. No reading would be given if a shot is unsuccessful. Results are expressed in kiloPascal (kPa) and correspond to the median of 10 validated measurements according to the manufacturer's recommendations.[10]

Transient Elastography: How Well Does it Work?

Reproducibility of TE is an important feature for its widespread clinical application. The reproducibility of LSM was excellent for both interobserver and intraobserver agreement, with intraclass correlation coefficients (ICC) of 0.98.[12] 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 hepatic 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 <25 kg/m^2 and ≥25 kg/m^2 were 0.98 and 0.94 respectively).

Using TE to assess liver fibrosis has been widely validated in different liver diseases, including chronic hepatitis C (CHC),[1,13-15] chronic hepatitis B (CHB),[16-18] coinfection with HIV,[19] nonalcoholic fatty liver disease (NAFLD),[20,21] alcoholic liver disease,[22] primary biliary cirrhosis, and primary sclerosing cholangitis,[23] and in the postliver transplantation setting.[24] In these studies, TE was validation 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, independent of the underlying etiology.[25-27] 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 the TE results. The suggested diagnostic performance and cutoff values for histologic cirrhosis (F4) based on published studies are summarized in Table 1.
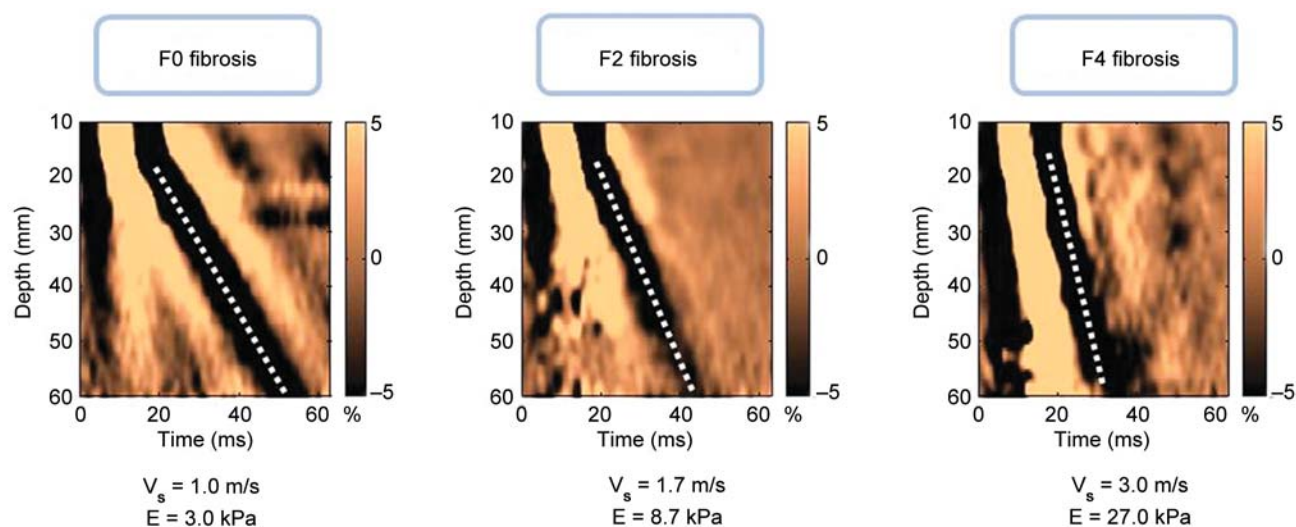

Fig. 1: Shear wave propagation velocity according to the severity of hepatic fibrosis (Metavir score); The elastic modulus E expressed as $E = 3\rho V^2$, where V is the shear velocity and ρ is the mass density (constant for tissues): The stiffer the tissue, the faster the shear wave propagates. Hence, for absent fibrosis (F0), velocity is 1.0 m/s and elasticity is 3.0 kPa, whereas for cirrhosis (F4) velocity is 3.0 m/s and elasticity is 27.0 kPa. Modified from Sandrin et al[10]

CLINICAL APPLICATIONS OF TRANSIENT ELASTOGRAPHY

Baseline 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.[2,3,28] Combo peg-interferon and ribavirin therapy is suggested in CHC patients with difficult-to-treat genotypes if liver biopsy shows significant disease activity.[29-31] As TE has been repeatedly shown to has 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.[16] TE is also found to be more cost-effective than liver biopsy.[32] TE has been recently incorporated in the latest versions of international guidelines of CHB and CHC.[2,29,31]

Follow-up Assessment of Liver Fibrosis

A few longitudinal studies have been reported that patients responding to treatment had low or decreased liver stiffness.[33,34] In fact, both reduction in fibrosis and necroinflammation might contribute to the decrease in liver stiffness.[35] 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.[36] Despite 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. It was recommended that resolution of advanced fibrosis could only be assumed in patients with significantly decreased liver stiffness to 5.0 kPa or lower after antiviral treatment.[36]

Prediction of Prognosis and Complications

The risk of complications varies even among cirrhotic patients, as those with more advanced disease would have more complications and poorer survival rates. TE is found useful to identify cirrhotic patients with higher risk of portal hypertension, and cutoff values of 17.6 and 21.0 kPa had sensitivity 90% or above to detect patients with a hepatic venous pressure gradient (HVPG) above 10 or 12 mm Hg.[37,38] Presence of varices could be excluded with a liver stiffness below 12.5 to 19.8 kPa.[39,40] Unfortunately, these suggested cutoff values overlap with those for detecting histologic cirrhosis in most chronic liver diseases. Hence there seems no additional information is provided by TE on the current recommendation on screening endoscopy for varices among cirrhotic patients. Whether TE would help further stratification of cirrhotic patients on risk of presence or even bleeding esophageal varices remains to be defined.

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 2). 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 to 15.0 kPa, 15.1 to 20.0 kPa, 20.1 to 25.0 kPa and above 25.0 kPa respectively in a prospective cohort of 866 CHC patients.[41] 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 to 13.0 kPa, 13.1 to 18.0 kPa, 18.1 to 23.0 kPa and above 23.0 kPa respectively in another cohort of 1,130 CHB patients.[42] 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.[43]

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 postoperative complications.[44] This cutoff might also identify patients with more severe operative blood loss and higher transfusion rate.[44] 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.[45]

Limitations of Transient Elastography

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 manifests as alanine aminotransferase (ALT) flares.[46,47] Severe hepatic necroinflammation may lead to LSM values well within the cirrhotic range even in the absence of fibrosis on histology.[35,48,49] 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 months after normalization or at least stabilization of ALT levels below five times the upper limit of normal[16,47] (Fig. 2). An ALT-based algorithm has been developed and higher LSM cutoff values for different stages of liver fibrosis should be used in patients with elevate ALT levels (Figs 3A and B).

Extrahepatic cholestasis,[50] hepatic congestion,[51] hepatic amyloidosis,[52] and recent food intake (within 60 minutes)[53]

Table 1: Diagnostic performance and suggested cutoff values of TE for the diagnosis of histologic cirrhosis (F4)

Authors	Fraquelli et al (2007)	Ganne-Carrie et al (2006)	Foucher et al (2006)	Gomez-Dominguez et al (2006)	Chan et al (2009)	Wong et al (2010)*	Marcellin et al (2009)	Coco et al (2007)	Ziol et al (2005)	Castera et al (2005)	Arena et al (2008)	de Ledinghen et al (2006)	Vergara et al (2007)	Rigamonti et al (2008)	Carrion et al (2006)	Yoneda et al (2007)	Nobili et al (2008)*	Wong et al (2010)	Nahon et al (2008)	Corpechot et al (2006)
No. of biopsies	200	775	354	94	161	238	173	228	251	183	150	72	169	95	124	67	52	246	174	95
Prevalence of cirrhosis (F4; %)	12.0	15.5	13.3	17.0	25.0	23.5	8.0	20.2	19.0	25.0	19.3	23.6	38.5	17.0	11.0	7.5	5.8	10.1	53.7	16.0
Etiologies	All	All	All	All	HBV	HBV	HBV	HCV and HBV	HCV	HCV	HCV	HCV-HIV	HCV-HIV	HCV-LT	HCV-LT	NAFLD	NAFLD	NAFLD	ALD	PBC and PSC
Proposed cutoff values (kPa)	11.9	14.6	17.6	16.0	13.4	9.0 (normal ALT) 12.0 (elevated ALT)	11.0	14.0	14.6	12.5	14.8	11.8	14.6	12.0	12.5	17.0	10.2	10.3	22.7	17.3
Sensitivity (%)	91	79	77	89	60	54	93	78	86	87	94	100	93	93	100	100	100	92	84	93
Specificity (%)	89	95	97	96	93	99	87	98	96	91	92	92.7	88	93	87	98	100	88	83	95
Negative predictive value (%)	98	96	92	98	88	67	99	82	97	95	98	82	94	99	100	95	100	99	82	99
Positive predictive value (%)	53	74	91	80	75	98	38	98	78	77	73	100	86	74	50	64	100	46	85	78
Positive LR	8.3	15.8	25.7	22.3	85	3.3	7.0	39.0	23.1	9.7	11.3	13.7	7.8	14.0	7.7	50.0	8	7.5	5.24	18.6
Negative LR	0.1	0.1	0.2	0.1	0.43	0.7	0.08	0.2	0.1	0.1	0.07	0	0.1	0.1	0	0	0	0.09	0.19	0.1
AUROC	0.90	0.95	0.96	0.94	0.93	0.88	0.93	0.96	0.97	0.95	0.99	0.97	0.95	0.90	0.98	0.99	1.00	0.95	0.87	0.96

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 coinfection; HCV-LT: Hepatitis C virus infection recurrence after liver transplantation; LR: Likelihood ratio; NAFLD: Nonalcoholic fatty liver disease; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis. *Cutoff values proposed for advanced fibrosis (F3 or above)

Table 2: LSM and the risk of HCC in chronic hepatitis B or C patients[41,42]			
CHB patients		*CHC patients*	
LSM	Hazard ratios of HCC	LSM	Hazard ratios of HCC
≤10.0 kPa	Referent	≤8.0 kPa	Referent
10.1-15.0 kPa	17	8.1-13.0 kPa	3.1
15.1-20.0 kPa	21	13.1-18.0 kPa	4.7
20.1-25.0 kPa	26	18.1-23.0 kPa	5.6
>25.0 kPa	46	>23.0 kPa	6.6
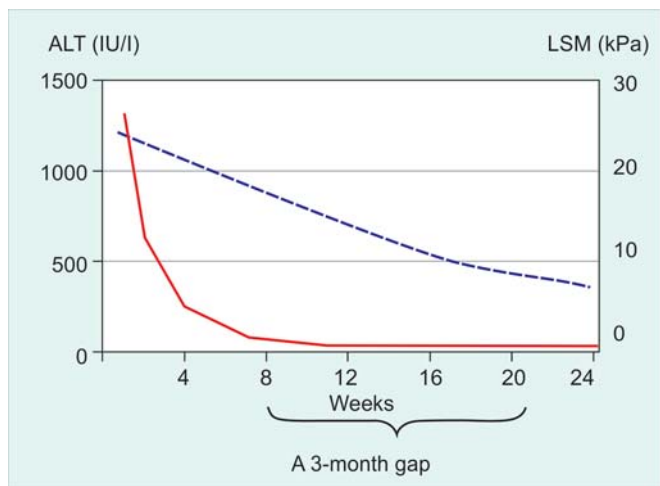
Fig. 2: Falsely elevated LSM results in a patient with grossly elevated ALT levels. LSM values decreased considerably after the resolution of acute hepatitis. Modified from Wong et al[35]

were also found associated with a falsely high LSM values. Fortunately, the degree of hepatic steatosis does not appear to affect LSM results, therefore TE remains an accurate tool for fibrosis assessment in CHC and NAFLD.[15,21]

It has been noted that unreliable and failed LSM occur in around 3 and 11.6 to 18.4% of all TE examinations respectively, and they are independently associated body mass index (BMI) >30 kg/m² in both Caucasians and Chinese.[54,55] The success rate of LSM with M probe would be as low as 75% in NAFLD patients with BMI >30 kg/m².[21] The low success rate of LSM 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.[55] Patients with extreme (both very high and very low) BMI were found to have higher LSM values in a recent Indian population study.[56] Subjects with narrow intercostal space, high riding liver, hyperinflated lungs, ascites or free peritoneal fluid[10] may also have lower success rate or failed acquisition of LSM.

Combining Transient Elastography with Serum Markers

In general, serum markers have modest accuracy to diagnose advanced liver fibrosis.[57,58] TE has certain advantages over serum markers, as TE provides a more direct measurement of fibrosis, is less affected by intercurrent 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.[35] Hence, a second noninvasive test independent of the serum ALT or AST levels may be a good supplementary test to LSM. Among various serum test formulae, Forns index[59] and Hui index[57] 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.[18] In this combined algorithm, low LSM or low Forns index ('OR' approach) 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 ('AND' approach) could improve the specificity up to 99 to 100%.[18]

The combination of TE and FibroTest was found to have the best diagnostic performance compared to either test alone.[1] When TE and FibroTest matched (present in 70 to 80% of cases), the results were also concordant in 84, 95 and 94% of patients with liver fibrosis ≥F2, ≥F3 and F = 4.[1] The combination of LSM and FibroTest allowed exclusion of significant fibrosis (≥F2) in nearly 80% of 100 CHB patients in inactive carrier stage.

New Features of Transient Elastography

S and XL Probes

The development of S and XL probes aim to cater for different population groups of different body build types (Fig. 4). S probe contains a higher frequency ultrasonic transducer and shallower measurements below the skin surface, which suit pediatric subjects and those with small
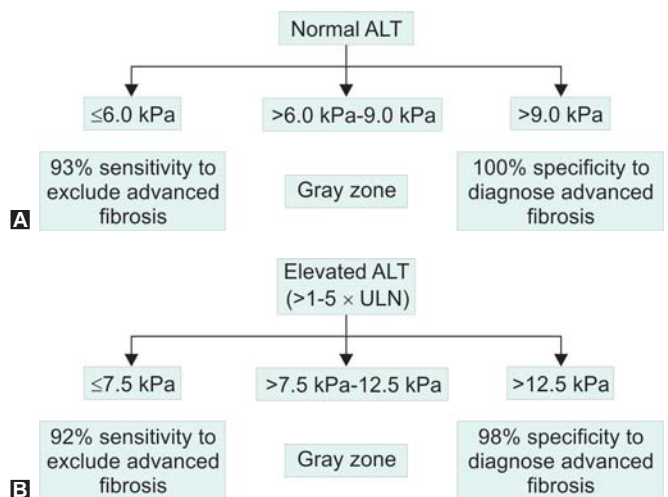
Figs 3A and B: An ALT-based algorithm for (A) normal ALT and (B) elevated ALT levels up to 5 times of upper limit of normal to exclude or establish advanced liver fibrosis for CHB patients. Modified from Chan et al[16]
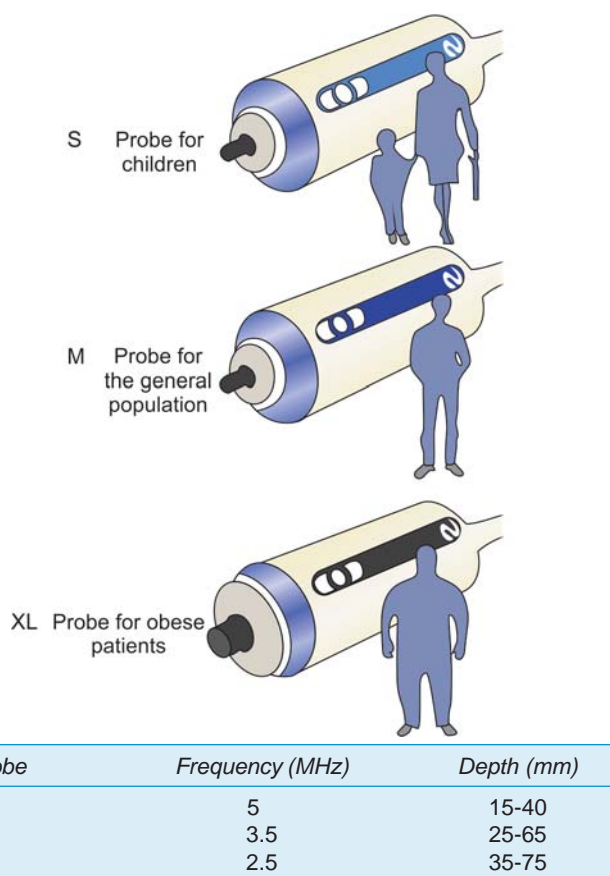
Probe	Frequency (MHz)	Depth (mm)
S	5	15-40
M	3.5	25-65
XL	2.5	35-75

Fig. 4: The characteristic of the new S and XL probes comparing to M probe

body build.[60] XL probe contains a lower frequency and a more sensitive ultrasonic transducer, a deeper focal length, larger vibration amplitude and a higher depth of measurements below the skin surface.[61] This probe serves obese subjects with 'XL' body builds. Data concerning the validations of these new probes are emerging.

With XL probe, LSM could be successfully performed in more obese patients compared to M probe.[62-64] In our validation study involving 286 patients, LSM using XL probe may obtained reliable results in 92% of patients, compared to 80% using M probe.[62] However, the median LSM by the XL probe was consistently found to be approximately 1.0 to 1.2 kPa lower than that by M probe at the same stage of liver fibrosis in all histologic series.[62-64] Hence, it will be not appropriate to directly apply the cutoff values of the M probe to predict different stages of liver fibrosis with the XL probe. More studies are warranted to delineate the proper cutoff values of LSM using XL probe.

Controlled Attenuation Parameter (CAP)

As obesity essentially becomes a pandemic and is increasingly encountered worldwide in the last few decades,[65] the prevalence of NAFLD has been substantially increased.[66] This makes the estimation of the degree of hepatic steatosis an essential part of patient assessment. Recently, a novel physical parameter based on the properties of ultrasonic signals acquired by the FibroScan machine has been developed applying the property that hepatic steatosis affects ultrasound propagation.[67] This novel parameter, named controlled attenuation parameter (CAP), measures the ultrasound attenuation at the center frequency of the M probe. In a recent study of 112 patients with liver biopsy, CAP was found efficient to detect low grade steatosis.[62] A cutoff value of 215 dB/m has a sensitivity of 90% to detect S1 steatosis.[62] These data support the use of CAP, which can be performed simultaneously with LSM, as the evaluation of hepatic steatosis.

CONCLUSION

TE is a noninvasive, accurate and reproducible test of liver fibrosis. Its diagnostic performance for liver fibrosis has been validated in a wide spectrum of liver diseases. This tool is also useful to predict patient outcomes. TE has changed the clinical practice and recently incorporated in international guidelines. Further studies should explore the appropriate cutoff values of new XL and S probes, as well as those of the novel CAP.

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