

Clinical Application of Transient Elastography in the Diagnosis of Liver Fibrosis: an Expert Panel Review and Opinion

Expert Panel on Liver Stiffness Measurement

Abstract

Liver fibrosis evaluation is pivotal for treatment decisions and prognosis assessment in patients with chronic liver disease. Liver transient elastography (TE) is a newly developed non-invasive technique for diagnosis of liver fibrosis. It can assess the state of liver fibrosis by liver stiffness measurements, and offers better performance for the diagnosis of liver cirrhosis than serum biological markers. It has now been approved for clinical use in China. The aim of this review is to provide a guide for clinicians to apply this technique appropriately. The recommendations are made under the auspices of China Foundation for Hepatitis Prevention and Control, and have been prepared by a panel experts, who have reviewed and summarized the clinical studies on TE in order to develop these recommendations.

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Introduction

It is well established that many patients with chronic hepatitis and even early cirrhosis may have no specific symptoms, signs, or biochemical abnormalities. Once symptoms or signs are detected, most cases already have well-established liver cirrhosis, and even hepatic failure. Timely assessment and detection of advanced liver fibrosis and early diagnosis of cirrhosis are critical steps in managing chronic liver disease. The use of liver biopsy, the current "gold standard" for diagnosis of liver fibrosis/cirrhosis, suffers from limitations such as low acceptability, invasiveness, risks of repeated sampling, sampling error, and inter-observer and intra-observer variability. Therefore, it is important to develop non-invasive diagnostic techniques for the diagnosis of liver fibrosis.

Keywords: Transient elastography; Liver fibrosis; Diagnosis; Expert opinion.

Abbreviations: AUC, area under receiver operating characteristics curve; AUROC, area under the receiver operating characteristic curve; CCI, Compensated Cirrhosis Index; CHB, chronic hepatitis B; LSM, liver stiffness measurement; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; TE, transient elastography.

Received: 17 February 2014; Revised: 24 May 2014; Accepted: 30 May 2014

* DOI of original article: 10.14218/JCTH.2014.00008.

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Liver transient elastography (TE) is a newly developed non-invasive technique for diagnosis of liver fibrosis. It can be used to assess the state of liver fibrosis by liver stiffness measurement (LSM). TE techniques (for example, Fibroscan) offer better diagnostic performance for liver cirrhosis than serum biological markers including FibroTest, FibroMeter, HepaScore, APRI, API, FIB-4, Forns Index, Hui Index, and Compensated Cirrhosis Index (CCI),¹⁻⁷ and it has been approved for clinical use in China. To assist in the optimal application of this technique in clinical practice, the China Foundation for Hepatitis Prevention and Control has brought together experts to develop *Expert Opinions on the Diagnosis of Liver Fibrosis with Transient Elastography*. The panel discussed and finalized the draft in November 2012 based on progress in clinical practice, and growing evidence in the field.

The statistical basis for assigning cutoff values

Ideally, the diagnostic cutoff values of non-invasive diagnosis should have a high negative predictive value (NPV) and low negative likelihood ratio (NLR) to rule out a diagnosis as well as a high positive predictive value (PPV) and high positive likelihood ratio (PLR) to confirm a diagnosis. There are necessary in order to avoid mis-diagnosis of liver fibrosis or missed diagnosis of advanced fibrosis and cirrhosis. To ensure the accuracy of the diagnosis, it is necessary to adopt low cutoffs to exclude the diagnosis and high cutoffs to confirm the diagnosis. When the measured values fall in the gray zone between the high and low cutoffs, liver biopsy is still necessary.⁸⁻⁹ Statistical analysis showed that cutoff values with a PLR > 10.0 afford sufficient confidence to confirm the diagnosis, whereas cutoff values with a NLR < 0.1 provide enough confidence to rule out a disease. Therefore, the determination of high and low cutoff values should meet these special requirements.

Recommendations for the application of TE in noninvasive diagnosis of liver fibrosis

Operational requirements

The operation of TE is mainly affected by obesity and narrow intercostal space. TE usually fails in patients with ascites. Operational failure or unreliable test results are independently associated with operator experience of < 500 examinations and patient characteristics of BMI > 30 kg/m², age > 52 years, female gender, hypertension, and type 2 diabetes.¹⁰ Abdominal obesity (abdominal circumference > 80 cm in women and > 90 cm in men) is also an independent

risk factor for operational failure or unreliable results.¹¹ In patients with BMI ≥ 28.0 kg/m², and an abdominal circumference ≥ 102 cm, an XL probe yields higher success rates than the M probe.^{12–13} An XL probe can generate reliable results in 51.6–61% of patients for whom the M probe is unable to obtain reliable detection results.^{12–14} The S probe is suitable for patients with narrow intercostal space and children. However this probe is associated with significantly higher failure rates in children under 5 years of age.¹⁵ It remains to be determined whether there are differences in the detection results obtained with the S probe or the M probe. The reliability of LSM depends mainly on the ratio of the interquartile range, and the median of detection values (IQR/M), where IQR/M ≤ 0.10 suggests very reliable results, $0.10 < \text{IQR/M} \leq 0.30$ or IQR/M > 0.30 with median LSM < 7.1 kPa suggests reliable results, and IQR/M > 0.30 and median LSM ≥ 7.1 kPa suggest unreliable results.¹⁶

Recommendation 1: TE operators should receive standard training and have relatively constant annual volumes of cases to ensure the reliability of test results.

Recommendation 2: The M probe should be the first choice for TE measurements. For overweight or obese patients from whom TE cannot obtain reliable results, the XL probe may be considered. The S probe may be considered for patients with narrow intercostal space or for children.

Recommendation 3: Test results must meet all the following conditions to be considered valid: at least 10 valid tests, success rate $> 60\%$, and IQR/M < 0.3 .

Influencing factors

LSM is influenced by factors such as hepatic necroinflammatory activity (manifested as elevated levels of transaminases or bilirubin),^{17–18} extrahepatic cholestasis,^{19–20} hepatic venous congestion,^{21–22} and food intake,^{23–24} and LSM decreases along with reductions in ALT and bilirubin levels.^{17–18}

Recommendation 4: TE should be performed after fasting or at least 2 hours postprandially, and ALT and bilirubin levels should be considered to make a hierarchical diagnosis. Extrahepatic cholestasis and heart failure should be ruled out.

Normal reference values

The normal reference ranges in healthy living liver donors and kidney donors in South Korea have been reported to be 3.7–7.0 kPa in men, and 3.3–6.8 kPa in women.²⁵ Normal LSM values of adult male residents without notable liver disease in Guangdong have been found to vary with age (age < 60 years: 5.2 ± 1.3 kPa; age ≥ 60 years: 5.9 ± 1.8 kPa).²⁶ The normal reference range in a South Asia population was found to be 3.2–8.5 kPa, and lean or obese people have higher values than those with normal BMIs.²⁷ The normal reference range in people with no significant liver disease in Hong Kong was found to be 2.8–7.4 kPa.²⁸ Because the number of individuals with high BMI who develop fatty liver in the population is increasing, and it is not grouped into the liver disease population, current normal reference values do not take into account for the impact of high BMIs.

Recommendation 5: The normal reference range of LSM should be 2.8–7.4 kPa.

Diagnostic cutoff values

A. Chronic hepatitis B:

The area under the receiver operating characteristic curve (AUROC) values for significant liver fibrosis (Metavir F ≥ 2), advanced liver fibrosis (F ≥ 3), and cirrhosis (F=4) due to chronic hepatitis B (CHB) were 0.78–0.87, 0.87–0.93, and 0.84–0.96, respectively (Table 1).^{7,29–33} It is possible to determine whether cirrhosis is present in more than 78% of patients with normal bilirubin levels, and whether advanced liver fibrosis is present in 80% of these patients. Increased bilirubin levels exert a significant impact on the diagnostic performance of TE: only 41% of patients can be identified as having cirrhosis, and 53% can be identified as having advanced liver fibrosis.^{7,33} The diagnostic performance of TE at cutoff values of 10.1 kPa (NLR 0.15 and PLR 7.3),³⁴ 12.9 kPa (PLR 7.33, NLR 0.52), 14.1 kPa (PLR 5.6, NLR 0.19), and 11 kPa (PLR 7.3, NLR 0.28) is unsatisfactory for diagnosis of liver cirrhosis in patients with normal ALT levels,^{5,35–36} suggesting that the cutoff value for confirming cirrhosis should be higher than 14.1 kPa, and the cutoff value for excluding cirrhosis should be less than 11 kPa. At cutoff values of 10.2 kPa and 8.1 kPa, NLR values were 0.15 and 0.15, and PLR values were 9.0 and 4.6, respectively, for the diagnosis of advanced liver fibrosis,^{35–36} suggesting that the high cutoff value for advanced liver fibrosis should be slightly higher than 10.2 kPa, while the lower cutoff value should be less than 8.1 kPa. Most cutoff values that help establish the diagnosis of significant liver fibrosis offer no clinical value due to a PLR < 5.0 or NLR > 0.2 .^{5,29,34–36}

Recommendation 6: In patients with abnormal bilirubin levels, LSM ≥ 29.2 kPa suggests cirrhosis, LSM ≥ 17.0 kPa suggests advanced liver fibrosis, LSM < 9.1 kPa excludes cirrhosis, and LSM < 7.8 kPa excludes advanced liver fibrosis. Patients with LSM values in the grey zone can be measured again after bilirubin levels return to normal, using normal bilirubin cutoffs for diagnosis, or will require liver biopsy.

Recommendation 7: In patients with normal bilirubin levels, LSM ≥ 17.5 kPa suggests cirrhosis, LSM ≥ 12.4 kPa (10.6 kPa if ALT $< 2 \times$ upper normal limit) suggests advanced liver fibrosis, LSM < 10.6 kPa rules out cirrhosis, LSM ≥ 9.4 kPa suggests significant fibrosis, and LSM < 7.4 kPa rules out advanced liver fibrosis. If clinical decision-making is difficult for patients with LSM between 7.4–9.4 kPa, a liver biopsy should be considered.

Recommendation 8: In patients with normal aminotransferase levels, LSM ≥ 12.0 kPa suggests cirrhosis, LSM ≥ 9.0 kPa suggests advanced liver fibrosis, LSM < 9.0 kPa rules out cirrhosis, and LSM < 6.0 kPa rules out advanced liver fibrosis. If clinical decision-making is difficult for patients with LSM between 6.0–9.0 kPa, a liver biopsy should be considered.

Given the significant impact of abnormal bilirubin levels on the diagnostic performance of TE, the measurement should be performed when bilirubin levels return to normal, and interventions may be taken based on clinical virology data as shown in Fig. 1.

B. Chronic hepatitis C:

The AUROC of LSM for hepatitis C cirrhosis is 0.90–0.97^{2,5,37–39} (Table 2), which is better than that for other non-invasive diagnostic modalities of liver fibrosis including FibroTest, APRI, Lok index, platelet count, and AST/ALT ratio.³⁸ In a large sample study (n = 913), the NLR and PLR

Table 1. Data on cut-off values for liver fibrosis assessment by transient elastography (kPa) in Patients with Chronic Hepatitis B

Fibrosis stages (Metavir)	Authors (n)	Stratification	AUC	Cutoff value	Sensitivity (%)	NPV (%)	NLR	Specificity (%)	PPV (%)	PLR
F4	Marcellin ²⁹ (173)		0.93	11.0	93	99	0.08	87	38	7.0
	Chan ³⁰ (161)	Normal ALT	0.96	18.2	57	96	0.44	97	67	19
		Abnormal ALT	0.94	12.0	100	100	0	77	60	3.0
	Chen ⁷ (315)	Normal bilirubin	0.90	8.4	60	87	0.42	95	82	12.9
		Abnormal bilirubin	0.84	13.4	96	98	0.07	54	40	2.1
	Vigano ³¹ (217)		-	10.6	75	92	0.27	93	78	11.1
	Jia ³²		0.90	16.9	93	98	0.09	76	49	3.9
F≥3	Marcellin ²⁹ (173)		0.93	9.1	59	90	0.45	94	72	10.2
	Chan ³⁰ (161)	Normal ALT	0.90	29.2	100	100	0	47	48	1.9
		Abnormal ALT	0.87	6.0	23	0	0.73	98	88	14.7
	Jia ³²		0.90	13.1	98	-	0.02	-	-	-
	Chen ³³ (226)	ALT < 2 × ULN	0.88	17.5	60	95	0.43	95	55	8.91
		ALT ≥ 2 × ULN	0.92	8.1	86	95	0.16	85	65	5.7
	Vigano ³¹ (217)		-	10.5	72	91	0.29	95	84	14.4
	Chen ³³ (226)	Normal ALT	0.89	6.0	93	88	0.15	47	62	1.8
		Abnormal ALT	0.87	9.0	71	79	0.29	100	100	-
	Jia ³²		0.88	7.5	96	94	0.07	59	65	2.3
	Chen ³³ (226)	ALT < 2 × ULN	0.92	12.0	51	68	0.5	98	96	25.5
		ALT ≥ 2 × ULN	0.89	12.4	58	81	0.44	95	86	12.3
	Vigano ³¹ (217)		-	7.4	92	93	0.11	73	72	3.4
	Chen ³³ (226)	Normal ALT	0.86	10.6	82	81	0.19	92	88	10.5
		Abnormal ALT	0.86	7.5	93	91	0.11	65	89	2.6
	Jia ³²		0.88	12.7	64	69	0.38	96	95	15.3
	Chen ³³ (226)	Normal ALT	0.86	5.0	99	88	0.04	-	-	-
		Abnormal ALT	0.86	9.8	-	-	-	95	97	11.0
	Vigano ³¹ (217)		-	6.2	94	-	0.10	-	-	-
			-	9.4	-	-	-	96	-	14

AUC: area under receiver operating characteristics curve; NPV: negative predictive value; NLR: negative likelihood ratio; PPV: positive predictive value; PLR: positive likelihood ratio

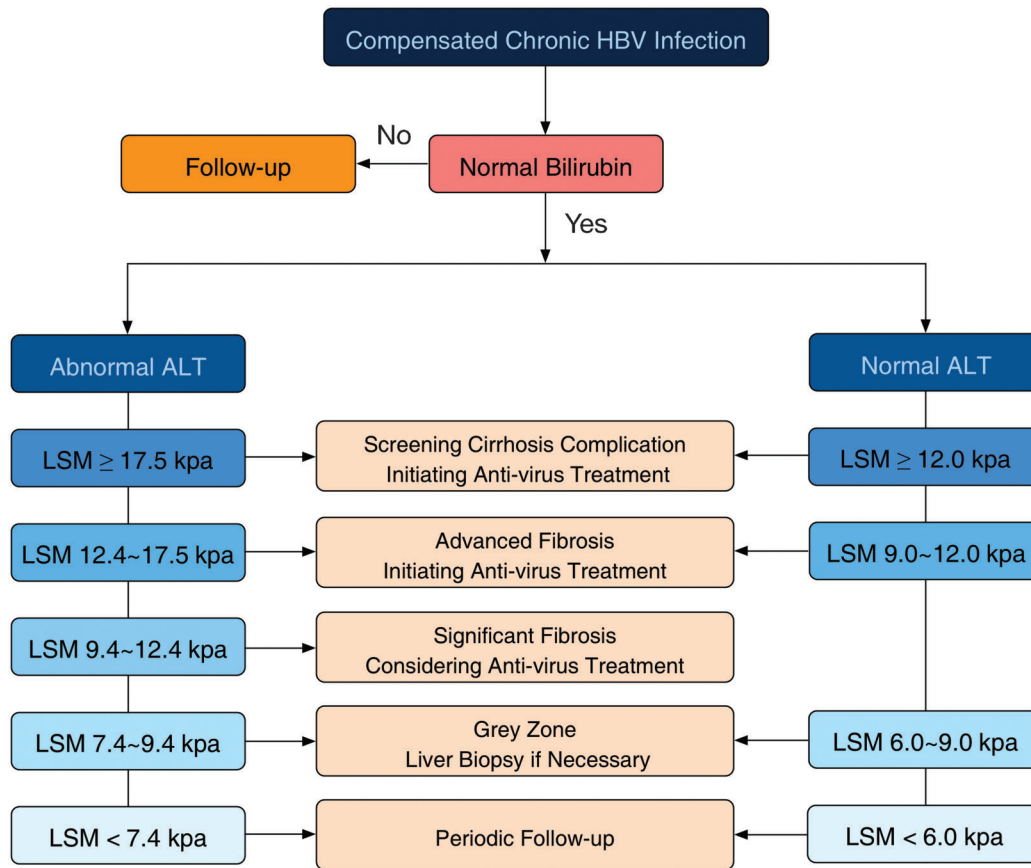


Fig. 1 Transient elastography for diagnosis of patients with HBV virus infection at different stages of liver fibrosis

were 0.31 and 6.77, respectively, at the recommended cutoff value of 12.9 kPa, suggesting the cutoff value for confirmative diagnosis of cirrhosis should be higher than 12.9 kPa.⁵ At a cutoff value of 14.6 kPa, the PLR was as high as 21.5, confirming the diagnosis of cirrhosis. The cutoff values for significant fibrosis suggested by a number of studies provide insufficient evidence to confirm or exclude the diagnosis of significant fibrosis (Table 2), and the cutoff values for confirmative diagnosis of significant fibrosis should be higher than 7.1 kPa.

Recommendation 9: LSM \geq 14.6 kPa suggests cirrhosis, whereas LSM $<$ 9.3 kPa excludes cirrhosis. LSM \geq 9.3 kPa suggests advanced liver fibrosis, whereas LSM $<$ 7.3 kPa rules out advanced liver fibrosis. LSM \geq 7.3 kPa suggests significant fibrosis.

C. Non-alcoholic fatty liver disease

The diagnostic performance of TE for advanced fibrosis and cirrhosis in non-alcoholic fatty liver is superior to AST/ALT ratio, APRI, FIB-4, BARD and NAFLD fibrosis scores, and other non-invasive serum markers, with AUROC values of TE for \geq F2, \geq F3, and F4 liver fibrosis being 0.84, 0.93, and 0.95, respectively. The NLR was 0.12 at a cutoff value of 7.9 kPa for the diagnosis of \geq F3 fibrosis, and 0.09 at a cutoff value of 10.3 kPa for the diagnosis of cirrhosis. The PLR was 8.9 at a cutoff value of 9.6 kPa for the diagnosis of \geq F3 fibrosis.⁴⁰ Measured LSM values obtained with the XL probe are lower than those obtained with the M probe (6.8 kPa vs. 7.8 kPa),¹²

and the diagnostic cutoffs of the M probe differed by 1–2 kPa from those of the XL probe.¹³

Recommendation 10: Advanced liver fibrosis may be considered for patients with LSM \geq 9.8 kPa, and clinical intervention should be taken. Patients with LSM between 7.9–9.8 kPa need to undergo liver biopsy to determine the stage of liver fibrosis. Patients with LSM $<$ 7.9 kPa should receive regular LSM monitoring and BMI reduction intervention.

Recommendations 11: The XL probe may be considered in patients who fail using the M probe, and the diagnostic cutoff value should be lowered by 1–2 kPa.

All the recommended diagnostic cutoff values for various liver diseases are summarized in Table 3.

Prospects of clinical application of TE

In the course of antiviral therapy, LSM decline does not solely reflect the reversal of liver fibrosis. It is also associated with decreased necroinflammation scores.⁴¹ Various antiviral drugs may exert different effects on improving liver necroinflammation, and further studies are needed to determine the cutoff values of TE for determining liver fibrosis stages in patients receiving antiviral therapy. A large-scale, community-based study that included 1190 patients over 45 years of age showed that 89 patients with LSM $>$ 8 kPa (of whom nine had LSM $>$ 13 kPa) had a certain chronic liver disease, and that liver biopsy confirmed the presence of liver cirrhosis in the nine patients with LSM $>$ 13 kPa,⁴² suggesting that TE can

Table 2. Data-on cut-off value for liver fibrosis assessment by transient elastography (kPa) in Patients with Chronic Hepatitis B

Fibrosis stages (Metavir)	Author (n)	Disease rate	AUC	Cutoff value	Sensitivity (%)	NPV (%)	NLR	Specificity (%)	PPV (%)	PLR
F4	Castera ³⁷ (297)	23.6%	0.96	12.5	83	95	0.18	95	85	16.6
	Ziol ³⁸ (251)	-	0.97	14.6	86	97	0.15	95	78	21.5
	Degos ⁵ (913)	13.8%	0.9	12.9	72.2	95.3	0.31	89.3	52	6.8
	Ferraioli ³⁹ (195)	16.4%	0.97	12.3	81.3	96.3	0.2	95.7	78.8	18.9
≥F3	Ferraioli ³⁹ (195)	26.1%	0.95	9.3	93.8	98.7	0.07	92.0	69.0	11.8
≥F2	Castera ¹ (183)	74%	0.83	7.1	67	48	0.37	89	95	6.1
	Ziol ³⁸ (251)	-	0.79	8.8	56	56	0.48	91	88	6.2
	Degos ⁵ (913)	28%	0.75	5.2	90	66	0.32	32	68	1.3
	Ferraioli ³⁹ (195)	49.7%	0.86	6.9	69.1	74.6	0.34	89.8	87.0	6.8

AUC, area under receiver operating characteristics curve; NPV, negative predictive value; NLR, negative likelihood ratio; PPV, positive predictive value; PLR, positive likelihood ratio

Table 3. Suggested cut-off values s for transient elastography according to disease

Causes	Diseases		
	Liver cirrhosis	Advanced liver fibrosis	Significant fibrosis
HBV			
Abnormal bilirubin levels	LSM ≥ 29.2 Yes	LSM ≥ 17.0 Yes	-
	LSM < 9.1 No	LSM < 7.8 No	
Normal bilirubin levels	LSM ≥ 17.5 Yes	LSM ≥ 12.4 Yes	LSM ≥ 9.4 Yes
	LSM < 10.6 No	LSM < 7.4 No	
Normal aminotransferase levels	LSM ≥ 12.0 Yes	LSM ≥ 9.0 Yes	-
	LSM < 9.0 No	LSM < 6.0 No	
HCV	LSM ≥ 14.6 Yes	LSM ≥ 9.3 Yes	LSM ≥ 7.3 Yes
	LSM < 9.3 No	LSM < 7.3 No	
NAFLD	-	LSM ≥ 9.8 # Yes	-

HBV, hepatitis B virus; HCV, hepatitis C virus, NAFLD, non-alcoholic fatty liver disease; LSM, liver stiffness measurement; “-”, no recommendation; #, the diagnostic cutoff value should be lowered by 1–2 kPa when XL probe was used in patients who fall with M probe

identify liver cirrhosis, and reveal previously undiagnosed chronic liver disease in the general population. The increase in LSM is associated with higher risk of hepatocellular carcinoma development,^{43–44} but there is no reliable cutoff value for the prediction of hepatocellular carcinoma. The AUROC of LSM for the prediction of hepatic decompensation is 0.90–0.92, and the AUROC of LSM for the prediction of Child-Pugh C cirrhosis is 0.91.^{45–46} However, further research is required to establish the predictive value of LSM for the progression of liver disease. High-risk esophageal varices (moderate and severe grade, mild grade with liver decompensation) require early clinical intervention to prevent bleeding. However, LSM offers limited value for prediction of high-risk esophageal varices (AUROC, 0.71–0.73),^{47–48} and the combined use of LSM and other non-invasive indicators seems to improve the predictive performance.^{47,49–50}

As TE measurements are affected by many factors, this technique may produce diagnoses inconsistent with other diagnostic methods. For example, liver cirrhosis with mild necroinflammation can present a low LSM. When different non-invasive diagnostic methods produce inconsistent diagnoses, abdominal ultrasonography, platelet count, and other clinical data can also be analyzed to help establish a definite diagnosis. For patients in whom a definite diagnosis cannot be reached due to TE values in the gray zone, serum biomarkers may provide complementary diagnostic parameters. When used in combination with TE, serum biomarkers, and imaging examinations (sequential or parallel diagnosis), the consequence of misdiagnosis or missed diagnosis should be considered. Sequential measurements raises the sensitivity, but may lead to higher misdiagnosis rates due to lower specificity, whereas parallel measurements can increase specificity and increase diagnostic reliability, but may also increase the risk of missed diagnosis by reducing sensitivity.

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Conflict of interest

None

Author contributions

Writing the paper (all authors).

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