



Clinical Application of Vibration Controlled Transient Elastography in Patients with Chronic Hepatitis B

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Abstract

Evaluation of the extent and progression of liver fibrosis and cirrhosis is of critical importance in the management and prognosis of patients with chronic hepatitis B. Due to the limitation of liver biopsy, non-invasive methods, especially liver stiffness measurement (LSM) by vibration controlled transient elastography, have been developed and widely applied for liver fibrosis assessment. LSM aims to reduce, but not to substitute, the need for liver biopsy for fibrosis/cirrhosis diagnosis. While LSM may have potential utility in monitoring treatment response, its applications in prediction of liver complications in terms of portal hypertension and esophageal varices, as well as disease prognosis, have been gradually validated. Here, we review the latest clinical applications of LSM in patients with chronic hepatitis B.

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Introduction

Hepatitis B virus (HBV)-related fibrosis or cirrhosis is a progressive disease, ultimately resulting in end-stage liver disease or hepatocellular carcinoma (HCC) and accounting for over one million deaths per year worldwide.^{1–4} Evaluation of the extent and progression of liver fibrosis and of the risk of cirrhosis, therefore, plays an important role in the management and prognosis of patients with chronic hepatitis B (CHB). In the management of CHB, the two clinically relevant endpoints for staging liver fibrosis are: first, detection of significant fibrosis (METAVIR F \geq 2 or Ishak \geq 3), which indicates that patients should receive antiviral treatment; and, second, detection of cirrhosis (METAVIR F4 or Ishak 5–6), which indicates not only the potential for prescribing long-term antiviral therapy but also monitoring for complications related to portal hypertension and regular screening for HCC.

Keywords: Hepatitis B; Liver fibrosis; Liver stiffness; Transient elastography.

Abbreviations: ALT, alanine aminotransferases; AUROC, area under the receiver operating characteristic curve; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NLR, negative likelihood ratio; PLR, positive likelihood ratio; ULN, upper limit of normal; VCTE, vibration controlled transient elastography.

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Liver biopsy has been the “gold standard” for liver fibrosis staging for decades. However, it is hampered by its invasive nature, risk of complications and patient discomfort.⁵ In addition, sampling error could result in underestimation of liver fibrosis and false negative diagnosis of cirrhosis (in 10%–30% of cases).⁶ To address these issues, non-invasive methods have been developed and validated for liver fibrosis assessment, among which liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE) is one of the most promising techniques. Besides staging fibrosis, LSM has been demonstrated to have potential utility in monitoring treatment response and surveillance of liver-related events.⁷

This article reviews the clinical application of VCTE in patients with CHB and discusses the points and prospects to be considered when using VCTE for the management of CHB.

Assessing significant fibrosis

Like other non-invasive methods, when interpreting the diagnostic performance of VCTE, several methodological problems should always be kept in mind.^{7,8} Application of the imperfect gold standard of liver biopsy as the reference for assessment of diagnostic accuracy of LSM reduces the potential to reach optimal diagnostic accuracies assessed using the area under the receiver operating characteristic curve (AUROC) of >0.9 .⁹ Therefore, an AUROC of 0.85–0.90 may be considered as highly accurate. On the other hand, direct comparisons of AUROCs and their related optimal diagnostic cutoffs derived from two specific populations is usually not suitable, as the spectrum effects of the population should be taken into consideration.

Prevalence of the disease among the investigated population also plays a role in the diagnostic performance, impacting the predictive value especially, of a non-invasive method. For the clinical application of LSM in staging fibrosis, it is rational to reduce the need of liver biopsy but not to substitute this gold standard.¹⁰ A likelihood ratio, which is independent of disease prevalence, of >10 or <0.1 used in cutoff determination is strong enough to confirm or exclude a diagnosis.¹¹ Accordingly, only the residual patients with LSM falling within the so-called grey zone (i.e. LSM lower than the confirming cutoff and higher than the excluding cutoff) need liver biopsies (Fig. 1).

Determination of the stage of liver disease is important in guiding antiviral therapy decisions and the need for surveillance. In terms of guiding antiviral therapy, differentiation of significant fibrosis (METAVIR F \geq 2 or Ishak \geq 3) from mild fibrosis (METAVIR F $<$ 2 or Ishak $<$ 3) has critical clinical

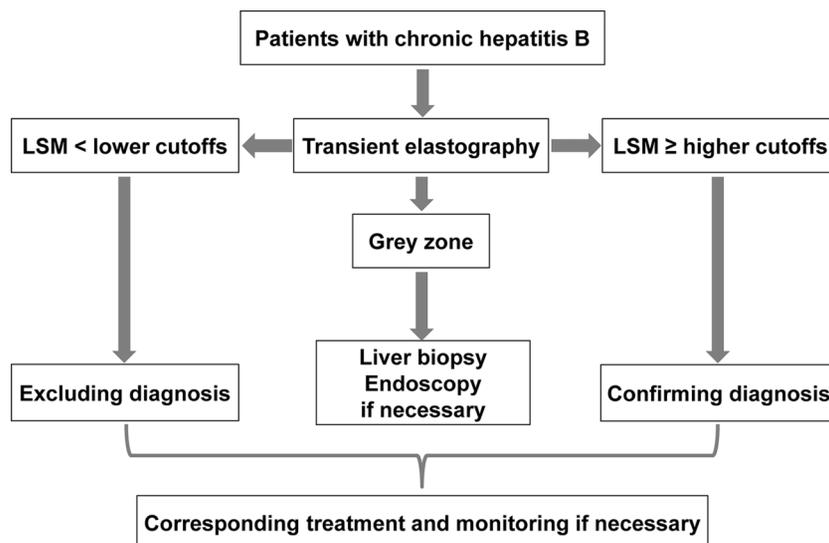


Fig. 1. Algorithm and schematic diagram for the adjuvant application of liver stiffness measurement (LSM) by vibration controlled transient elastography for non-invasive diagnosis of liver fibrosis/cirrhosis and portal hypertension in patients with chronic hepatitis B.

implications for initiation, especially for patients over the age of 30 years, with intermediate elevated alanine aminotransferase (ALT; i.e. <2 times the upper limit of normal (ULN)) and high HBV DNA levels. Therefore, determining the absolute stage of fibrosis is less important than determining whether patients have advanced liver disease with fibrosis METAVIR F ≥ 2 or Ishak ≥ 3 .

The performance of LSM in detecting significant fibrosis is inferior to that for cirrhosis, with AUROC 0.66–0.87 for significant fibrosis (Table 1). Among the suggested cutoffs for detecting significant fibrosis, only cutoffs by Jia *et al.*,¹² Chen *et al.*¹³ and Viganò *et al.*¹⁴ were characterized with negative likelihood ratio (NLR) of nearly 0.1 or positive likelihood ratio (PLR) of nearly 10.0, which could determine significant fibrosis with enough strong statistical evidence. Considering the lack of relevant clinical consequences of false negative cases and the considerable costs of antiviral treatment of false positive cases, it is recommended that the confirming diagnosis of significant fibrosis may be of more value for clinical practice. Thus, LSM of 9.4 kPa (PLR of 14.0) and of 9.8 kPa (PLR of 11.0) could be selected as confirming diagnosis cutoffs, with the latter derived from a large cohort but a larger biopsy sample study may be superior.

It has been reported that hepatitis flares may affect LSM results; therefore, serum levels of ALT should always be taken into account when interpreting results from VCTE.¹⁵ To avoid the risk of false positive diagnosis, certain investigators have suggested that LSM cutoffs should be adjusted according to ALT levels.^{16,17} However, a study of large biopsy samples indicated that ALT level exerted influence on cutoffs for detecting advanced fibrosis but not significant fibrosis.¹³ Regarding the purpose of guiding antiviral therapy, LSM use is preferred in patients with normal ALT or intermediate elevated ALT (<2 ULN).¹⁸ There have been studies reporting that LSM could be used as a supplemental tool to HBV DNA, to follow inactive carriers or to better identify patients who may have ongoing disease activity or significant fibrosis and who require liver biopsy.^{18,19} A recent study also suggested a combination of HBV DNA ≤ 2000 IU/mL and LSM ≤ 6.2 kPa to detect

inactive HBV carriers with positive predictive value of 98.5% in a single time point evaluation.²⁰

Detecting cirrhosis

Current nucleos(t)ide treatment of hepatitis B is not curative, and may generally be lifelong for patients with liver cirrhosis. Besides, cirrhotic patients are subject to development of subsequent complications and need intensive surveillance for development of HCC. Thus, non-invasive methods to identify patients with cirrhosis must have high sensitivity, to reduce the risk of false negatives, as well as high specificity, to avoid diagnostic errors resulting in increased economic burden of long-term surveillance of the cirrhotic complication. LSM has proven potent accuracy for cirrhosis diagnosis, with AUROC 0.80–0.97 and suggestive cutoff of 8.4–29.2 (Table 2).

LSM 11.6 kPa was suggested by a large cohort study ($n = 567$) with sufficient biopsy sample size (≥ 15 mm) from Korea, characterized with NLR of 0.20 and PLR of 5.70;²¹ these findings implied that cutoff for confirming diagnosis should be far higher than 11.6 kPa and, therefore, the cutoff for excluding diagnosis should be slightly lower than 11.6 kPa. Another large cohort study ($n = 469$) from China may be criticized by its inclusion of patients with insufficient biopsy sample size (lower than 15 mm),¹² which would have impaired confidence of the findings from the “gold standard” liver biopsy. In a study from India, the reported suggested cutoff for cirrhosis may be unreliable, due to the low prevalence of cirrhosis (5.9%).²²

For cutoffs determining cirrhosis, the suggested LSMs ranging between 11.8 kPa and 18.5 kPa were characterized with PLR of >10.0 . The LSM of 18.5 kPa with PLR of 15.2 suggested by Liang *et al.*²³ and the LSM of 18.2 kPa with PLR of 19.0 suggested by Marcellin *et al.*²⁴ implied that the rational cutoff for ruling in diagnosis should be lower than 18.2 kPa. While cutoffs of 13.4 kPa and 13.1 kPa were derived from study cohorts of nearly 100 patients, cutoffs of 16.9 kPa and 17.0 kPa were suggested by study cohorts with

Table 1. Diagnostic performance of VCTE for significant fibrosis (METAVIR F \geq 2) in patients with chronic hepatitis B

Author	Country/year	Patients, <i>n</i>	F \geq 2, %	Cutoff kPa	AUROC	Se, %	NLR	Sp, %	PLR
Seo <i>et al.</i> ²¹	Korean 2015	567	71.6	7.8	0.77	71.2	0.40	73.9	2.70
Jia <i>et al.</i> ¹²	China 2015	469	61.2	9.1	0.82	32.0	0.72	0.95	6.4
				4.7		95	0.10	51	1.94
Goyal <i>et al.</i> ²²	India 2013	357	23.2	6.0	0.84	82.0	-	67.0	-
Chen <i>et al.</i> ¹³	China 2012	291	79.4	9.8	0.86			94.5	11.0
				5.0		99.1	0.04		
Kim <i>et al.</i> ⁶²	Korea 2012	194	84.5	8.8	0.87	78.0	0.25	86.7	5.8
Cardoso <i>et al.</i> ⁶³	France 2012	202	42.1	7.2	0.87	74.0	0.30	88.0	6.20
Verveer <i>et al.</i> ⁶⁴	Netherlands 2012	125	53.5	6.0	0.85	-	-	-	-
Viganò <i>et al.</i> ¹⁴	Italy 2011	125	52.8	9.4	-	-	-	96.0	14.0
				6.2	-	94.0	0.10	-	-
Degos <i>et al.</i> ⁶⁵	France 2010	284	41.5	5.2	0.78	89.0	0.29	38.0	1.43
Kim <i>et al.</i> ¹⁷	Korea 2010	104	~90	6.0	-	86.4	0.21	63.5	2.36
		(ALT \leq ULN)							
		52 (ULN < ALT \leq 2ULN)	~90	8.9	-	73.9	0.21	75.0	2.96
Sporea <i>et al.</i> ⁶⁶	Romania 2010	140	76.4	7.0	0.66	59.0	0.59	70.0	1.97
Marcellin <i>et al.</i> ²⁴	France 2009	173	50.3	7.2	0.81	70.0	0.36	83.0	4.10
Wang <i>et al.</i> ⁶⁷	Taiwan, China 2009	88	NA	8.0	0.86	80.0	0.26	77.0	3.50

Abbreviations: ALT, alanine aminotransferase; AUROC, area under receiver operating characteristic curve; F, METAVIR fibrosis stage; NLR, negative likelihood ratio; PLR, positive likelihood ratio; Se, sensitivity; Sp, specificity; ULN, upper limit of normal; VCTE, vibration controlled transient elastography.

more than 200 patients. For exclusion of cirrhosis diagnosis, the suggested cutoffs with NLR of <0.1 have ranged between 8.4 kPa and 11.0 kPa.

The cutoff of 9.1 kPa suggested by Liang *et al.*²⁵ was derived from a study cohort that included patients with abnormal bilirubin. However, abnormal bilirubin impairs the performance for cirrhosis detection, and a previous study has recommended bilirubin normalization as being important for improving VCTE performance.²⁶ The cutoff of 9.4 kPa with NLR of 0.02 suggested by Viganò *et al.*¹⁴ indicated that higher LSM with NLR near 0.1 may be more suitable for excluding diagnosis. Therefore, the suggested LSM of 10.6 kPa by Chen *et al.*²⁶ and of 11.0 kPa suggested by Marcellin *et al.*²⁴ derived from studies using normal bilirubin could be used for excluding cirrhosis diagnosis.

Thus, in antiviral treatment-naïve patients with normal bilirubin and compensated CHB, LSM of 10.6 kPa and 17.0 kPa could be used as cutoffs for excluding and confirming cirrhosis diagnosis, respectively. For patients showing values corresponding to the grey zone between LSM 10.6–17.0 kPa, cutoffs of 10.6 kPa for ALT <2 ULN and 12.7 kPa for ALT >2 ULN could be applied for confirming diagnosis of advanced fibrosis (METAVIR F \geq 3) to indicate immediate antiviral treatment.²⁶

With dual cutoffs of LSM for cirrhosis detection, some patients would still be left undiagnosed. To address this issue, stepwise combinations of VCTE with other routine available markers, such as FIB-4, aspartate aminotransferase to platelet ratio index and red cell distribution width-platelet ratio, were applied to minimize the proportion of patients involved in the grey zone.^{25,27} The stepwise combination

could also minimize the proportion of patients wrongly diagnosed as cirrhotic, due to fluctuating levels of ALT or hepatitis flares, which cause misleadingly high LSM even at 3–6 months after ALT normalization in patients with severe acute exacerbation of CHB.²⁸ To the contrary, cirrhotic patients with mild necro-inflammation would be characterized as having lower LSM, thereby resulting in false negative diagnosis. LSM-based index combined with other noninvasive parameters, such as albumin, international normalization ratio, and platelet and ultrasonic parameters, have been initially demonstrated as effective for abating this defect.²³

Monitoring treatment response

The dynamic change of liver fibrosis during antiviral therapy is one of the critical endpoints of assessing treatment response, as fibrosis stages are associated with prognosis of CHB. Use of potent antiviral agents has allowed the majority of CHB patients to obtain sustained virus suppression, following long-term therapy. Liver biopsy is, thus, not routinely performed in CHB patients that have treatment-suppressed HBV. On the other hand, large cohort studies have suggested that patients with liver fibrosis, and even cirrhosis, may achieve disease regression after 5 years of entecavir or tenofovir therapy.^{29,30}

The need for monitoring fibrotic changes still exists, however. As a repeatable non-invasive method, VCTE is feasible for monitoring histological response in patients on antiviral therapy. Studies have reported significant decline in LSM after antiviral therapy, implicating potential regression of liver fibrosis in the patients.^{31–33} One issue that should be

Table 2. Diagnostic performance of VCTE for liver cirrhosis (METAVIR F4) in patients with chronic hepatitis B

Author	Country/year	Patients, <i>n</i>	<i>F</i> = 4, %	Cutoff kPa	AUROC	Se, %	NLR	Sp, %	PLR
Seo <i>et al.</i> ²¹	Korean 2015	567	20.5	11.6	0.90	85.3	0.20	84.9	5.70
Jia <i>et al.</i> ¹²	China 2015	469	12.2	8.2	0.90	95.0	0.07	69	3.03
				21.3		40	0.63	95	8
Goyal <i>et al.</i> ²²	India 2013	357	5.9	9.0	0.93	81.0	0.21	90.0	8.1
Kim <i>et al.</i> ⁶²	Korea 2012	194	38.7	14.1	0.91	84.0	0.19	84.9	5.56
Cardoso <i>et al.</i> ⁶³	France 2012	202	7.9	11.0	0.94	75.0	0.28	90.0	7.34
Chen <i>et al.</i> ²⁶	China 2012	213 (normal bilirubin)	20.7	10.6	0.90	93.2	0.09	75.7	3.90
				16.9		59.1	0.45	94.2	10.2
		93 (abnormal bilirubin)	32.2	9.1	0.84	100	0	46.9	1.90
				29.2		23.3	0.73	98.4	14.7
Verveer <i>et al.</i> ⁶⁴	Netherlands 2012	125	6.4	13.0	0.90	–	–	–	–
Viganò <i>et al.</i> ¹⁴	Italy 2011	125	16.0	13.1	–	–	–	95.0	14.0
				9.4	–	98.0	0.02	–	–
Degos <i>et al.</i> ⁶⁵	France 2010	284	10.2	12.9	0.85	51.7	0.52	92.9	7.33
Kim <i>et al.</i> ⁶⁸	Korea 2010	104 (ALT ≤ ULN)	~47	10.1	0.88	86.7	0.15	88.1	7.26-
		52 (ULN < ALT ≤ 2ULN)	~47	15.5	–	66.7	0.33	100	∞
Sporea <i>et al.</i> ⁶⁶	Romania 2010	140	5.0	13.6	0.97	86.0	0.14	99.0	86
Marcellin <i>et al.</i> ²⁴	France 2009	173	8.1	11.0	0.93	93.0	0.08	87.0	7.20
				18.2		57.0	0.44	97.0	19.0
Chan <i>et al.</i> ¹⁶	Hong Kong, China 2009	58 (normal ALT)	26.0	9.0	0.96	100	0	88.0	8.60
				12.0		60.0	0.42	95.0	12.9
		98 (abnormal ALT)	25.0	8.4	0.94	96.0	0.07	54.0	2.10
				13.4		75.0	0.27	93.0	11.1
Kim <i>et al.</i> ⁶⁹	Korea 2008	91	42.9	10.3	0.80	59.0	0.53	78.0	2.68
Oliveri <i>et al.</i> ⁷⁰	Italy 2008	188	20.0	11.8	0.97	86.5	0.14	96.3	23.2
Wang <i>et al.</i> ⁶⁷	Taiwan, China 2009	88	NA	10.0	0.89	85.0	0.17	88.0	7.20

Abbreviations: ALT, alanine aminotransferase; AUROC, area under receiver operating characteristic curve; *F*, METAVIR fibrosis stage; NLR, negative likelihood ratio; PLR, positive likelihood ratio; Se, sensitivity; Sp, specificity; ULN, upper limit of normal; VCTE, vibration controlled transient elastography.

kept in mind is that LSM was validated initially for the assessment of fibrosis progression and not for regression; it is also important to consider that the absolute cutoffs of LSM were derived from studies of treatment-naïve CHB patients. Whether these pre-treatment cutoffs still work well in HBV-suppressed patients has been challenged.

Wong *et al.*³³ studied 71 CHB patients undergoing paired liver biopsy, with VCTE performed before and at week 48 of antiviral treatment. Only 11/28 (39%) patients who showed LSM decreased by >30%, and 1/2 (50%) patients who showed LSM increased by >30% had decreased and increased

histological fibrosis stages, respectively. Up to 60% of patients had insignificant change in LSM. The author explained that decrease in serum ALT levels and hepatic necro-inflammation may lead to reduced LSM regardless of change in liver fibrosis at week 48, and that decrease in absolute LSM was unreliable as an indicator of liver fibrosis regression at week 48. Thus, the obvious effect of ALT normalization on the interpretation of LSM changes should be taken into consideration in patients under treatment with antiviral therapy.

Later studies reported the longitudinal changes in LSM over relatively longer periods. One study found that LSM

declined continuously and significantly from pretreatment baseline compared to treatment years 1, 2 and 3 (medians: 12.9 kPa, 7.5 kPa, 6.5 kPa and 4.7 kPa, respectively; all $P < 0.05$). In addition, LSM was significantly decreased at year 2 ($P = 0.0210$) compared with that at year 1.³⁴ In another study, median LSM decreased significantly from 14.3 kPa at baseline to 7.3 kPa after 3 years of entecavir treatment ($P < 0.001$). A higher baseline LSM was recognized as the single independent predictor of a significant decline in LSM on multivariate analysis.³¹

Taken together these reported findings suggest LSM as a useful tool for monitoring changes of liver fibrosis in CHB patients under antiviral treatment. However, without paired liver biopsies from before and after treatment for confirmation, the role of VCTE for liver fibrosis assessment in CHB patients undergoing long-term therapy with antivirals remains to be determined. Nonetheless, the decline in LSM, whether it results from regression of fibrosis, remission of necro-inflammation or both, can be regarded as a favorable predictor for treatment response and may also be associated with prognosis.³⁵

Predicting portal hypertension and esophageal varices

As the end stage of chronic liver disease, the semi-quantitative diagnosis of liver cirrhosis (e.g. METAVIR F4) is a morphologic definition that does not allow for distinction between a fibrogenic process that is still in progress but potentially reversible, and a more advanced stage of the liver disease that becomes irreversible. Regarding the histologic features of cirrhosis that have not been traditionally linked to clinical outcomes, several authors have suggested performing sub-classifications of compensated and decompensated cirrhosis based on substages.³⁶ For example, compensated cirrhosis could be further refined as: (1) no portal hypertension (hepatic venous pressure gradient [HVPG] < 6 mmHg); (2) portal hypertension that is not clinically significant (HVPG between 6 and 10 mmHg); and (3) clinically significant portal hypertension (HVPG > 10 mmHg or presence of collaterals); moreover, the sub-stages 1 and 2 (HVPG < 10 mmHg) would be considered as compensated cirrhosis without varices, while the sub-stage 3 (HVPG > 10 mmHg) would be considered as compensated cirrhosis with varices. In this scenario, HVPG (or varices) plays an important role in further discrimination of the pathological and functional states of the liver.

Considering the complexity of testing HVPG and screening esophagogastroduodenoscopy, LSM has been validated and recently recommended for predicting portal hypertension and esophageal varices.^{37,38} In the report of the Baveno VI Consensus Workshop,³⁷ LSM > 15 kPa is highly suggestive of compensated cirrhosis (or compensated advanced chronic liver disease), while LSM ≥ 20 –25 kPa, alone or combined with platelet concentration and spleen size, is sufficient to rule-in clinically significant portal hypertension (HVPG > 10 mmHg). Furthermore, this report suggested that patients with LSM < 20 kPa and with platelet count $> 150,000$ have a very low risk of having varices that will require treatment, and can thus avoid the screening endoscopy.

In addition, LSM may not be accurate in predicting HVPG for decompensated cirrhosis cases in which, in addition to intrahepatic vascular resistance, there are complex hemodynamic changes.³⁶ In a large CHB patient cohort study, poor

correlation (Kendall's tau_b 0.236) was found between LSM and the size of esophageal varices.³⁹ In a different, briefly described cohort,⁴⁰ almost 40% of patients who had LSM > 20 kPa or platelet count $< 150,000$ and should undergo endoscopy actually did not have varices, resulting in low specificity and positive predictive value of the Baveno's VI criteria. To some extent, the role of LSM in predicting portal hypertension and esophageal varices mainly aims at ruling out, rather than ruling in, varices needing treatment and consequently avoiding unnecessary endoscopies (Fig. 1).

Predicting disease progression and prognosis

Disease progression in terms of development of HCC and hepatic decompensation is a severe clinical event associated with high mortality in patients with CHB. Detection of patients at high risk of disease progression is critical for better management of CHB. Histologic severity of liver fibrosis is known to be correlated with development of HCC and hepatic decompensation.³ Thus, based on the close relationship between LSM and histological fibrosis stage, many studies have validated that higher LSM value was associated with higher risk of disease progression.

In a consecutive cohort including 600 patients with CHB, patient prognosis decreased as LSM increased. The 5-year overall survival was 97.1% in patients with LSM < 9 kPa and 61.5% in patients with LSM > 20 kPa, and multivariate analysis showed that LSM had the highest hazard ratio with survival.⁴¹ Lee *et al.*⁴² stratified CHB patients into three groups according to LSM levels (< 8.0 kPa, 8.0–13.0 kPa, and > 13.0 kPa) when achieving complete virological response. Patients with LS value > 13.0 kPa (hazard ratio: 12.336) or 8.0–13.0 kPa (hazard ratio: 8.832) were at significantly greater risk of developing liver-related events (any cirrhotic complication, HCC, and liver-related mortality) compared with those with LSM < 8.0 kPa. The potential of LSM for predicting clinical outcomes seems to be greater than that of liver biopsy, probably LSM is capable of assessing ongoing pathophysiological processes and functions that a biopsy cannot.

A recent study showed that baseline LSM, rather than histological fibrosis stage, was independently predictive of HCC development in patients with CHB when starting antiviral therapy.⁴² While CHB patients with LSM ≥ 13 kPa were identified as having subclinical cirrhosis, LSM-defined subclinical cirrhosis was found to be independently associated with a risk of developing HCC, regardless of antiviral therapy (hazard ratio: 3.344 and 4.680 for with and without antiviral therapy, respectively).⁴³

Given the association between LSM and the development of HCC, LSM-based algorithms have been developed and validated recently. Wong *et al.*⁴⁴ showed that LSM-HCC score constructed from LSM, age, serum albumin and HBV DNA level was accurate for prediction of HCC in CHB patients, with AUROC 0.83 at year 3 and 0.89 at year 5, which was higher than that of an ultrasound-based score, CU-HCC (AUROC, 0.75–0.81). Another LS-based prediction model, LSPS (=LS value \times spleen diameter/platelet count) for HCC prediction that had been developed in 227 CHB patients, was identified as capable of independent prediction of HCC development (hazard ratio: 1.541) after adjusting for age, serum albumin level and histological fibrosis stage.⁴⁵ After incorporating LSM into the REACH-B scoring model (replacing the serum HBV DNA level), a better predictive performance was

observed compared with a conventional approach (AUROC, 0.814 vs 0.629, respectively).^{42,46} Though the combined use of LSM and FibroTest significantly predicted forthcoming liver-related events development, it had only a slight additional benefit compared to LSM or FibroTest alone.⁴⁷

In order to continue to improve the LSM-based algorithms for long-term outcome prediction, several issues need to be taken into consideration. The LSM-based algorithms have been derived from specific populations, for example, a community-based population or a population with advanced liver disease. Thus, the application of these LSM-based algorithms in the general population needs further validation. Most of the algorithms use single LSM or LSM at baseline for outcome prediction, whereas dynamic monitoring of LSM may evaluate the risk of HCC development more efficiently. In a consecutive cohort study of 198 patients with chronic hepatitis C, follow-up LSM was performed at least 1 year after the initial LSM. During a median follow-up period of 47.8 months, HCC incidence was 7/13 (53.8%) in patients with initial LSM >12 kPa and follow-up LSM >12 kPa, 1/16(6.3%) in initial LSM >12 kPa and follow-up LSM <12 kPa and 0/77 in initial LSM <12 kPa and follow-up LSM <12 kPa.⁴⁸ The on-treatment LSM, as well as the dynamic changes of LSM for outcome prediction in CHB patients have not been well evaluated.^{49,50}

Confounding factors and limitations of VCTE

Although VCTE is validated and has been widely applied in non-invasive evaluation of liver fibrosis and cirrhosis in various clinical settings, including in cases of CHB, the confounding factors of LSM should always be taken into consideration when interpreting the clinical significance of LSM values. Factors that influence viscoelastic properties of the liver have been reported to potentially increase liver stiffness; these include the presence of acute exacerbation of hepatitis, extrahepatic arteriovenous or biliary obstruction, and congestive heart failure.^{51–54} Thus, EASL recommended that VCTE should not be used in patients with very high ALT levels ($>10 \times \text{ULN}$).³⁸ In addition, definitive evidence has also indicated that food intake affects the accuracy of LSM for the prediction of fibrosis stage; therefore, it is advised that VCTE be undertaken when the patient has been fasting for at least 2 hours.^{55,56} While at least 10 validated measurements and an interquartile range <30% of the median value are required for a reliable LSM, an interquartile range <21% is associated with higher accuracy of VCTE for fibrosis diagnosis.⁵⁷ Last but not least, not all patients achieve reliable and successful LSM. Around 3% of patients have LSM failure and >10% of patients have unreliable LSM.^{58,59}

It has been reported that body mass index $\geq 28\text{--}30 \text{ kg/m}^2$, central obesity, ascites, narrow inter-rib spaces, advanced age and female sex were the risk factors of unreliable LSM and LSM failure. In case of no valid shot or unreliable measurement in obese patients, the XL probe could be used. Although the probes have comparable accuracy, lower liver stiffness cutoffs will be necessary when the XL probe is used to noninvasively assess liver fibrosis.^{60,61}

Conclusions

VCTE is a noninvasive tool with high accuracy and reproducibility for effectively evaluating liver fibrosis stages in patients with CHB. LSM could also serve in helping to make clinical

decisions for antiviral therapy, monitoring antiviral response, surveillance of liver-related complications and long-term outcomes. With the recommendations of LSM by clinical practice guidelines and consensus, the clinical application of LSM in patients with CHB has become widely developed and validated, but still needs further standardization.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Involved in the study design and data collection (XEL, YPC), wrote the manuscript (XEL), guarantee of the manuscript, revised and finalized the manuscript (YPC). Both authors had full access to the final version of the paper and agreed to the submission.

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