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Changing liver stiffness predict regression in advanced fibrosis patients with chronic hepatitis B, but not in moderate fibrosis patients

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Study concept and design (Chenghai Liu), acquisition of data (Zhengxin Li, Gaofeng Chen, Li Shen), analysis and interpretation of data (Zhengxin Li, Tingting Zhu), drafting of the manuscript (Zhengxin Li, Tingting Zhu), critical revision of the manuscript for important intellectual content (Zhimin Zhao, Hongtu Gu), administrative, technical, or material support (Zhimin Zhao, Li Shen), and study supervision (Chenghai Liu). All authors have made a significant contribution to this study and have approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

LSM, Liver stiffness measurement; CHB, chronic hepatitis B; AUROC, area under the receiver operating characteristics curve; CLD, chronic liver diseases; ETV, entecavir; LB, liver biopsies.

Citation

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Abstract

Background and objective: Liver stiffness measurement (LSM) may effectively correlate to the presence of liver fibrosis, but it is controversial to use for the prediction of clinical outcomes. Therefore, we aimed to evaluate the predictive value of liver stiffness for the regression of liver fibrosis.

Methods: In this study, we collected data from a clinical cohort of patients who are received anti-virus therapies for 48 weeks. 180 naive chronic hepatitis B (CHB) patients, who received paired LSM and liver biopsy with pre- and post-treatments were analyzed. Two methods (FibroScan and iLivTouch) test LSM.

Result: The area under the receiver operating characteristics curve (AUROC) of changing LSM for fibrosis regression is higher in advanced fibrosis patients (F5/6) than in moderate fibrosis patients (F3/4) in both FibroScan (0.719, 95%CI, 0.590–0.848; $P=0.003$; vs 0.617, 95%CI, 0.379–0.856, $P=0.282$) and iLivTouch (0.707, 95%CI, 0.567–0.847; $P=0.011$; vs 0.583, 95%CI, 0.422–0.744; $P=0.377$). A higher kappa value was received in advanced stage than in moderate stage both in FibroScan (0.392, $P=0.001$ vs 0.265, $P=0.053$) and iLivTouch (0.326, $P=0.019$ vs 0.030, $P=0.833$). Cut-off set as 4.10 kPa (sen, 69.4%; spe, 73.9%) in FibroScan, as 4.25 kPa (sen, 56.8%; spe, 72.2%) in iLivTouch.

Conclusion: The changing LSM can be used for predicting the liver fibrosis regression in advanced stage of CHB patients.

Keywords: chronic hepatitis B; liver stiffness measurement; liver fibrosis; non-invasive test

Introduction

Liver fibrosis, existed in a lot of chronic liver diseases (CLD) including chronic hepatitis B, alcoholic hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis, etc. and characterized as the accumulation of extracellular matrix or "scar" in liver, could leads to cirrhosis and threaten the patient's quality-of-life, morbidity and mortality [1]. Therefore, the inhibition or regression of liver fibrosis is crucial strategy for the management of CLD [2–4].

The diagnostic assessment of liver fibrosis, a major evaluation of disease severity, is an important step in the management of patients with chronic liver diseases. The liver biopsy is still considered the gold standard, it not only establish or confirm through pathological

examination on biopsy specimen, given the concept and classification of liver diseases are rooted in morphology [5, 6]. And more frequently used for semi-quantitating the efficacy of anti-fibrotic therapy or predicting disease prognosis through grading inflammation and staging fibrosis [7–9]. However, liver biopsy has several limitations, since the procedure is invasive and associated with risk such as bleeding, the sampling errors could occur given the biopsy sample only sample very small portion of the liver (1/50000), and there are the readout variations among inter-observers and intra-observers [10, 11]. Therefore, the non-invasive assessments of liver fibrosis are needed and developed recent years.

Among these non-invasive methods, TE is –optimal option. liver stiffness measurement (LSM) is assayed by transient elastography and based on the measurement of the velocity of shear waves generated by mechanically exciting liver tissue by ultrasound pushes, has a good correlation with fibrosis stage, in particular in cirrhosis [12, 13]. Better diagnostic performance of TE for cirrhosis than for fibrosis [14]. Although the accumulated documents have approved LSM value in diagnosing liver fibrosis, surprising and puzzling, it is very controversial that LSM/TE could use for monitoring efficacy of anti-fibrotic compounds [15–19]. Some scholars believe that LSM can only predict the recovery of inflammations.

To analyze the evaluation role of LSM in patients with low levels of inflammation. In the current study, we collected the data from the patients with liver fibrosis and cirrhosis due to HBV, who took twice liver biopsy and TE examination before and after 48 weeks treatment of entecavir (ETV) or ETV and Fuzheng Huayu. And the patients were divided into two groups according to the machine of TE – Fibroscan or iLivTouch. As the Ishak fibrosis stages were used as the reference methods, the correlation between changing LSM and Ishak fibrosis stages, and role of changing LSM were analyzed when the patients were stratified into 2 sub-groups—moderate fibrosis stage (F3/4) and advanced fibrosis stage (F5/6, cirrhosis). We found that–the advanced fibrosis or cirrhosis instead of moderate fibrosis, changing LSM could predict the fibrosis regression.

Materials and Methods

Patients and setting

All patients we have enrolled from a multi-center, double-blind, randomized controlled clinical trial (October 2014–December 2017). The inclusion criteria of this study were as follows: (i) naive patients with chronic hepatitis B (CHB); (ii) Child-Pugh score <7; (iii) HBV-DNA $\geq$ 20IU/ml. (iv) eligibility for LSM assessment (alanine aminotransferase [ALT] $<5\times$ ULN, note: ULN = upper limit of normal; 50U/L for ALT); (iii) fibrosis stage $\geq$ F3 in Ishak fibrosis stages. The exclusion criteria included (i) coinfection with other viruses; (ii) other liver diseases; (iii) any cancer; (iv) pregnancy or breastfeeding. More details of eligibility criteria have been published (NCT02241590) [20].

Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Shuguang Hospital (2014–331–27–01).

All enrolled patients were given ETV 0.5 mg orally once a day, combined with Fuzheng Huayu tablets or placebo according to the random number of patients (randomly assigned in a 1:1 ratio). The clinical trial treatments last for 48 weeks.

Serum biochemical testing

The laboratory of local clinical centers was responsible for platelets testing. The biochemical laboratory of Shanghai Dian Medical Testing Laboratory was responsible for serum biochemical analysis and measurement of all subjects recorded, including total bilirubin (TBil), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB) (Cobas 8000 c702, Roche) and HBV-DNA (SPRAPAGEME MX3000, Agilent).

Liver stiffness measurement

LSM was performed on patients at pre- and post-treatment using FibroScan (Echosens, Paris, France) or iLivTouch (FT100, Wuxi Hisky Med, China). All operators have been well trained before the trail and they had no information about the patients' clinical data. Only a procedure with at least ten valid measurements, an interquartile range (IQR)/median value (IQR/M) $<$ 20% and a success rate $>$ 80% was considered reliable [21].

The changing LSM means pre-treatment LSM minus post-treatment LSM.

Collections of Liver biopsies

At baseline and after 48 weeks of treatment, all enrolled patients underwent liver biopsies (LB). The length of liver tissue was 1.5–2cm. Hematoxylin/eosin staining, reticular fiber staining, and Sirius red staining were performed for the assessment of inflammation and fibrosis, and the Ishak scoring system was used to evaluate the stage of liver fibrosis and histological inflammation.

Evaluations of Liver biopsies

The results of LB were determined by a professional pathological team, consisting of three liver pathologists and one senior liver pathologist. The first three pathologists reviewed the LB independently. When two or more pathologists were same results after evaluating, then this result are the final pathological result; otherwise, the senior liver pathologist decided the final pathological results in the form of meeting discussions. According to the final results of LB, the Ishak score decreased $\geq$ 1 point was defined as the regression; decreased = 0 point was defined as the stable; increased $\geq$ 1 point was defined as the progression. The Ishak fibrosis score in F1/2 was defined as the mild stage, F3/4 was defined as the moderate stage, and F5/6 was defined as the advanced stage.

Histological inflammation assessments were referred to Ishak system, 0–6 as no/mild inflammation, 7–12 as moderate inflammation and 13–16 as severe inflammation. The improvements of inflammation defined as qualitatively reduced, such as moderate or severe inflammation change to no/mild inflammation. The progression of inflammation defined qualitatively too, such as no/mild inflammation change to moderate or severe inflammation.

Statistical analysis

SPSS 20.0 software (SPSS Inc, Chicago, IL, USA) and MedCalc 20.0.3 software (MedCalc Software Ltd, Ostend, West Flanders, Belgium) was used for data analysis. When data conform to normal distribution, they were described as mean $\pm$ standard deviation ($x \pm s$); therefore, comparisons between groups were performed by one-way analysis of variance. When data were not conformed to normal distribution, or with uneven variance, they were described as median and interquartile range (M [Q1, Q3]), and the Wilcoxon test was used for comparisons between groups. The Chi-square test was used for the comparison of count data between groups. Spearmen correlation was used for correlation analysis. Receiver operating characteristic (ROC) curve analyses were used to assess the diagnostic accuracy of LSM in predicting the outcomes of liver fibrosis, the cut-off value was used Youden Index, calculating the area under the ROC curve (AUROC) 95% confidence interval (95%CI), and sensitivity/specificity approaches to describe the outcomes. Delong test was used to compare AUROCs. A two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

116 patients evaluated by FibroScan were included, 54 patients received entecavir combined with FuzhengHuayu table and 62 patients only received entecavir; before treatment there were 44 patients in F3–4 stages, 72 patients in F5–6 stages with Ishak system; after treatment, 58 cases were the regression, and 41 cases were the stable and 20 patients were the progression. 98 patients evaluated by iLivTouch were included, 46 patients received entecavir combined with Fuzheng Huayu table and 52 patients only received entecavir;

before treatment, there were 46 patients in F3–4 stages, 52 patients in F5–6 stages with Ishak system; after treatment, 44 cases were the regression and 38 cases were the stable and 16 patients were the progression. The basic clinical conditions of the patients included in the study are shown in the Table1.

The clinical lab tests revealed statistical differences between baseline and post-treatment measures in ALT and AST. Given that the values of ALT and AST were both $< 5 \times$ ULN, and most patients (102/116 or 93/98) had scores between 0–6 in the Ishak inflammation system, we considered that the changes of LSM are related to decreasing Ishak scores, rather than the presence or absence of inflammations.

The AUROC was 0.662 (95%CI, 0.561–0.764; $P=0.002$; sensitivity, 51.4%; specificity, 77.3%) with the LSM of FibroScan value set at 17.2kPa for cirrhosis (Figure 2a). And the AUROC was 0.715 (95%CI, 0.611–0.818; $P=0.000$; sensitivity, 75%; specificity, 65.2%) with the LSM of iLivTouch value set at 13.35kPa for cirrhosis (Figure 3a).

Table1 Clinical characteristics of the study population

		FibroScan (n = 116)		*P*	iLivTouch (n = 98)		*P*
		0w	48w		0w	48w	
Gender	M/F	93/23			78/20		
Age, year	$\bar{x} \pm s$	43.24 ± 8.54			43.55 ± 8.74		
BMI	$\bar{x} \pm s$	23.66 ± 3.32			23.26 ± 3.24		
ALB, g/L	$\bar{x} \pm s$	43.99 ± 5.05	46.38 ± 4.57	0.004	44.08 ± 5.49	46.92 ± 4.56	0.002
ALT, U/L	M (Q1, Q3)	40.00 (29.75, 62.75)	27.00 (18.00, 35.00)	0.000	44.00 (28.00, 58.25)	27.00 (18.00, 35.00)	0.000
AST, U/L	M (Q1, Q3)	33.50 (25.00, 53.85)	26.00 (22.00, 34.00)	0.000	36.50 (28.00, 48.92)	27.00 (22.00, 33.00)	0.000
TBil, mmol/L	M (Q1, Q3)	13.35 (9.00, 17.92)	13.60 (9.00, 19.70)	0.987	12.10 (9.20, 17.02)	12.20 (9.90, 16.30)	0.687
Plt, $\times 10^9$/L	M (Q1, Q3)	122.00 (89.00, 166.00)	135.00 (100.00, 178.00)	0.256	122.00 (87.00, 161.25)	134.00 (98.50, 169.00)	0.442
Ishak Fibrosis Stage, n (%)	F1/2	0 (0.0)	3 (2.6)	0.001	0 (0)	3 (3.0)	0.000
	F3	26 (22.4)	35 (30.2)		20 (20.5)	29 (29.5)	
	F4	18 (15.5)	37 (31.9)		26 (26.5)	25 (25.5)	
	F5	53 (45.7)	34 (29.3)		33 (33.6)	34 (34.6)	
	F6	19 (16.4)	7 (6.0)		19 (19.3)	7 (7.1)	
Ishak Inflammation Score, n (%)	0–6	102 (87.9)	111 (95.7)	0.055	93 (94.9)	95 (96.9)	0.718
	7–12	14 (12.1)	5 (4.3)		5 (5.1)	3 (3.1)	
	13–18	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

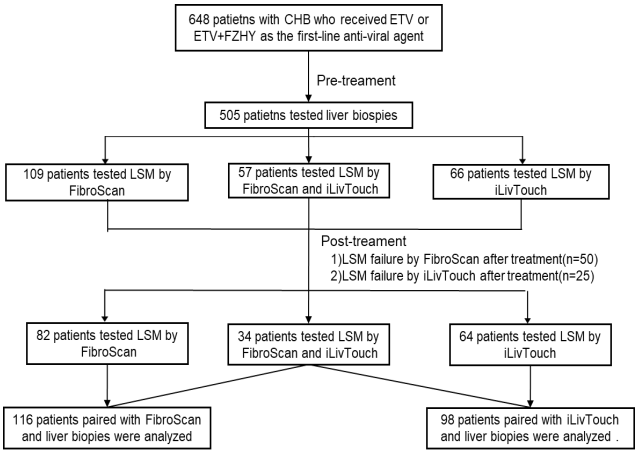

Figure 1 Flowchart of recruiting study cohort.
A total of 648 patients with CHB were recruited. 505 of 648 patients were tested liver biopies at the baseline. 109 of 505 patients were tested for LSM by FibroScan, 66 of 505 patients were tested for LSM by iLivTouch, and 57 of 505 patients were tested for LSM both by FibroScan and iLivTouch. Aftertreatment 50 patients failed to test LSM by FibroScan and 25 patients failed to test LSM by iLivTouch. Finally, 116 of 648 patients were selected for statistical analysis with paired FibroScan and liver biopies. 98 of 648 patients were selected for statistical analysis with paired iLivTouch and liver biopies.

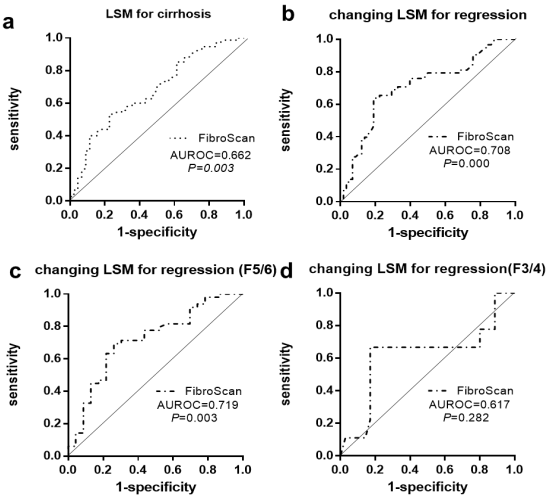

Figure 2 ROC of LSM tested by FibroScan
(a) Diagnosing cirrhosis(F ⩾ 5), the cut-off LSM value was calculated as17.2kPa with an AUROC of 0.662 (95%CI, 0.561–0.764; $P=0.002$; sen, 51.4%; spe, 77.3%). (b) ROC of changing LSM tested by FibroScan for diagnosing the regression, the cut-off changing LSM value of all liver fibrosis stages was calculated as 5.80 kPa with an AUROC of 0.708 (95%CI, 0.612–0.804; $P=0.000$; sen, 63.8%; spe, 81.0%). (c) The cut-off changing LSM value of stages (F5/6) was calculated as 4.10 kPa with an AUROC of 0.719 (95%CI, 0.590–0.848; $P=0.003$; sen, 69.4%; spe, 73.9%). (d) The AUROC of stages(F ⩽ 4) was 0.617 (95%CI, 0.379–0.856; $P=0.282$).

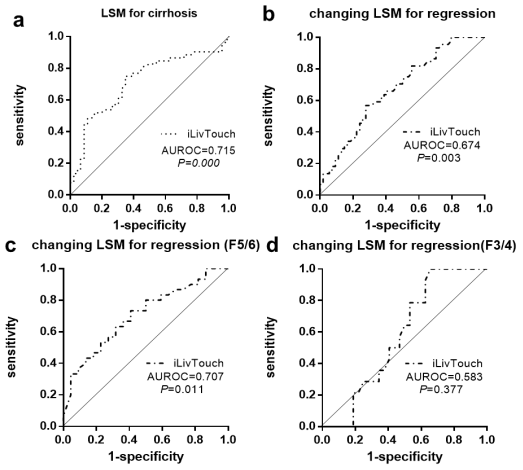

Figure 3 ROC of LSM tested by iLivTouch

(a) Diagnosing cirrhosis (F≥5), the cut-off LSM value was calculated as 13.35 kPa with an AUROC of 0.715 (95%CI, 0.611–0.818; $P=0.000$; sen, 75%; spe, 65.2%). (b) ROC of changing LSM tested by iLivTouch for diagnosing the regression, the cut-off changing LSM value of all liver stages was calculated as 4.25 kPa with an AUROC of 0.674 (95%CI, 0.569–0.779; $P=0.003$; sen, 56.8%; spe, 72.2%). (c) The cut-off changing LSM value of stages (F5/6) was calculated as 4.25 kPa with an AUROC of 0.707 (95%CI, 0.567–0.847; $P=0.011$; sen,73.3%; spe, 59.1%). (d) The AUROC of stages (F≤4) was 0.583 (95%CI, 0.422–0.744; $P=0.377$).

Correlations between changing LSM and changing Ishak scores

Through Spearman correlation analysis, it was found that the changing LSM tested by FibroScan has a weak correlation with changing scores of the Ishak fibrosis system (r=0.298, $P=0.001$), but no correlation with and changing scores of Ishak inflammation system (r=-0.072, $P=0.441$). (Table 2)

Similar results can be found using the iLivTouch approach: it was found that the changing LSM tested by iLivTouch has a weak correlation with changing scores of the Ishak fibrosis system (r=0.301, $P=0.003$), but no correlation with and changing scores of Ishak inflammation system (r=0.081, $P=0.430$). (Table 2)

Given to the values of ALT and AST were both ＜5×ULN at the baseline, and changing LSM has no correlation with and changing scores of Ishak inflammation. The above results indicate that changing LSM were related rather varies of liver fibrosis stages than varies of inflammation.

Table 2 Correlations between changing LSM and changing scores of Ishak system

	Correlation coefficient rate	
	Fibrosis stage	Inflammation score
FibroScan	0.298*	-0.072# ($P=0.441$)
iLivTouch	0.301*	0.081# ($P=0.430$)

Note: *: $P<0.05$, #: $P>0.05$.

The changing LSM of FibroScan is related to decreasing stages of liver fibrosis in the advanced stage, but not in moderate stage.

The AUROC was 0.708 (95%CI, 0.612–0.804; $P=0.000$; sensitivity, 63.8%; specificity, 81.0%) with the changing LSM of FibroScan value set at 5.80kPa for fibrosis regression of all stages, which is defined as one-stage reduction in the Ishak fibrosis-stage. The AUROC was 0.719 (95%CI, 0.590–0.848; $P=0.003$; sensitivity, 69.4%; specificity, 73.9%) with the changing LSM of FibroScan value set at 4.10 kPa for fibrosis regression of advanced stage (F5/6). The AUROC was 0.617 (95%CI, 0.379–0.856; $P=0.282$) for fibrosis regression of moderate stage (F3/4). (Figure 2b/c/d)

The AUROC for fibrosis regression in advanced stage was higher than in all stages (0.719 vs 0.708), but no significance in moderate stage which AUROC was 0.617($P=0.282$).

The above results indicate that changing LSM is related with regression of liver fibrosis in Ishak system, especially in advanced stage.

The changing LSM of iLivTouch is related to decreasing stages of liver fibrosis in the advanced stage, but not in moderate stage.

Similar results can be found using the iLivTouch approach:

The AUROC was 0.674 (95%CI, 0.569–0.779; $P=0.003$; sensitivity, 56.8%; specificity, 72.2%) with the changing LSM of iLivTouch value set at 4.25kPa for fibrosis regression of all stages. The AUROC was 0.707 (95%CI, 0.567–0.847; $P=0.011$; sensitivity,73.3%; specificity, 59.1%) with the changing LSM of iLivTouch value set at 4.25kPa for fibrosis regression of advanced stage (F5/6). The AUROC was 0.583 (95%CI, 0.422–0.744; $P=0.377$) for fibrosis regression of moderate stage(F3/4) (Figure 3b/c/d).

The AUROC for fibrosis regression in advanced stage was higher than in all stages (0.707 vs 0.674), but no significance in moderate stage which AUROC was 0.583 ($P=0.377$).

The above results indicate that changing LSM is related to regression of liver fibrosis in Ishak system, especially in advanced stage.

LSM and LB achieved consistencies of predicting fibrosis regression in advanced fibrosis.

Based on the cut-off results obtained by AUROC, we then compared the consistencies between LSM and LB in predicting liver fibrosis regression. A higher kappa value was received in advanced stage than in moderate stage both in FibroScan (0.392, $P=0.001$ vs 0.265, $P=0.053$) and iLivTouch (0.326, $P=0.019$ vs 0.030, $P=0.833$). (Table 3)

The above results indicate that changing LSM could predict the fibrosis regression in advanced stage.

Table 3 Consistency between changing LSM and changing scores of Ishak system

	Stage at baseline		Ishak		Kappa (P)
			Regression	Non-regression	
FibroScan	F5/6	Regression	34	6	0.392 (0.001)
		Non-regression	15	17	
	F3/4	Regression	6	11	0.265 (0.053)
		Non-regression	3	24	
iLivTouch	F5/6	Regression	22	9	0.326 (0.019)
		Non-regression	8	13	
	F3/4	Regression	3	6	0.030 (0.833)
		Non-regression	11	26	

Similar performances of iLivTouch and FibroScan in the staging and predicting liver fibrosis.

The AUROC of diagnosing cirrhosis, iLivTouch is higher than FibroScan (0.715 vs 0.662, $P=0.482$). On the AUROC of predicting fibrosis regression, iLivTouch is similar to FibroScan (0.707 vs 0.719, $P=0.899$) in advanced stage. (Table 4)

The above results indicate that iLivTouch perform similar with FibroScan in the staging liver fibrosis and predicting fibrosis regression.

Table 4 Comparisons of AUROCs in LSM

Prediction	FibroScan (n=116) AUROC (95%CI)	iLivTouch (n=98) AUROC (95%CI)	Z	P
Cirrhosis	0.662 (0.561-0.764)	0.715 (0.611-0.818)	0.702	0.482
Regression	0.719	0.707	0.126	0.899

Prediction	FibroScan (n = 116) AUROC (95%CI)	iLivTouch (n = 98) AUROC (95%CI)	Z	P
(F5/6)	(0.590-0.848)	(0.567-0.847)		

Discussion

In the current study, we conducted AUROC analysis with liver cirrhosis as a stratified factor from the clinic trail, and found that LSM has a good prognostic value in advanced liver fibrosis, and could predict the efficacy of anti-fibrotic agents better in the HBV caused advanced fibrosis (cirrhosis) than moderate fibrosis.

In previous studies [22–24], the diagnostic value for cirrhosis in CHB was quite reliable, and cut-off value varied 9.40–14.00 kPa. In our study, the diagnostic cut-off value in FibroScan was 17.2kPa and it was 13.35kPa for the diagnostic cut-off value of iLivTouch; the high cut-off value which we matched may be due to the high proportion of cirrhosis patients. The number of patients with cirrhosis accounted for 62.07% (72/116) using FibroScan and 53.06% (52/98) using iLivTouch, which much higher than previous reported.

Although LSM diagnosis advanced liver fibrosis in cross-sectional studies is reliable, but the results are controversial in reporting about LSM on prognosis of liver fibrosis outcomes in clinical trails. LSM itself will be interfered by many factors, such as ascites, fatty liver and etc. And the more important factors are inflammations and fibrotic stages. As some studies [17,18] found changing LSM more related to inflammatory improvements than fibrosis regression. As inflammation is the main factor for fibrosis progression, and improvement of inflammation is an essential precondition for the regression of fibrosis [6, 25]. In CHB patients who had achieved virologic response after anti-virus therapies, fibrosis regression could be seen frequently in moderate fibrosis stage [26–28]. That is may be why changing LSM more related to inflammatory improvements. We also found there is no significance for changing LSM predicting the fibrosis regression in moderate stage (F3/4), it was same to previous studies reported.

However, there are still some patients have not been well controlled after anti-virus therapies in advanced fibrosis stage [29]. Which indicted simply improving inflammation cannot effectively alleviate liver fibrosis. And it have been proved that a higher AUROC will be reached when fibrotic stages grow [14]. Therefore changing LSM might be more influenced by fibrosis regression than improvements of inflammation in advanced fibrosis stages. Our study enrolled higher proportions of advanced fibrosis patients than previously reported. Given to the low rate of cirrhosis patients previously enrolled, the fibrosis stage may be underestimated in evaluating the LSM on prognosis of liver fibrosis. In this study, we confirmed that fibrotic stages is the important factor which influencing LSM on prognosis of liver fibrosis in advanced fibrosis patients, although inflammation could not be excluded.

In a recent study [30], 55.7% (405/727) of advanced fibrosis patients were enrolled, they also found changing LSM was do relate with decreasing fibrosis stages by logistic analysis before adjustment for regression to the mean (RtM), however, it stated that LSM is unreliable estimating fibrosis regression after adjustment for RtM. This contrarily conclusion may because they did not perform a stratified analysis for only advanced fibrosis patients. Above all, we suggest that changing LSM do relate with fibrosis regression in advanced fibrosis stage.

There are two methods testing LSM, FibroScan and iLivTouch. From the AUROCs value of LSM on liver fibrosis regressions, we found iLivTouch perform similar with FibroScan in predicting regression (0.719 vs 0.707, $P>0.05$). And the cut-off value of LSM is also similar too (FibroScan 4.10kpa vs iLivTouch 4.25kpa). Our results pointed out that both methods could be used a same standard in clinical follow-ups.

Our research has some limitations, such as the sample size is not big in the study, the changes of LSM could not be dynamically observed at each visit phase, and the enrolled patients lacked non-Asian patients. Differences in drug intake among patients were not excluded, but as an objective evaluation method (LSM), its efficacy should not be affected by drug intervention.

Conclusions

In conclusion, we demonstrated that changing LSM is a noninvasive method for predicting liver fibrosis regression in advanced fibrosis of CHB patients.

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