Transient elastography in hepatitis B virus infection

Liver stiffness discrepancy due to sampling location

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ABSTRACT

الأهداف: للتحقق من تغير في صلابة الكبد LS و يقاس باستخدام الاستوجرافي العابر، وتحديد العوامل المؤثرة في العدوى المحتملة بفيروس التهاب الكبدB .

الطريقة: أجريت هذه الدراسة المستعرضة في قسم الأمراض المعدية في مستشفى تونغجي، كلية تونغجي الطبية، جامعة هواتشونغ للعلوم و التكنولوجيا، ووهان بمقاطعة هوبي، الصين، خلال الفترة من مارس إلى يونيو 2010م. حصلنا على 3 قياسات ناجحة في مواقع مختلفة ل 123 مريضاً وتم حساب تباين LS. وقيمت تأثير البيانات السريرية تعارض النتيجة.

النتائج: كان التباين 1.3 (0.2-16.5) كيلو باسكال وزيادة بشكل مستقل مع مرحلة التليف: 0.9(0.2-4.4)كيلو باسكال في F0/F1 ، 1.5 (0.4-3.7) كيلو باسكال في F2، 3.0 (0.3-9.4) كيلو باسكال في F3، و7.4(3.1-16.5) كيلو باسكال في F4. لوحظ وجود تفاوت ≥2 كيلو باسكال في 45 (36.6%) من المرض: 8(11.9%) مع F0/F1، 7(31.8%) مع F2، 15 (73.7%) مع F3 و 15(100%) مع F4. حدوث التفاوت ≥2 كيلو باسكال كان مرتبطاً فقط مع مرحلة التليف في تحليل الانحدار المتعدد. لوحظ التوافق على مرحلة التليف في 33 (26.8%) من المرضى، وكان الأكثر شيوعاً في مرحلة F2 (F0/F1، 10.45%؛ F2، 68.2%؛ F3، 38.8%، F4، 26.7%).

الخاتمة: إن تباين LS هو أمر شائع و يتوافق مع مرحلة التليف بشكل مستقل.

Objectives: To investigate the variability in liver stiffness (LS), measured by transient elastography, and determine the possible influencing factors in hepatitis B virus infection.

Methods: This cross-sectional study was conducted at the Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China from March to June 2010. Three successful measurements at different sites in 123 patients were obtained, and the LS discrepancy was calculated. The influence of clinical data on the discrepancy was also assessed.

Results: The LS discrepancy was 1.3 (0.2-16.5) kPa and independently increased with a fibrosis stage: 0.9 (0.2-4.4) kPa in F0/F1, 1.5 (0.4-3.7) kPa in F2, 3.0 (0.3-9.4) kPa in F3, and 7.4 (3.1-16.5) kPa in F4. A discrepancy ≥2 kPa was observed in 45 (36.6%) patients: 8 (11.9%) with F0/F1, 7 (31.8%) with F2, 15 (73.7%) with F3, and 15 (100%) with F4. The incidence of discrepancy ≥2 kPa was only associated with fibrosis stage in multiple regression analysis. Discordance in fibrosis stages was observed in 33 (26.8%) patients, and was most frequent in stage F2 (F0/F1, 10.45%; F2, 68.2%; F3, 36.8%; and F4, 26.7%).

Conclusion: The LS discrepancy is common and associated with fibrosis stage independently. While determining the fibrosis stage and disease progression, LS discrepancy should be considered.

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Hepatitis B virus (HBV) infection is a major health issue in China, with 120 million carriers and 30 million chronically infected people. Further, in China, there are approximately 300,000 deaths annually from HBV-related diseases.[1-3] Liver fibrosis is associated with HBV infection progression and is an indicator of anti-viral treatment for pre-cirrhotic patients with normal or mildly elevated serum HBV DNA and alanine aminotransferase levels.[4,5] The current gold standard for assessing liver fibrosis is liver biopsy, which is limited by its invasiveness, possibly life-threatening complications, sampling errors, and inter-observer discrepancies. Hence, a reliable, non-invasive, rapid, and affordable liver fibrosis assessment method is necessary.

Transient elastography (TE) has recently been applied worldwide for examining liver stiffness (LS) in chronic liver diseases.[6-13] Liver stiffness correlates well with the liver fibrosis staging by histology.[6-8,14] Due to its diagnostic accuracy and reproducibility, TE is recommended as the first-line technique for diagnosing liver fibrosis.[15-19] Some studies have reported LS variability that is dependent on the sampling position.[20-22] However, the incidence and degree of discrepancies in LS owing to the sampling location in HBV patients remain unclear. Moreover, the effects of gender, age, body mass index (BMI), and laboratory markers including alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TB),[23] and direct bilirubin (DB) on LS discrepancy are unknown. Further, the correlations between LS discrepancy and demonstration of liver cirrhosis by ultrasonography (US), as well as the fibrosis stage diagnosed by TE require elucidation. Boursier et al[15] considered the position on the median axillary line in the first intercostal space under the upper limit of the liver dullness to be the best examination site (**Figure 1**). But, Ingiliz et al[20] regarded the position that was 2-3 cm ahead of the intersection of the xiphoid process level and median axillary line in the same intercostal space as the best site (**Figure 1**). The first site provided inter-observer reproducibility, while the second one promised successful measurements.[15,20] However, no site is accurate for determining the extent of fibrosis of the whole liver. Moreover, LS measurements (LSM) cannot be performed in the same position in every patient due to its anatomic differences. An experienced operator usually shifts from the established position to get a more reliable sampling position. Hence, LS discrepancy due to sampling variability should be considered when determining the liver fibrosis stage in a single measurement, and when comparing measurements from different medical visits or by different operators.

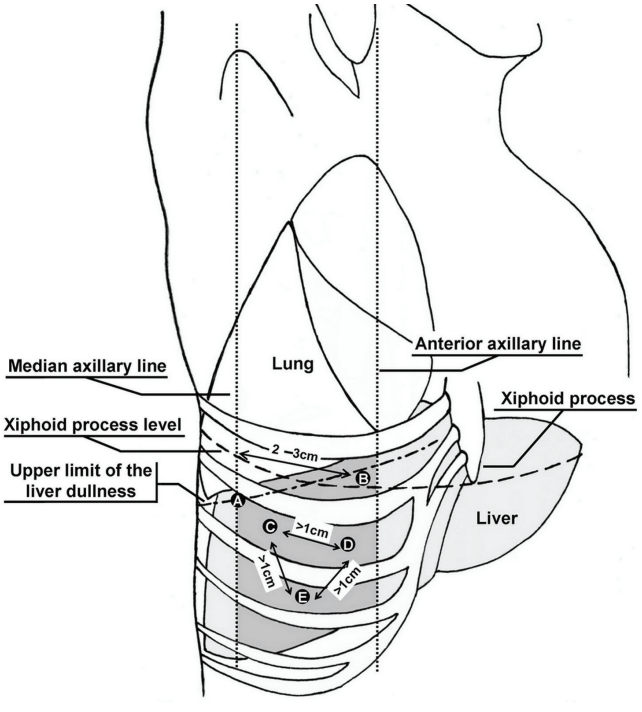

Figure 1 - The sampling sites to perform liver stiffness measurement. Site A and site B were considered to provide best inter-observer reproducibility and successful measurements respectively. Site C, D, and E were examples of the 3 sampling sites.

In this study, 3 successful measurements at different locations were obtained for each patient to define the degree of LS discrepancy owing to the sampling position. Further, the effects of additional factors, including gender, age, BMI, ALT, AST, DB, TB, and liver cirrhosis demonstrated by US, as well as fibrosis stage diagnosed by TE, in HBV infection were evaluated.

Methods. Between March and June 2010, we recruited 134 consecutive patients from the Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China for this cross-sectional study, in whom the hepatitis B surface antigen could be detected in the serum for more than 6 months. Patients with coexisting hepatitis C virus infection, alcohol abuse (mean alcohol consumption >40 g/day for men and >20 g/day for women), liver steatosis (determined by US), hepatic schistosomiasis, hepatocellular carcinoma, and other known chronic liver diseases were excluded. All patients obtained informed consent for the use of data for research purposes. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki.

A single experienced physician performed LSM using the FibroScan device (FibroScan® 502, Echosens, Paris, France) with the M probe according to the manufacturers' recommendations. During the measurements, patients lay on their backs with their right arms behind their heads. Each patient underwent 3 examinations at different sites in the intercostal space, between the anterior axillary line and median axillary line within the right hepatic lobe (**Figure 1**). All the sites were at least one cm apart from each other (**Figure 1**). Liver stiffness measurements were performed in regions free from other structures (such as large vessels) with a minimal parenchymal thickness of 6 cm that was confirmed by time-motion ultrasonic imaging. Stiffness results were expressed in kilopascal (kPa) as the median of all valid shots. Successful measurements were defined by acquisition with a success rate (SR) >60%, at least 10 valid shots, and an interquartile-range/median LS values (IQR/M) <0.3.[8] The discrepancy between the maximal and minimal LS values of the 3 measurements was defined as ΔLSM. A ΔLSM ≥2 kPa was considered clinically relevant, as described previously.[24] Consequently, the patients were divided into ΔLSM <2 kPa and ΔLSM ≥2 kPa groups.

As all the patients were infected with HBV exclusively, the stiffness cut-off values published by Marcellin et al[7] were selected to diagnose the fibrosis stage: ≤7.1 kPa for F0/F1; 7.2-10.4 kPa for F2; 10.5-18.1 kPa for F3; and ≥18.2 kPa for F4. For each patient, the fibrosis stage corresponding to the minimal, median, and maximal LS value of the 3 LSMs were respectively defined as the minimal, median, and maximal fibrosis stage.

Patients with 3 equal fibrosis stages constituted the fibrosis stage concordance group, while the other patients were included in the fibrosis stage discordance group. The median fibrosis stage was used to define the fibrosis stage diagnosed by TE.

Anthropometric parameters included age, gender, body weight, and body height. The BMI (kg/m^2) was calculated as weight (kg) divided by the height (m) squared. The results of laboratory tests, including ALT, AST, TB, and DB, and a liver ultrasound were recorded. All the examinations were performed within one week of the LSM. Cirrhotic liver was diagnosed by US if all of the following was observed: enlargement of left/caudate lobes, atrophy of the right lobe, nodularity of the liver surface, enhancement of the parenchyma echogenicity, presence of micronodules and macronodules, dilatation of the portal veins, or splenomegaly.[23,25]

Statistical analysis. Continuous variables were expressed as mean ± SD or median with range, depending on the data distribution. Two independent samples were compared using Students t-test, or Mann-Whitney U-test as appropriate. Categorical variables were compared by Chi squared test. To test the strength of concordance between the fibrosis stages, the kappa reliability test was used. The ΔLSM was logarithmically transformed and the log10 of ΔLSM was used in regression analysis. The variables associated with the log10 of ΔLSM in the univariate analysis were further analyzed by multiple linear regression. Multiple logistic regression was performed to identify the independent predictors for ΔLSM ≥2 kPa and discordance in the fibrosis stage. Statistical analysis was carried using the Statisitical Package for Social Sciences Version 12.0 software. A p value of less than 0.05 was considered statistically significant for all analyses.

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Results. Liver stiffness measurements was performed in 134 consecutive patients, and 123 patients had 3 successful LSMs. Hence, 123 patients and 369 successful LSMs were selected for further analysis. The median age was 35 years (17-64 years) and 90 (73.2%) patients were male. The mean BMI was 21.6±2.6 kg/m^2. The ALT measurement was available in 106 patients, AST in 103, TB in 103, and DB laboratory in 95. The median ALT values were 28.5 IU/L (7.0-479.0 IU/L), AST 28.0 IU/L (10.0-151.0 IU/L), TB 13.3 μmol/L (5.2-60.2 μmol/L), and DB 3.8 μmol/L (1.7-15.9 μmol/L). A total of 34 patients had definite cirrhosis as demonstrated by US imaging, and 64 patients had no signs of liver cirrhosis.

Liver stiffness measurements and LS discrepancy. The median LSM values of the 369 measurements were 6.7 kPa (2.8-46.4 kPa), IQR/M 0.13 (0.01-0.3), and SR 100% (67-100%). Of the 369 successful LSMs, an IQR/M <0.21 was observed in 314 (85.1%) LSMs. When categorizing LS to fibrosis stage, there were 67 patients in F0/F1, 22 patients in F2, 19 patients in F3, and 15 patients in F4 (**Table 1**). The ΔLSM ranged from 0.2 kPa to 16.5 kPa, with a median value of 1.3 kPa. In 45 patients (36.6%), a ΔLSM ≥2 kPa was observed. Discordance in fibrosis stages was observed in 33 (26.8%) patients (**Table 1**). The kappa value was 0.835 for the comparison of the minimal and median fibrosis stage, and was 0.752 for the comparison of the median and maximal fibrosis stage, suggesting good agreement (p<0.001). Only moderate agreement was observed for the comparison of the minimal and maximal fibrosis stage, with a kappa value of 0.578 (p<0.001).

Factors potentially influencing LS discrepancy. In the univariate regression analysis, age, DB, gender, fibrosis stage, and demonstration of liver cirrhosis by US correlated with the log10 of ΔLSM (p<0.05). The other clinical data including BMI (p=0.335), ALT (p=0.606), AST (p=0.142) and TB (p=0.127) were not correlated with the log10 of ΔLSM. The variables correlated with the log10 of ΔLSM in the univariate analysis were further examined in the multiple linear regression analysis. Only fibrosis stage was the independent variable to predict log10 of ΔLSM (p<0.001), but age (p=0.869), DB (p=0.697), gender (p=0.254), and demonstration of liver cirrhosis (p=0.054) by US were not. The median ΔLSM increased with the fibrosis level: 0.9 kPa (0.2-4.4 kPa) in F0/F1, 1.5 kPa (0.4-3.7 kPa) in F2, 3.0 kPa (0.3-9.4 kPa) in F3, and 7.4 kPa (3.1-16.5 kPa) in F4 (p<0.001; **Figure 2**).

The clinical characteristics of the ΔLSM <2kPa group and ΔLSM ≥2kPa group were compared (**Table 2**). Age, ALT, DB and the proportion of patients with liver cirrhosis demonstrated by US differed significantly between the 2 groups. The proportion of patients with a ΔLSM ≥2kPa differed between the fibrosis stages (p<0.001, **Table 3**). Multiple logistic regression analysis revealed that the fibrosis stage diagnosed by TE was the only factor independently correlated with ΔLSM ≥2 kPa (ß: -3.994; odds ratio [OR]: 5.837; 95% confidence intervals [CI]: 3.271-10.414; p<0.001).

The fibrosis stage concordance group and the fibrosis stage discordance group were compared (**Table 2**). Serum AST levels and the proportion of patients with liver cirrhosis demonstrated by US were significantly higher in the fibrosis stage discordance group than in the fibrosis stage concordance group. The incidence of discordance was higher in F2 than those in F0/F1, F3, and F4 (p<0.001; **Table 3**). The correlation between

Table 1 - Fibrosis stages of the 3 successful measurements of liver stiffness in patients.

Three fibrosis stages			Fibrosis stage diagnosed by TE	Number of patients
Maximal	Median	Minimal		
Fibrosis stage concordance group (n=90)				
F0/F1	F0/F1	F0/F1	F0/F1	60
F2	F2	F2	F2	7
F3	F3	F3	F3	12
F4	F4	F4	F4	11
Fibrosis stage discordance group (n=33)				
F0/F1	F0/F1	F2	F0/F1	7
F0/F1	F2	F2	F2	9
F2	F2	F3	F2	6
F3	F3	F4	F3	7
F3	F4	F4	F4	4

The median fibrosis stage was defined as the fibrosis stage diagnosed by transient elastrography (TE)

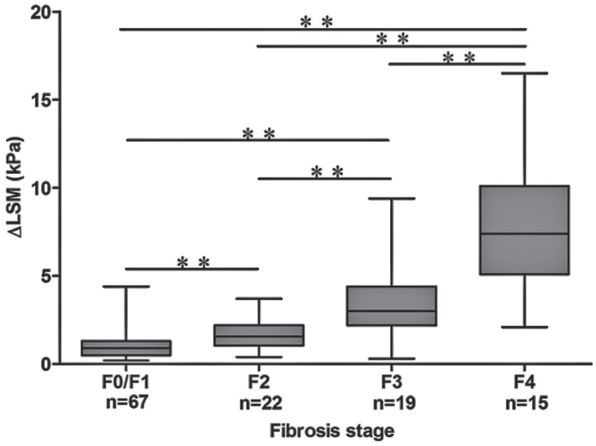

Figure 2 - The ΔLSM in each liver fibrosis grade. ΔLSM - the difference between maximal and minimal liver stiffness values of the 3 liver stiffness measurements (LSM).

Table 2 - Clinical data of the patients with different degrees of LS discrepancy.

Clinical characteristics	ΔLSM <2kPa group (n=78)	ΔLSM ≥2kPa group (n=45)	*P-value	Fibrosis stage concordance group (n=90)	Fibrosis stage discordance group (n=33)	†P-value
Male (%)	54 (69.2)	36 (80.0)	0.277	65 (72.2)	25 (75.8)	0.871
Age (year)	34 (17-64)	39 (20-59)	0.024	35 (17-63)	39 (20-64)	0.126
BMI (kg/m^2)	21.4 ± 2.4	22.1 ± 3.0	0.162	21.7 ± 2.7	21.4 ± 2.5	0.598
ALT (IU/L) (n=106)	25 (7-479)	36 (10-116)	0.030	27 (7-139)	33.5 (10-479)	0.097
AST (IU/L) (n=103)	25 (10-151)	30 (16-59)	0.064	25 (10-68)	34 (16-151)	0.039
TB (μmol/L)(n=103)	12.3 (5.2-60.2)	15.2 (6.8-47.7)	0.074	13.0 (5.2-60.2)	14.1 (6.8-52.4)	0.235
DB (μmol/L)(n=95)	3.5 (1.7-15.9)	4.6 (1.8-12.7)	0.033	3.8 (1.7-15.9)	3.6 (2.2-9.6)	0.990
Liver US (n)	64	34		74	24	
Cirrhotic liver (%)	14 (21.9)	20 (58.8)	< 0.001	20 (27.0)	14 (58.3)	0.011

*p-value for the comparison between the ΔLSM<2kPa group and ΔLSM ≥2kPa group, †p-value for the comparison between the fibrosis stage concordance group and fibrosis stage discordance group. ΔLSM - the difference between maximal and minimal liver stiffness values of the 3 liver stiffness measurements, ALT - alanine aminotransferase, AST - aspartate aminotransferase, BMI - body mass index, DB - direct bilirubin, TB - total bilirubin, US - ultrasonography, LS - liver stiffness

Table 3 - Distribution of ΔLSM ≥2kPa and discordance in fibrosis stages in each liver fibrosis stage.

Groups	F0/F1 (n=67)	F2 (n=22)	F3 (n=19)	F4 (n=15)	*P*-value
	n (%)	n (%)	n (%)	n (%)	
ΔLSM <2kPa group	59 (88.1)	15 (68.2)	4 (26.3)	0 (0)	<0.001
ΔLSM ≥2kPa group	8 (11.9)	7 (31.8)	15 (73.7)	15 (100)	
Fibrosis stage concordance group	60 (89.6)	7 (31.8)	12 (63.2)	11 (73.3)	<0.001
Fibrosis stage discordance group	7 (10.5)	15 (68.2)	7 (36.8)	4 (26.7)	

ΔLSM - the difference between maximal and minimal liver stiffness values of the 3 liver stiffness measurements.
The proportion of patients with a ΔLSM ≥2kPa differed between the stages significantly (p<0.001).
The proportion of patients with discordance in fibrosis stages differed between the stages significantly (p<0.001).

fibrosis stage and discordance of fibrosis stages was nonlinear; only AST and the presence of liver cirrhosis demonstrated by US were analyzed in multiple logistic regression, and neither was associated with discordance of fibrosis stages (ß: 0.029; OR: 1.029; 95% CI: 0.998-1.061; p=0.069; and ß: 1.021; OR: 2.775; 95% CI: 0.969-7.944; p=0.057).

Discussion. In this study, we improved the understanding of LS discrepancy caused by sampling variability in HBV infection patients. Patients with a higher fibrosis stage tended to have a larger LS discrepancy. Discordance in fibrosis stages was observed in more than 25% of the patients and was most frequent for the F2 stage.

Liver stiffness discrepancy will prevent the evaluation of liver fibrosis. It has been suggested that the presence of esophageal varices stage 2/3 can be predicted by cut-off values of 27.5 kPa, cirrhosis Child-Pugh B or C 37.5 kPa, hepatocellular carcinoma 53.7 kPa, and esophageal bleeding 62.7 kPa.[8] Consequently, the prediction of complications would be incorrect due to the high LS discrepancy in cirrhotic patients. To date, there has been no optimal cut-off value available to determine fibrosis progression. A cut-off value of 2 kPa was assigned based on the difference between the cut-off values of F2 and F3 in the Castera classification.[6,24] According to our study, the overestimation of fibrosis progression contributed by sampling variability may exist in 36.6% of the patients with ΔLSM ≥2 kPa, and the possibility of overestimation will increase with the degree of fibrosis. Therefore, it is essential to perform LSMs in the same position when monitoring fibrosis. Similar to previous data, the incidence of discordance in fibrosis stages was 20-30% and was the highest in F2 stage.[22] The lower discordance rate for LSM than that for percutaneous liver biopsy (25-35%)[26] may be attributed to the sampling volume in LSM, which is 100 times larger than that for needle biopsy. In contrast to a previous study,[22] the discordance in fibrosis stages of 2 or 3 stages was not observed, and the agreement of the fibrosis stage was moderate to good. One possible explanation is the investigation of patients infected only with HBV and the use of a cut-off system applicable to HBV infection. The hepatic pathology varying with etiology determines the different cut-off system in the categorization of fibrosis stage.[27,28] In previous studies, the patients had miscellaneous chronic liver diseases,

but the cut-off values employed were obtained from hepatitis C virus infection patients.[6,18,20,22] Therefore, the discordance rate may have been overestimated.

Consistent with previous studies,[20,22] BMI had no effect on sampling variability. Alanine transaminase, AST, TB, and DB, which have been suggested as factors that may affect the accuracy of LSM,[11,29-32] were also assessed in this study. In the univariate analysis, older age, male gender, higher serum ALT, AST, and DB level, and presence of liver cirrhosis by US tended to correlate with the LS discrepancy. But, in multiple regression analysis, only liver fibrosis stage diagnosed by TE was found to be significantly and independently correlated with LS discrepancy. It is not surprising that age, male gender, higher serum levels of ALT, AST, and DB, and presence of liver cirrhosis by US were not independently correlated with LS discrepancy, as these factors are all known to be linked to the severity of and the risk of developing fibrosis.

The performance characteristics including SR and IQR/M were reported to relate with accuracy of LSM. In this investigation, we controlled the SR and IQR/M for each measurement to obtain a reliable acquisition.[31] It indicated that improvement of performance failed to prevent the discrepancy of LSMs.

These results confirm that the LS discrepancy may be attributed to histological heterogeneity.[22] Livers with higher stage of fibrosis tend to be more heterogeneous. In addition, the inefficiency in distinguishing significant fibrosis by TE may explain the observation of high levels of discordance in fibrosis stages for the F2 stage. Boursier et al[15] have also shown that the discordance rate for fibrosis stage between observers was the highest in the patients with F2 stage.

Unlike Ingiliz et al[20] and Kim et al,[21] we did not set a fixed anatomic position such as "an anterior position 2-3 cm ahead of the reference position in the same intercostal space" or compare the median stiffness values at different positions. There is interindividual variability with respect to the best sampling position in individuals. Therefore, the best positions guaranteeing reliable measurement were chosen by an experienced operator in this study. In addition, the stiffness values were first compared at the individual level to calculate the range of LS discrepancy in the population.

This study reported the incidence and exact values of LS discrepancy owing to the sampling location in HBV infection and in subgroups of patients with different fibrosis stages. We also assessed the impact of clinical data on LS discrepancy.

Study limitations. We failed to perform liver biopsy in the patients and assessed the liver fibrosis by the gold standard. This may lead to incorrect liver fibrosis staging. As a result, further study using liver biopsy is needed to illustrate the exact correlation of LS discrepancy and fibrosis stage. The fibrosis stages were determined by LS instead of histology in this study. However, the patients enrolled had a median fibrosis stage equal to minimal and/or maximal fibrosis stage, indicating that it was reliable to define the median fibrosis stage as the fibrosis stage for the patient. Another limitation is the homogeneity of ALT, AST, TB, DB, and BMI in the patients, which might give a bias to conclude the influence of these factors on LS discrepancy. All the subjects recruited were outpatients, and had mild to moderate hepatitis. Hence, the serum ALT, AST, TB, and DB levels were generally low. Further research should specifically examine the effect of high levels of serum ALT, AST, TB, and DB on the LS discrepancy. The BMI was reported to lead the inaccuracy and even failure of LSM.[11,18] Some patients with high BMI were not included in the analysis, as we failed to perform 3 successful LSMs for them with an M probe (M probe is for the patients with a thoracic perimeter >75 cm and a skin-to-capsule distance <2.5cm). An XL probe (XL probe is for the patients >18 years and with a skin-to-capsule distance >2.5cm) has been available recently to perform LSM in obesity patients, and this probe can be used to assess the influence of high BMI on LS discrepancy in the future.

In conclusion, LSM is a useful noninvasive tool in the diagnosis of fibrosis in HBV infection when using the correct cut-off value system. The LS discrepancy due to sampling variability should be considered in the interpretation of results and when monitoring fibrosis progression.

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