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Der Nutzen der neuen Scherwellen-Elastografie für die nichtinvasive Beurteilung der Leberfibrose bei Patienten mit chronischer Hepatitis B: Eine prospektive multizentrische Studie

Authors

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Key words

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ABSTRACT

Purpose To explore the usefulness of liver stiffness measurements (LSMs) by sound touch elastography (STE) and sound touch quantification (STQ) in chronic hepatitis B (CHB) patients for staging fibrosis.

Methods This prospective multicenter study recruited normal volunteers and CHB patients between May 2018 and October 2019. The volunteers underwent LSM by STE and supersonic shear imaging (SSI) or by STQ and acoustic radiation force impulse imaging (ARFI). CHB patients underwent liver biopsy and LSM by both STE/STQ. The areas under the receiver operating characteristic curves (AUCs) for staging fibrosis were calculated.

Results Overall, 97 volunteers and 524 CHB patients were finally eligible for the study. The successful STE and STQ measurement rates were both 100 % in volunteers and 99.4 % in CHB patients. The intraclass correlation coefficients (ICCs) for the intra-observer stability of STE and STQ (0.94; 0.90) were similar to those of SSI and ARFI (0.95; 0.87), respectively. STE and STQ showed better accuracy than the aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) (AUC: 0.87 vs 0.86 vs 0.73 vs 0.77) in staging cirrhosis. However, both STE and STQ were not superior to APRI and FIB-4 in staging significant fibrosis (AUC: 0.76 vs 0.73 vs 0.70 vs 0.71, all P-values > 0.05).

Conclusion STE and STQ are convenient techniques with a reliable LSM value. They have a similar diagnostic performance and are superior to serum biomarkers in staging cirrhosis in CHB patients.

ZUSAMMENFASSUNG

Ziel Untersuchung des Nutzens von Lebersteifigkeitsmessungen (LSMs) mittels Sound-Touch-Elastografie (STE) und Sound-Touch-Quantifizierung (STQ) für das Fibrosestaging von Patienten mit chronischer Hepatitis B (CHB).

Methoden In diese prospektive multizentrische Studie an 26 Zentren wurden normale Freiwillige und CHB-Patienten zwischen Mai 2018 und Oktober 2019 eingeschlossen. Die Normalprobanden unterzogen sich einer LSM mittels STE und Supersonic Shear Imaging (SSI) oder mittels STQ und Acoustic Radiation Force Impulse Imaging (ARFI). Bei den CHB-Patienten wurden eine Leberbiopsie und eine LSM sowohl mit STE als auch STQ durchgeführt. Die Flächen unter den Receiver Operating Characteristic Curves (AUCs) wurden für das Fibrosestaging berechnet.

Ergebnisse An dieser Studie nahmen 97 Freiwillige und 524 CHB-Patienten teil. Die Quoten der erfolgreichen STE- und STQ-Messungen betrugen jeweils 100 % bei den Normalprobanden und 99,4 % bei den CHB-Patienten. Die Intraklasse-Korrelationskoeffizienten (ICCs) für die Intraobserver-Stabilität von STE und STQ (0,94; 0,90) waren ähnlich denen von SSI und ARFI (0,95; 0,87). STE und STQ zeigten eine bessere Genauigkeit als der APRI-Test („aspartate aminotransferase to platelet ratio index“) und der Fibosis-4-Index (FIB-4) (AUC: 0,87 vs. 0,86 vs. 0,73 vs. 0,77) beim Staging der Zirrhose. Allerdings waren sowohl STE als auch STQ dem APRI-Test und dem FIB-4 beim Staging einer höhergradigen Fibrose nicht überlegen (AUC: 0,76 vs. 0,73 vs. 0,70 vs. 0,71; alle p-Werte > 0,05).

Schlussfolgerung STE und STQ sind praktische Techniken mit verlässlichem LSM-Wert; sie haben eine ähnliche diagnostische Leistung und sind den Serum-Biomarkern beim Staging der Zirrhose bei CHB-Patienten überlegen.

Introduction

Chronic hepatitis B (CHB) infection remains a major health problem among the Chinese population [1, 2]. The progression and prognosis of CHB is strongly associated with the presence of liver fibrosis [3]. Although liver biopsy retains the traditional reference method for assessing liver fibrosis, noninvasive methods for evaluating fibrosis progression have been widely accepted [2–4]. Currently, liver stiffness measurement (LSM) by elastography is recommended as a first-line noninvasive method for assessing liver fibrosis in patients with CHB [4, 5].

Clinically available elastography techniques for obtaining LSMs include transient elastography, point shear wave elastography (p-SWE) and two-dimensional shear wave elastography (2D SWE) [6]. Both p-SWE and 2 D SWE are common US-based elastography techniques with a higher success rate than transient elastography

in patients with obesity and ascites [7]. With the increased application of elastography techniques, there has been an increasing number of US systems with their own elastography techniques in recent years. However, as the shear wave speed obtained with different systems is different [5], the normal range as well as the cut-off values for staging liver fibrosis should be system-specific.

Sound touch elastography (STE) and sound touch quantification (STQ) are recently developed US elastography techniques (Mindray Resona 7, Shenzhen, China) and are based on the technical principles of 2 D SWE and p-SWE, respectively. Both STE and STQ are available in one US machine system, offering multiple choices for users to perform LSM. However, no research has yet provided the recommended cut-off LSM values by STE and STQ for staging liver fibrosis in patients with CHB. Moreover, little information is available about the comparison of the accuracy of LSM by 2 D SWE and p-SWE in staging liver fibrosis.

Therefore, we aimed to determine the cut-off values and compare the accuracy of LSM by STE and STQ for assessing liver fibrosis in patients with CHB.

Materials and methods

Study design

This prospective multicenter study included two groups of participants: healthy volunteers and participants with CHB between May 2018 and October 2019. The healthy volunteers were randomly allocated into two subgroups for the comparison of intra-observer stability of STE vs. supersonic shear imaging (SSI) or STQ vs. acoustic radiation force impulse imaging (ARFI). The intraclass correlation coefficient (ICC) analysis was performed in the Third Affiliated Hospital of Sun Yat-sen University and the Third Hospital of Longgang.

The study initially involved 29 institutions from China (ClinicalTrials.gov identifier: NCT 03530657). Three centers with qualified cases less than 60 % and with total cases less than 5 were excluded from analysis, leaving the data of 26 centers for final analysis. The study was approved by the institutional ethics review board of each institution. Written informed consent was obtained from all participants.

Participants

The healthy volunteers were all over 18 years old and without liver disease based on the evidence of ultrasound findings and serological tests.

The inclusion criteria for participants with CHB were as follows: (a) subject positive for the hepatitis B surface antigen ≥ 6 months; (b) underwent LSM within a week from liver biopsy. The exclusion criteria were as follows: (a) coinfected with other liver diseases or human immunodeficiency virus; (b) age ≤ 18 years old; (c) previous history of liver transplantation; (d) previous history of antiviral therapy; (e) unqualified liver biopsy samples: biopsy samples less than 15 mm long or with fewer than six portal tracts; and (f) a maximum tumor diameter ≥ 5 cm or tumors located in the right lobe of the liver that might affect LSM acquisition.

Liver stiffness measurements

Ultrasonic equipment

LSM by STE and STQ was performed on Mindray Resona 7 ultrasound systems (Mindray, Shenzhen, China) with SC6–1U (frequency of 1.2–6.0 MHz) convex probes. LSM by SSI was performed using Aixplorer US systems (Supersonic Shear Imaging, Aix-en-Provence, France), and LSM by ARFI was conducted on Acuson S2000 (Siemens Medical Solutions, Erlangen, Germany) imaging systems.

Operators

For the healthy volunteers, one sonographer (M.W. with 1 year of US elastography experience) performed LSM using STE, STQ, SSI, and ARFI. For participants with CHB, the investigators of each center (all have performed at least 50 liver elastography examinations) performed LSM.

All operators were blinded to the clinical and serological data of the enrolled participants.

LSM by SSI and ARFI

All participants fasted for at least 4 hours before undergoing LSM and were examined in the supine position. The details of the examination methods of LSM by SSI and ARFI were in accordance with the updated guidelines on liver elastography [8–10]. In each subject, a total of five valid measurements were taken with SSI and ARFI, respectively. The corresponding median and interquartile range (IQR)/median values were calculated.

LSM by STE and STQ

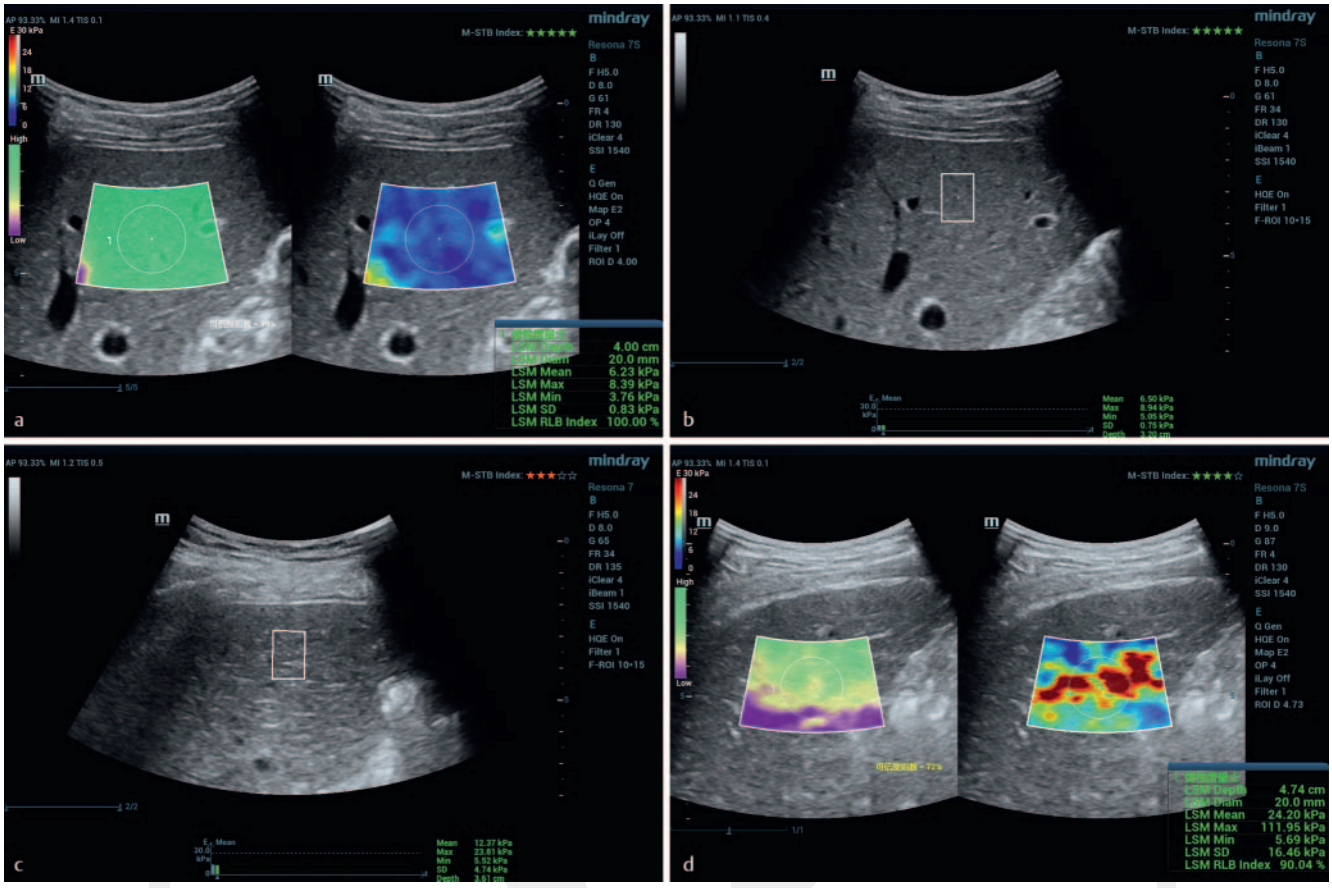
The elasticity image box of STE was approximately 4 × 3 cm, and the STQ elastic box was fixed at 1.5 × 1.0 cm (▶ **Fig. 1a, b**). The circular region of interest of the STE elastic box was 2 cm in diameter. Both elastic boxes of STE and STQ were placed in an area of the liver parenchyma free of large vessels 1–2 cm under Glisson's capsule of the right lobe of the liver using high-quality mode. The elastic box should be at least 2 cm away from the margin of liver tumors. In each subject, a total of five valid measurements were taken with STE and STQ, respectively. The corresponding median and IQR/median values were calculated.

Stability and quality judgement of LSM by STE and STQ

Each STE and STQ image was displayed with an automatic motion stability index (▶ **Fig. 1c**). The motion stability index ranged from 1 star to 5 stars, with stars ≥ 4 considered acceptable according to the manufacturer's instructions. For each STE measurement, the reliability index should be greater than or equal to 90 % (▶ **Fig. 1 d**), or it would be considered an invalid measurement.

Quality control of the multicenter study

Systematic and standardized training was implemented at the beginning of our study. All investigators received training to obtain LSMs using STE/STQ with a standardized procedure.



▶ **Fig. 1** Liver stiffness measurements obtained by sound touch elastography (STE) **a** and sound touch quantification (STQ) techniques **b** in a 35-year-old participant with chronic hepatitis B. Example of unqualified image of liver stiffness measurement obtained by STQ with an automatic motion stability index < 4 stars **c** and unqualified image of liver stiffness measurement obtained by STE with reliability index < 90 % **d**.

A case was defined as unreliable if the interquartile range/median was > 30 % or success rates ≤ 60 %. The median LSM value (in kilopascals) was regarded as the representative value.

Clinical and laboratory data

The epidemiological data of the participants were recorded, and blood samples were obtained within one week of LSM. Serological markers of liver fibrosis included the aspartate aminotransferase-to-platelet ratio index (APRI) [10] and fibrosis-4 index (FIB-4) [11].

Liver histological assessment

US-guided percutaneous liver biopsy was performed using a 16-gauge or 18-gauge biopsy needle (Bard Magnum; Covington, Ga). Staging of chronic viral hepatitis was assessed according to the METAVIR scoring system [12] as follows: F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis and few septa; F3: numerous septa without cirrhosis; and F4: cirrhosis. Necro-inflammatory activity was graded as follows: A0: none; A1: mild; A2: moderate; and A3: severe.

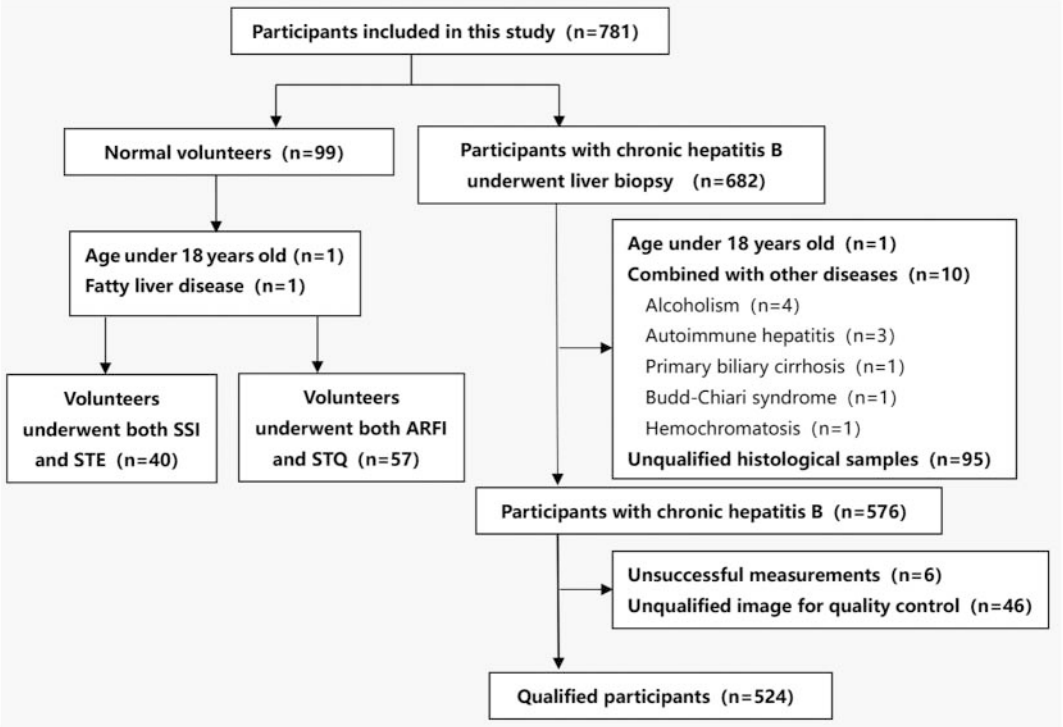
For quality control, all liver specimens were assessed by two experienced liver pathologists (both with more than 10 years of experience) separately. The pathologists were blinded to the LSM and clinical data of the enrolled participants.

Statistical analysis

Statistical analyses were performed by using SPSS software (version 21.0; SPSS, Chicago, Ill) and PASS software (PASS 2008; NSCC Statistical Software, Kaysville, Utah).

Post hoc power analysis was conducted to determine the sample size. The largest sample size of participants with CHB was determined for staging significant fibrosis or worse (≥ F2). A minimum of 408 participants is needed for a confidence of 0.950 (sensitivity of 0.86 and specificity of 0.87) [8].

Quantitative data were described as mean, SD and compared by Student's t-test if data followed normal distribution. For non-normal distribution, data were described as median, IQR and compared by non-parametric tests. Correlations between LSMs and correlated factors were assessed with the Spearman correlation test. The ICC was calculated to evaluate the intra-observer reliability of the different elastography methods. The diagnostic accuracy of different parameters for assessing liver fibrosis was evaluated by the areas under the receiver operating characteristic curves (AUCs) and their 95 % confidence intervals (CIs). To limit the bias of the prevalence spectrum, standardization of AUCs for diagnostic evaluation of the LSM was assess based the difference between the mean fibrosis stage of advanced fibrosis and the mean fibrosis stage of the nonadvanced fibrosis (DANA) score [13]. Compari-



▶ **Fig. 2** Flowchart of study participants. SSI: supersonic shear imaging; STE: sound touch elastography; ARFI: acoustic radiation force impulse imaging; STQ: sound touch quantification.

sons of AUCs were evaluated by the DeLong test. The optimal cut-off value was generated by the Youden index. A P-value of < 0.05 indicated significance.

Results

Baseline characteristics

A total of 781 participants (99 healthy volunteers and 682 patients with CHB) were initially recruited. The successful STE and STQ measurement rates were both 100.0 % (99/99) in healthy volunteers and 99.4 % (678/682) in patients with CHB. The reasons for technical failures included the inability to hold breath (n = 3), liver atrophy (n = 2), and obesity (n = 1).

▶ **Fig. 2** shows the flowchart of the study population and 621 participants were eligible for the study, with 97 healthy volunteers [mean age, 38.0 ± 11.8 years; sex ratio (male/female), 28/69] and 524 patients with CHB [mean age, 38.9 ± 10.9 years; sex ratio (male/female), 363/161]. In 524 patients with CHB, there were 15 unreliable STE results and 13 unreliable STQ results, leaving 509 STE measurements and 511 STQ measurements available for analysis.

The baseline characteristics of the participants are shown in ▶ **Table 1**. LSMs by STE and STQ both had a moderate to high association with liver fibrosis stage ($r = 0.62$, $P < 0.001$ and $r = 0.57$, $P < 0.001$, respectively) and inflammation activity grade ($r = 0.57$, $P < 0.001$ and $r = 0.59$, $P < 0.001$, respectively), but showed no statistical correlation with steatosis grade ($r = 0.07$, $P = 0.12$ and $r = -0.08$, $P = 0.08$, respectively).

Intra-observer stability of LSMs by STE and STQ vs. SSI and ARFI

For the healthy volunteers, reliable LSMs were all obtained successfully. ▶ **Table 2** shows the comparison of the intra-observer stability of LSMs using different techniques. For the 40 volunteers with LSMs obtained by both SSI and STE, the intra-observer agreement of STE (ICC, 0.94; 95 % CI: 0.91, 0.97) was comparable to that of SSI (ICC, 0.95; 95 % CI: 0.92, 0.97; $P = 0.81$). For the 57 volunteers with LSMs obtained with both ARFI and STQ, STQ (ICC, 0.90; 95 % CI: 0.85, 0.93) showed a similar intra-observer stability of LSMs to ARFI (ICC, 0.87; 95 % CI: 0.81, 0.92; $P = 0.58$).

LSMs in healthy volunteers and patients with CHB

The values of the LSMs in healthy volunteers and patients with CHB are shown in ▶ **Table 3**.

For healthy volunteers, the median LSM value by STE (5.8 kPa, interquartile range: 5.3 kPa, 6.4 kPa) was significantly higher than that of LSMs by SSI ($P = 0.003$) (▶ **Supplementary Fig. 1a**), and also the median LSM value by STQ (5.8 kPa, interquartile range: 5.0 kPa, 6.4 kPa) was significantly higher than that of LSMs by ARFI ($P < 0.001$) (▶ **Supplementary Fig. 1b**).

For patients with CHB, the LSMs by STE and STQ ranged from 4.0 kPa to 40.3 kPa and 4.4 kPa to 48.5 kPa, respectively. As the fibrosis stage increased, the median LSM value by STE and STQ of the corresponding fibrosis stage generally increased. Patients in

▶ **Table 1** Summary of baseline patient characteristics.

variable	normal volunteers	participants with CHB	P-value
age, years*	34.6 ± 11.8	38.9 ± 10.9	0.001
gender, male (%)‡	51 (52.6)	363 (69.3)	0.002
body mass index, kg/m²*	22.1 ± 3.4	23.4 ± 8.9	0.18
aspartate aminotransferase, U/L†	21.0 (17.0–31.5)	32.0 (23.0–55.0)	0.59
alanine aminotransferase, U/L†	20.0 (14.0–30.0)	40.0 (25.0–77.8)	0.001
total bilirubin, μmol/L†	12.7 (9.1–14.7)	12.9 (9.6–19.0)	0.12
platelet count, 10^9/L†	236.0 (224.5–251.0)	193.5 (149.5–236.8)	< 0.001
APRI†	0.24 (0.18–0.33)	0.45 (0.27–0.81)	0.09
FIB-4†	0.65 (0.52–1.1)	1.0 (0.69–1.6)	0.55
METAVIR fibrosis stage, n (%)‡			
F0–1	NA	135 (25.8)	NA
F2	NA	195 (37.2)	NA
F3	NA	114 (21.7)	NA
F4	NA	80 (15.3)	NA
METAVIR activity grade, n (%)‡			
A0	NA	62 (11.8)	NA
A1	NA	287 (54.8)	NA
A2	NA	109 (20.8)	NA
A3	NA	66 (12.6)	NA
steatosis grade, n (%)‡			
absent (< 5 %)	NA	384 (73.3)	NA
present (≥ 5 %)	NA	140 (26.7)	NA
▪ significant (≥ 10 %)	NA	67 (12.8)	NA
▪ moderate-severe (≥ 20 %)	NA	41 (7.8)	NA
▪ severe (≥ 30 %)	NA	26 (5.0)	NA

CHB: chronic hepatitis B; NA: not applicable; APRI: aspartate aminotransferase–to-platelet ratio index; FIB-4: fibrosis-4 index.
* Data are expressed as the mean ± standard deviation.
‡ Data in parentheses are percentages.
† Data are the median, with the interquartile range in parentheses.

▶ **Table 2** Comparison of intra-observer stability for liver stiffness measurement using different elastography techniques.

variable	ICC (95 % CI)	P-value
two-dimensional shear-wave elastography		0.81
▪ LSM by STE (n = 40)	0.94 (0.91, 0.97)	
▪ LSM by SSI (n = 40)	0.95 (0.92, 0.97)	
point shear wave elastography		0.58
▪ LSM by STQ (n = 57)	0.90 (0.85, 0.93)	
▪ LSM by ARFI (n = 57)	0.87 (0.81, 0.92)	

Detection durations are expressed as the mean ± standard deviation. ICC: intraclass correlation coefficient; CI: confidence interval; LSM: liver stiffness measurement; SSI: supersonic shear imaging; STE: sound touch elastography; ARFI: acoustic radiation force impulse imaging; STQ: sound touch quantification.

▶ **Table 3** Values of liver stiffness measurements by different elastography techniques in normal volunteers and patients with hepatitis B at different fibrosis stages.

liver stiffness measurement (kPa)	STE	STQ	SSI	ARFI
normal volunteers				
median value	5.8	5.8	5.1	3
interquartile range	(5.3, 6.4)	(5.0, 6.4)	(4.7, 5.4)	(2.8, 3.4)
participants with hepatitis B				
F0-F1				
median value	6.8	7.2	NA	NA
interquartile range	(6.1, 7.8)	(6.4, 8.5)	NA	NA
F2				
median value	7.6	7.8	NA	NA
interquartile range	(6.5, 9.1)	(6.7, 9.6)	NA	NA
F3				
median value	10.7	10.9	NA	NA
interquartile range	(8.7, 14.1)	(9.1, 15.1)	NA	NA
F4				
median value	13.6	15.7	NA	NA
interquartile range	(10.8, 20.0)	(12.0, 22.5)	NA	NA

NA: not applicable; SSI: supersonic shear imaging; STE: sound touch elastography; ARFI: acoustic radiation force impulse imaging; STQ: sound touch quantification.

each fibrosis stage had significantly higher median LSM values by both STE and STQ than those with a lower fibrosis stage (▶ **Fig. 3a, b**).

Diagnostic performance of STE/STQ in the prediction of significant fibrosis and cirrhosis in comparison with serum biomarkers

▶ **Table 4** presents the diagnostic accuracies of different parameters for staging significant fibrosis and cirrhosis. The optimal cut-off LSM values for predicting significant fibrosis (F ≥ 2) and cirrhosis (F = 4) were 8.35 and 10.34 kPa for STE and 8.54 and 11.70 kPa for STQ, respectively. LSMs by STE (AUC: 0.87; 95 % CI: 0.84, 0.90) and STQ (AUC: 0.86; 95 % CI: 0.83, 0.89) both showed higher performance in the evaluation of cirrhosis (F = 4) than APRI (AUC: 0.73; 95 % CI: 0.69, 0.77) and FIB-4 (AUC: 0.77; 95 % CI: 0.73, 0.81) (STE vs. APRI, P < 0.001; STE vs. FIB-4, P < 0.001; STQ vs. APRI, P < 0.001; STQ vs. FIB-4, P < 0.001) (▶ **Fig. 4a**). However, in differentiating significant fibrosis (F ≥ 2) in patients with CHB, the performance of LSMs by STE and STQ was slightly higher than that of APRI and FIB-4 but without significant difference (STE vs. APRI, P = 0.07; STE vs. FIB-4, P = 0.08; STQ vs. APRI, P = 0.12; STQ vs. FIB-4, P = 0.13) (▶ **Fig. 4b**). There were no significant differences between the AUCs of STE and STQ for the differentiation of significant fibrosis (P = 0.07) and cirrhosis (P = 0.06). After including 46 patients with an unqualified image for quality control for analysis using intention to diagnose approach, the results did not change at all (▶ **Supplementary Table 1**).

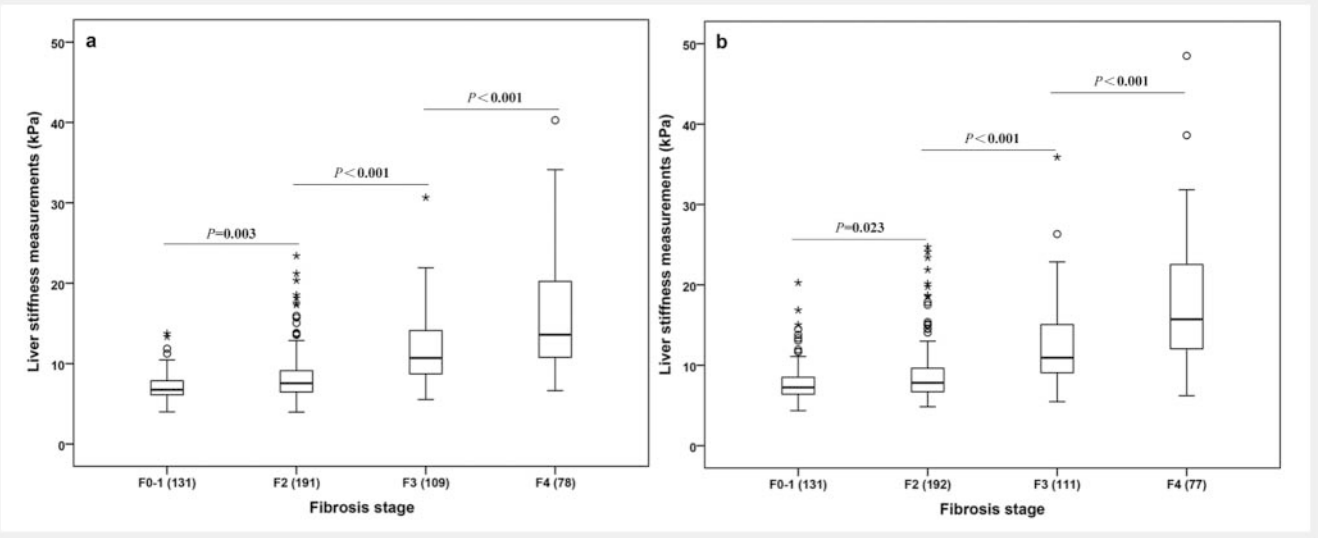
The adjusted AUCs of STE/STQ in staging fibrosis using the DANA methods

By using the DANA methods, the adjusted AUC of LSMs by STE, STQ, APRI, and FIB-4 were 0.86, 0.83, 0.80, and 0.81 for detecting significant fibrosis (F ≥ 2), and were 0.92, 0.92, 0.79, and 0.83 for detecting cirrhosis (F = 4), respectively (▶ **Supplementary Table 2**, ▶ **Supplementary Fig. 2**).

Discussion

This prospective multicenter study used histopathology as the gold standard and analyzed the diagnostic accuracy of STE/STQ for the evaluation of liver fibrosis. In the study, we established a normal range as well as an optimal cut-off value for LSMs by STE and STQ for staging fibrosis in patients with CHB. LSMs obtained by STE and STQ provided similar diagnostic performance in staging liver fibrosis, with better diagnostic value than serum biomarkers. Moreover, our data demonstrated that STE and STQ yield many advantages with similarly high intra-observer stabilities compared with SSI and ARFI.

These new elastography systems have comparable success rates and intra-observer reproducibility compared to other elastographic modes at least in healthy subjects, while patients have not been tested [14–17]. STE/STQ are not truly innovative methods overall but are new in Mindray equipment which concurrently provides both STE and STQ in one US system, offering multiple



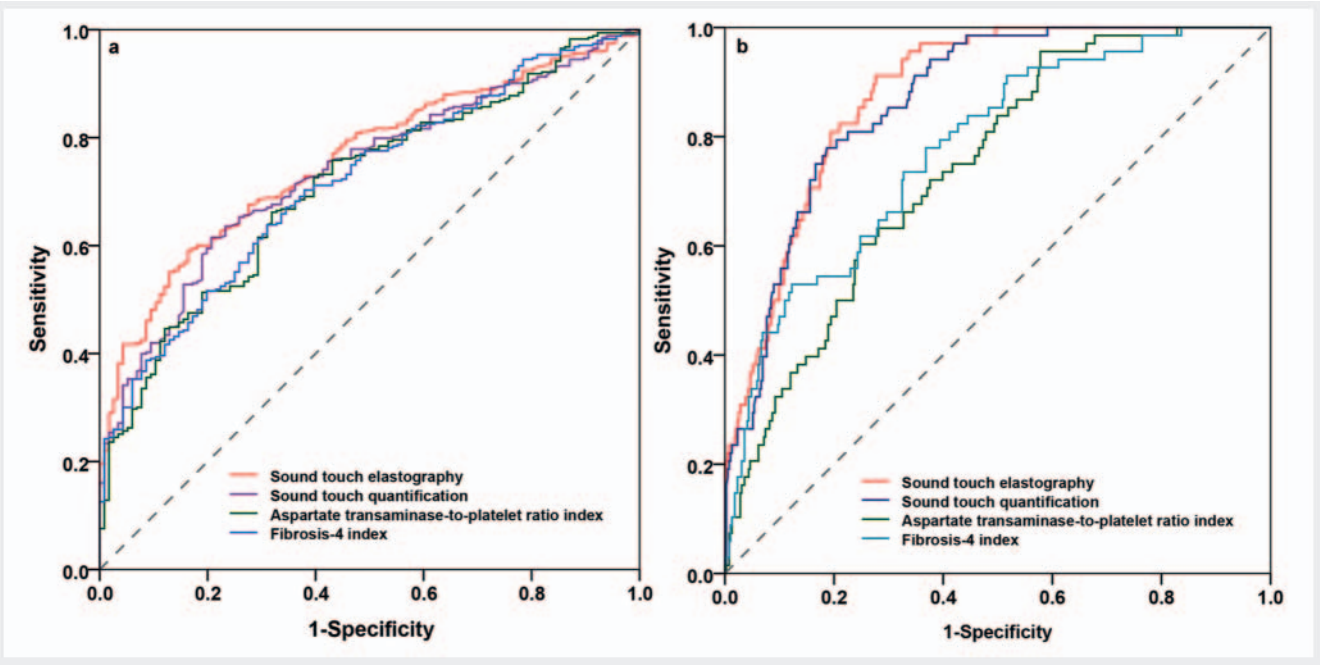
▶ **Fig. 3** Box plots of liver stiffness measurements obtained by sound touch elastography **a** and sound touch quantification **b** for different fibrosis stages in participants with chronic hepatitis B. The central box represents the interquartile range. The line through each box represents the median value of liver stiffness measurements. Error bars show minimum and maximum non-extreme values, and P-values were liver stiffness measurements compared with a different fibrosis stage. 0: outside values; : outliers.

▶ **Table 4** Diagnostic performance of LSM by STE/STQ and serum biomarkers (APRI and FIB-4) in the prediction of significant fibrosis (F ≥ 2) and cirrhosis (F = 4).

	N (%)	AUC	cutoffs	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)	LR+	LR–
significant fibrosis (≥ F2)									
STE	513 (97.2)	0.76 (0.72, 0. 80)	8.35 kPa	60.5 (55.4, 65.4)	84.0 (76.5, 89.8)	91.7 (87.5, 94.8)	42.1 (36.1, 48.4)	3.8 (3.4, 4.2)	0.5 (0.3, 0.7)
STQ	511 (96.8)	0.73 (0.69, 0.77)	8.54 kPa	62.6 (57.6, 67.5)	77.1 (68.9, 84.0)	88.8 (84.4, 92.3)	41.6 (35.3, 48.0)	2.7 (2.4, 3.1)	0.5 (0.3, 0.7)
APRI	495 (93.8)	0.70 (0.66, 0.74)	0.37	65.6 (60.5, 70.4)	66.7 (57.7, 74.8)	85.2 (80.5, 89.1)	39.8 (33.1, 46.8)	2.0 (1.7, 2.3)	0.5 (0.4, 0.7)
FIB-4	490 (92.8)	0.71 (0.67, 0.75)	0.92	63.7 (58.5, 68.6)	68.6 (59.6, 76.6)	85.7 (80.9, 89.6)	39.0 (32.5, 45.8)	2.0 (1.8, 2.3)	0.5 (0.4, 0.7)
cirrhosis (F = 4)									
STE	513 (97.2)	0.87 (0.84, 0.90)	10.34 kPa	81.3 (71.0, 89.1)	79.1 (75.0, 82.8)	41.4 (33.6, 49.5)	95.9 (93.3, 97.7)	3.9 (3.5, 4.4)	0.2 (0.1, 0.4)
STQ	511 (96.8)	0.86 (0.83, 0.89)	11.70 kPa	77.9 (67.0, 86.6)	80.7 (76.6, 84.3)	41.7 (33.5, 50.2)	95.4 (92.7, 97.3)	4.0 (3.5, 4.6)	0.3 (0.2, 0.4)
APRI	495 (93.8)	0.73 (0.69, 0.77)	0.33	94.6 (86.7, 98.5)	42.0 (37.3, 46.9)	22.3 (17.8, 27.3)	97.8 (94.4, 99.4)	1.6 (1.4, 1.8)	0.1 (0.05, 0.3)
FIB-4	490 (92.8)	0.77 (0.73, 0.81)	1.12	76.7 (65.4, 85.8)	62.8 (58.0, 67.5)	26.5 (20.7, 33.0)	93.9 (90.4, 96.4)	2.1 (1.8, 2.4)	0.4 (0.2, 0.6)

Data are expressed as value with 95 % confidence interval in parentheses. LSM: liver stiffness measurement; STE: sound touch elastography; STQ: sound touch quantification; APRI: aspartate transaminase-to-platelet ratio index; FIB-4: fibrosis-4 index; AUC: areas under the receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

choices for users to perform ultrasound elastography in different situations. Although LSM by STE had better accuracy in staging fibrosis compared to STQ, LSM by STQ might have higher success rates with a smaller elastic detection box in some cirrhotic patients with severe right liver atrophy. Similarly, spleen stiffness measurement by STQ could have higher success rates in patients with smaller spleens.



▶ **Fig. 4** Areas under the receiver operating characteristic curves (AUCs) of sound touch elastography, sound touch quantification, the aspartate aminotransferase-to-platelet ratio index and the fibrosis-4 index for predicting significant fibrosis **a** and cirrhosis **b** in participants with chronic hepatitis B.

Regarding the staging of liver fibrosis in patients with CHB, LSMs by STE showed a higher diagnostic accuracy in the staging of both cirrhosis (AUC: 0.87 vs. 0.86) and significant fibrosis (AUC: 0.76 vs. 0.73) compared to that by STQ. However, there were no significant differences in the AUCs between these two methods in the staging of cirrhosis (P = 0.07) and significant fibrosis (P = 0.06). The diagnostic performance of LSMs by STE and STQ was significantly higher than that of serum biomarkers in the staging of cirrhosis but was not superior to that of serum biomarkers in the staging od significant fibrosis.

Previous studies have shown that sonographic elastography techniques are more accurate at diagnosing cirrhosis than noninvasive serum tests, which is in agreement with our findings [17, 18]. In contrast, in the staging of significant fibrosis, our data showed that sonographic elastography techniques were not superior to serological noninvasive markers. On the one hand, a substantial overlap of liver stiffness values was observed between adjacent fibrosis stages, especially in patients with lower fibrosis stages, which could be a result of the extreme LSM values among patients with severe necro-inflammatory activity. In our data, most of the extreme LSM values were from patients with significantly elevated alanine aminotransferase level. As mentioned in the clinical guidelines [2, 5, 7], patients with severe liver inflammation are likely to cause overestimation of liver fibrosis and therefore LSMs should be interpreted with caution among patients with severe necro-inflammatory activity. On the other hand, as with previous reports, elastography techniques are more accurate at detecting cirrhosis (AUCs ranging from 0.80 to 0.99 for transient elastography, 0.75 to 0.97 for p-SWE and 0.88 to 0.98 for 2 D SWE) than significant fibrosis (AUCs ranging from 0.65 to 0.97 for transient elastography, 0.73 to 0.93 for p-SWE and 0.78 to 0.94 for 2 D SWE) [19–22]. Although the performance of LSM by both STE and STQ is relatively lower in patients with lower fibrosis stages in our study, the detection of cirrhosis has greater clinical significance, as patients with cirrhosis are at higher risk of hepatocellular carcinoma and liver-related events.

Our study has several limitations. First, it included a small proportion of patients with hepatocellular carcinoma (n = 22), which might affect LSM results. However, our study only included participants who were diagnosed as untreated small hepatocellular carcinoma with Child-Pugh class A liver function. Moreover, our study followed a very strict procedure protocol to eliminate the influence of liver tumors on LSM results. Second, the results of our study were limited to patients with untreated CHB. Therefore, the findings cannot be applied to patients with antiviral therapy or other liver diseases. Further studies are required to explore the diagnostic accuracy of STE and STQ in CHB patients on antiviral treatment.

In summary, this prospective multicenter study confirmed that STE and STQ are reliable LSM detection methods. The diagnostic value of STE/STQ in the detection of cirrhosis is superior to that of serological liver fibrosis tests. STE/STQ can be used as a valuable noninvasive tool to exclude significant fibrosis and detect cirrhosis in patients with untreated CHB.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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