ORIGINAL RESEARCH

Liver and Spleen Stiffness Measurements by Sound Touch Elastography and Sound Touch Quantification

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Objective: To evaluate the technical success rate and reproducibility of sound touch elastography (STE) and sound touch quantification (STQ) in liver and spleen stiffness measurement and the reference ranges of normal liver and spleen stiffness. We also compared with a previous validated acoustic radiation force impulse (ARFI) technique.

Methods: Two hundred and fifty-three healthy adults and 40 chronic hepatitis B patients were recruited. All patients underwent liver and spleen stiffness measurements using STE, STQ, and ARFI. A hundred and five patients (36 patients with chronic hepatitis and 69 healthy adults) were examined twice, by two trained sonographers who are familiar with STE and STQ techniques independently. Another 36 healthy adults were examined twice by ARFI imaging. The technical success rates and reproducibility were evaluated.

Results: The success rates of STE, STQ, and ARFI were 96.5%, 95.1%, and 94.8% in liver, and 87.5%, 84.0%, and 78.0% in spleen, respectively. The inter-observer reproducibility of STE, STQ and ARFI were 0.914, 0.896, and 0.845 in liver, and 0.629, 0.601, and 0.543 in spleen, respectively. When the thickness of spleen was greater than 30mm, the reproducibility was 0.704 in STE and 0.668 in STQ. The normal ranges of liver stiffness were 5.80-6.04 kPa measured by STE and 5.87-6.13 kPa measured by STQ, and normal spleen stiffness ranged from 14.83-15.54 kPa measured by STE and 15.85-16.62 kPa measured by STQ.

Conclusion: Our study showed STE and STQ in liver and spleen stiffness measurement had a high success rate with good reproducibility, which were comparable to ARFI. The inter-observer reproducibility of spleen was barely satisfactory, but was good when the thickness of spleen was greater than 30mm.

Key Words: Liver stiffness; Spleen stiffness; Sound touch elastography; Sound touch quantification; Elasticity imaging techniques

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Chronic liver disease (CLD) due to hepatitis B or C virus infection affects an estimated 280 million cases worldwide [1,2] and kills 1.75 million people every year. Shear wave elastography is recommended for assessing the degree of fibrosis in CLD [4,5]. However, there are various shear wave

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elastography techniques, and each technique has its own reference range and diagnostic threshold.

The portal hypertension associated with CLD directly leads to splenomegaly. Recently, spleen stiffness measurement has provided promising results for assessing the presence of portal hypertension in CLD. However, the detection method, feasibility, normal reference range, and diagnostic threshold are still not clear yet, and need to be further studied.

Sound touch elastography (STE) and sound touch quantification (STQ) are recent techniques based on the generation of shear wave. STE is based on two-dimensional shear wave elastography (2D-SWE) and STQ is based on point shear wave elastography (pSWE). There are two advantages of STE and STQ. First, both techniques can be placed on the same device. Second, it has better penetration depth. To date, few studies have validated STE and STQ in liver stiffness measurement, and no study in spleen stiffness measurement.

The aims of this study were: (1) to evaluate the technical success rate and the reproducibility of STE and STQ in liver and spleen stiffness measurement and to compare with a previous validated acoustic radiation force impulse (ARFI) technique; (2) to explore the reference ranges of STE and STQ in normal liver and spleen measurements.

Materials and Methods

Patient enrollment

From January 2018 to April 2019, consecutive volunteers at our hospital were prospectively recruited, including 253 healthy adults (healthy group) and 40 patients with chronic hepatitis B (chronic hepatitis group). The inclusion criteria of our study were: age older than or equal to 18 years, the most recent liver function test was within 3 months, and the volunteers from the healthy group must have normal B-mode images. The exclusion criteria were: (a) a previous history of hepatobiliary surgery; (b) malignancies; (c) a previous history of liver transplantation; (d) a previous history with splenectomy; (e) pregnant women. Six patients were not included in our analysis due to the following reasons: hepatocellular carcinoma (n = 1), age younger than 18 (n = 3), and withdrawal of consent (n = 2). All included patients and people from the healthy group underwent liver and spleen stiffness measurements using STE (Mindray, China), STQ (Mindray, China), and ARFI (Siemens, Germany) imaging. The details were summarized in Figure 1.

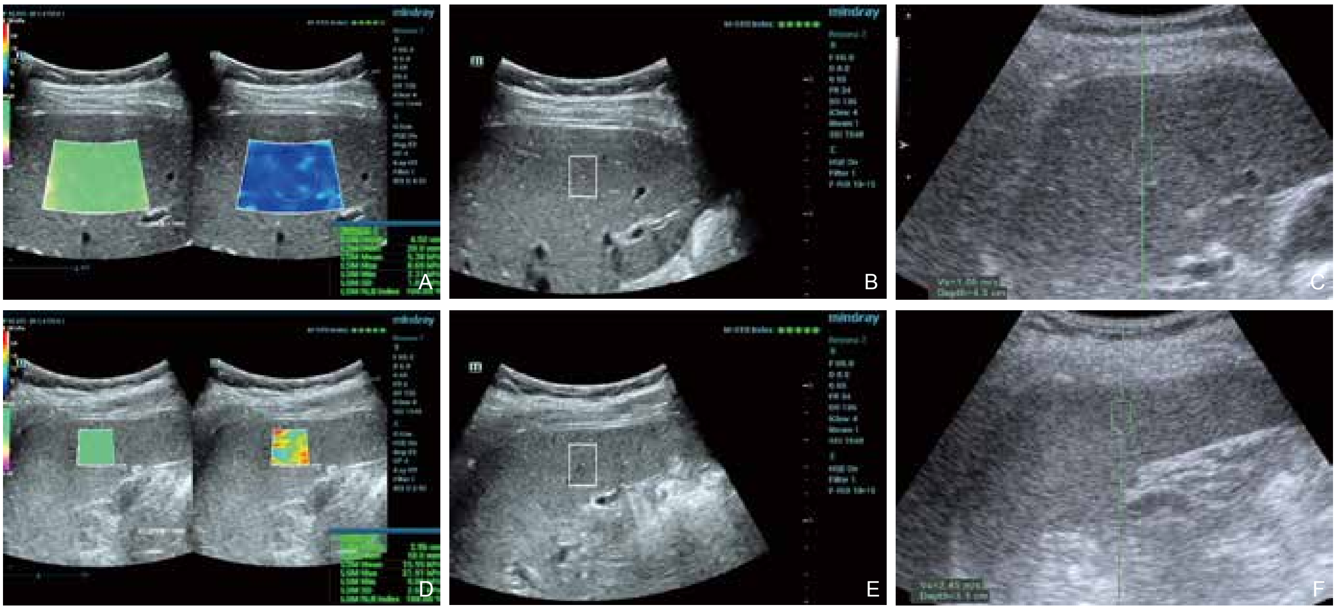


Figure 1 A 21-years-old-man healthy volunteers, liver stiffness measured by sound touch elastography (STE) was 5.38 kPa (A), by sound touch quantification (STQ) was 4.85 kPa (B), and by acoustic radiation force impulse (ARFI) was 1.05 m/s (C); spleen stiffness measured by STE was 15.95 kPa (D), by STQ was 17.81 kPa (E), AND by ARFI was 2.45 m/s (F).

A hundred and five participants (36 patients with chronic hepatitis and 69 healthy adults) were examined twice by two independent sonographers who specialize in STE and STQ techniques. Another 36 healthy adults were examined twice by ARFI imaging. The remaining healthy volunteers were examined once to obtain the normal value of liver and spleen stiffness measurements using STE, STQ, and ARFI imaging.

This prospective study was approved by our institutional ethics committee (clinical trial registration number: NCT03530657) and informed written consent was obtained from all consecutive participants.

Liver STE and STQ

The new implementation of shear-wave elastography, known as STE and STQ, were performed on Mindray Resona 7 ultrasound system (Mindray, China) with a SC6-1U (frequency of 1–6 MHz) convex probe. Liver STE and STQ measurements were both conducted in the right lobe of the liver with participants lying in the supine position. The elasticity image box of liver STE was about 4 x 3 cm, and it was placed 1–2 cm from Glisson's capsule of the liver and away from large vessels. The region of interest (ROI) of liver STE was defined as 2 cm in diameter with a homogeneous color of the STE box. The ROI box of liver STQ (fixed dimensions of 1.5 × 1.0 cm) was similarly positioned in the area of liver parenchyma free of large vessels under 1-2 cm from Glisson's capsule of the liver. Five consecutive liver STE images and ten consecutive liver STQ images were obtained from each individual.

Spleen STE and STQ

Spleen STE and STQ were also performed on Mindray Resona 7 ultrasound system (Mindray, China) with a SC6-1U (frequency of 1–6 MHz) convex probe. Spleen STE and STQ were conducted in the splenic parenchyma free of large vessels with participants lying in the right lateral position. The elasticity image box of spleen STE was about 1.5 x 1.5 cm, and it was placed 0.5–1 cm under the splenic capsule. The region of interest (ROI) of spleen STE was defined as 1 cm in diameter with an area of homogeneous color of the STE box. The ROI box of spleen STQ (fixed dimensions of 1.5 × 1.0 cm) was similarly positioned in the area of splenic parenchyma free of large vessels under 0.5-1 cm under the splenic capsule. Five consecutive spleen STE images and ten consecutive spleen STQ images were obtained from each individual.

Liver and spleen ARFI

ARFI imaging was conducted using the Acuson S3000 (Siemens Medical Solutions, Erlangen, Germany) imaging system with a convex probe (frequency of 1–6 MHz). Liver ARFI was detected in the liver parenchyma free of large vessels and deeper than 2 cm from the liver capsule. Spleen ARFI was positioned in the splenic parenchyma free of large vessels under 0.5-1 cm from the splenic capsule. Ten consecutive liver and spleen ARFI images were performed on each individual.

Quality control of elastography procedure

For quality control, two experienced sonographers reviewed all the elastography images to exclude invalid cases. For each STE and STQ image, the Motion Stability Index (M-STB Index) was required to acquire more than three stars and the reliability index should be more than or equal to 90%, or it would be considered as an invalid measurement. The cases were considered as a technical failure if success rates less than 60% or interquartile ranges (IQR) greater than 30% of the median value of stiffness measurements.

Statistical analysis

Cases with technical failure were excluded from final analysis. Data were first tested for normal distribution by Shapiro-Wilk test. Descriptive data were expressed as the mean ± standard deviation (SD) or *n* (%) as appropriate. The differences in liver and spleen stiffness measurements assessed by a different technical imaging system were compared by using the paired t test.

The intraclass correlation coefficient (ICC) was obtained to assess intra-observer and inter-observer reproducibility of STE and STQ. The intra-observer and inter-observer agreement were regarded as excellent (ICC $\geqslant$ 0.75), fair to good (0.40 $\leqslant$ ICC < 0.70), or poor (ICC < 0.40).

The statistical analyses of our data were conducted by SPSS software for Windows (Version 13.0; SPSS, Chicago, IL, USA). All statistical tests were two-sided in our analysis, and α value was set at 0.05. *P* value < 0.05 was considered statistically significant.

Results

Technical success rate

Two hundred and eighty-seven subjects were finally included. The overall success rates of liver and spleen STE, STQ, and ARFI were shown in Table 1. Detailed reasons of technical failure were summarized in Figure 1 with IQR/Median >30% happened to be the main reason of failures. The spleen transverse diameters were 31.85 ± 5.12 mm vs 29.31 ± 6.37 mm (*P* = 0.082) in spleen STE success cases and failure cases, 31.69 ± 5.11 mm vs 29.88 ± 6.96 mm (*P* = 0.087) in spleen STQ success cases and failure cases, and 31.64 ± 5.40 mm vs 30.48 ± 5.40 mm (*P* = 0.542) in spleen ARFI success cases and failure cases.

The success rate of spleen STE was significantly higher than spleen ARFI (*P* = 0.003). However, the difference between the success rate of spleen STQ and spleen ARFI was not significant (*P* = 0.070). A significant higher success rate of spleen stiffness measurement was seen in patients with a spleen transverse diameter greater than 30 mm (*P* = 0.029 and 0.005 for STE and STQ) (Table 1). There was no significant difference among the success rates of liver STE, liver STQ, and liver ARFI (all *P* > 0.05) (Table 1).

Table 1 Comparison of different detection methods for success rate

Detection method	Success rate	*P* value*
Liver stiffness measurement		
Liver STE	96.5% (277/287)	0.427
Liver STQ	95.1% (273/287)	0.979
Liver ARFI	94.8% (272/287)	-
Spleen stiffness measurement		
Spleen STE	87.5% (251/287)	0.004
Spleen STQ	84.0% (241/287)	0.084
Spleen ARFI	78.0% (224/287)	-
Spleen stiffness Subgroup analysis		
Transverse spleen diameter ⩽ 30 cm		
Spleen STE	82.7% (105/127)	0.094
Spleen STQ	77.2% (98/127)	0.559
Spleen ARFI	74.0% (94/127)	-
Transverse spleen diameter > 30 cm		
Spleen STE	91.3% (146/160)	0.009
Spleen STQ	89.4% (143/160)	0.040
Spleen ARFI	81.3% (130/160)	-

STE, Sound touch elastography; STQ, Sound touch quantification; ARFI, Acoustic radiation force impulse imaging.
*P value for comparisons with ARFI imaging.

Intra-observer and inter-observer agreement

The intra-operator and inter-operator agreements for liver STE and liver STQ were considered to be excellent in both healthy group and chronic hepatitis group (Table 2). There were no difference among different ARFI measurements in healthy group.

The intra-observer agreements for spleen STE and spleen STQ were also regarded as good, while the performance of the inter-observer agreement for spleen STE and spleen STQ was relatively not satisfied, and there was no difference compared with ARFI (Table 2). Subgroup analyses for spleen transverse diameter greater than 30mm and distance from skin to splenic capsule of 18 mm or less yield higher inter-observer agreement (Table 3).

Normal value of liver and spleen stiffness measurements using STE/STQ

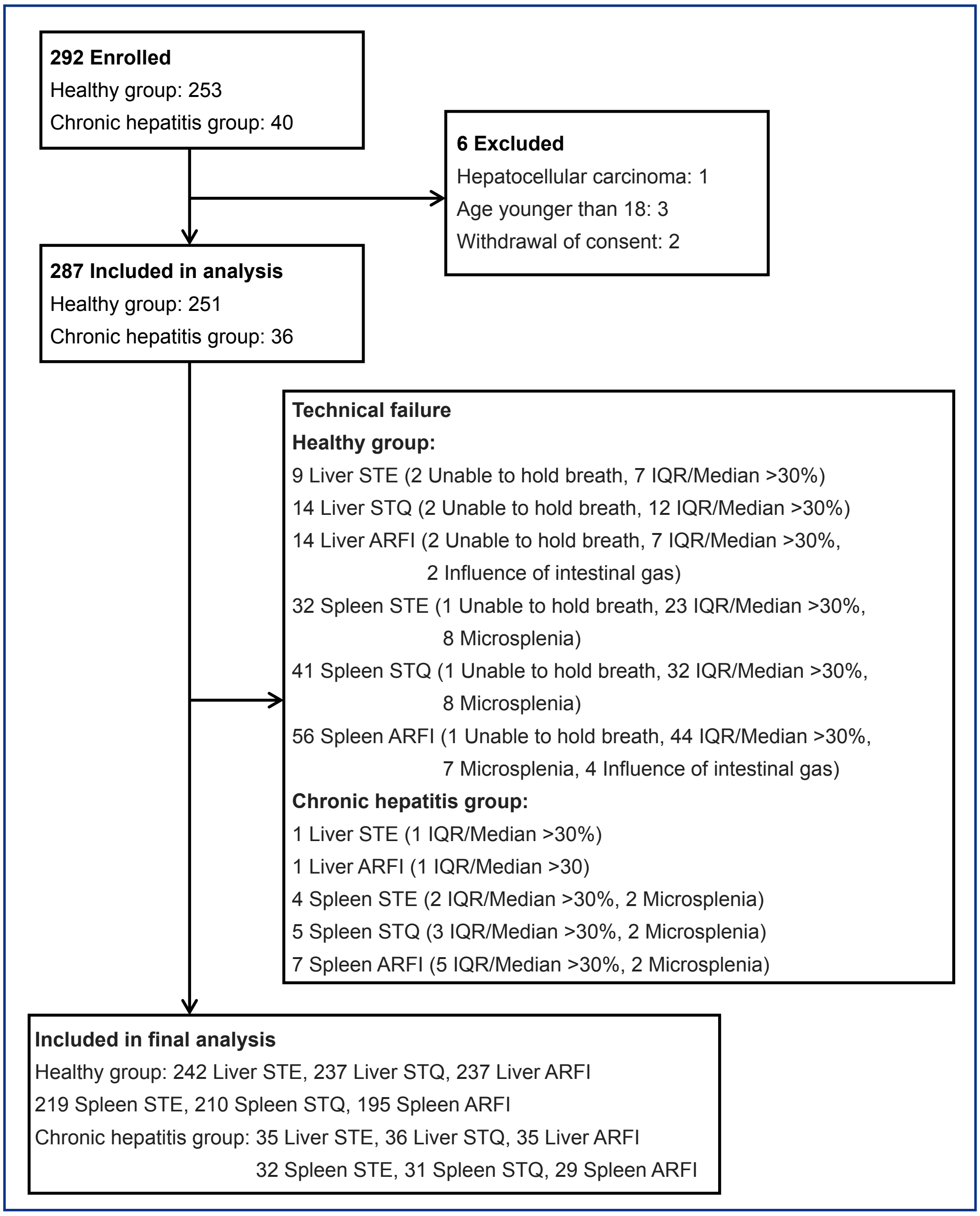
A total of 251 healthy adults were finally included in our normal value analysis. The mean value of liver stiffness measurement was 5.92 kPa (95%CI: 5.80-6.04) when using STE and 6.00 kPa (95%CI: 5.87-6.13) when using STQ (Table 3). The difference between the normal value of liver STE and liver STQ was statistically significant ($P = 0.003$).

The mean value of spleen stiffness measurement was 15.19 kPa (95%CI: 14.83-15.54) when using STE and 16.22 kPa (95%CI: 15.85-16.62) when using STQ (Table 3). The difference between the normal value of spleen STE and STQ was statistically significant ($P < 0.001$).

Table 2 Inter-observer reliability and intra-observer reliability for liver and spleen STE and STQ

Variable	Inter-observer Reliability (ICC [95% CI])	*P* value	Intra-observer Reliability (ICC [95% CI])	
			Operator 1	Operator 2
Healthy adults' group				
Liver stiffness measurement				
Liver STE	0.914 (0.873-0.941)	0.142	0.871 (0.833-0.904)	0.904 (0.884-0.922)
Liver STQ	0.896 (0.848-0.930)	0.317	0.895 (0.873-0.914)	0.858 (0.816-0.894)
Liver ARFI	0.845 (0.673-0.926)	–	0.904 (0.852-0.944)	0.818 (0.743-0.876)
Spleen stiffness measurement				
Spleen STE	0.629 (0.441-0.754)	0.538	0.829 (0.753-0.886)	0.822 (0.739-0.885)
Spleen STQ	0.601 (0.395-0.737)	0.686	0.804 (0.712-0.873)	0.809 (0.718-0.877)
Spleen ARFI	0.543 (0.057-0.802)	–	0.751 (0.641-0.845)	0.660 (0.529-0.781)
Chronic liver disease group				
Liver stiffness measurement				
Liver STE	0.925 (0.851-0.962)	–	0.886 (0.823-0.934)	0.917 (0.870-0.952)
Liver STQ	0.905 (0.819-0.951)	–	0.859 (0.714-0.917)	0.846 (0.766-0.909)
Spleen stiffness measurement				
Spleen STE	0.681 (0.354-0.842)	–	0.865 (0.772-0.928)	0.863 (0.764-0.928)
Spleen STQ	0.540 (0.057-0.775)	–	0.834 (0.719-0.911)	0.854 (0.812-0.877)

STE, sound touch elastography; STQ, sound touch quantification; ARFI, acoustic radiation force impulse imaging
*P value for inter-observer reliability comparisons with ARFI imaging.



Discussion

Despite the rapid development of shear wave elastography, obtaining higher quality and more reliable elastography images are still facing many challenges. STE and STQ are new elastography technologies with the advantages of fast imaging speed and good penetration. However, few studies have reported on the feasibility and repeatability of STE and STQ in liver and spleen stiffness measurements.

The results of this study showed that STE and STQ in the liver stiffness had a high detection success rate and reproducibility. It has been reported in the literature that the early technique transient elastography (TE) is easily affected by many factors, such as narrow intercostal space, obesity, and ascites, etc., and nearly 15% of the results were unreliably. However, 2D-SWE and pSWE techniques have a higher detection success rate and are not easily affected by ascites and other factors, which is consistent with the results of this study. The reproducibility of liver STE and STQ is excellent in this study, with ICC up to above 0.9, representing a good clinical application prospect.

For the spleen stiffness, STE and STQ success rates were 87.5% and 84.0% in this study, respectively. Poor respiratory coordination and variation in the measured value were the major causes of failure. Previous study reported the success rate of 2D-SWE of spleen stiffness in normal adults was only 52.9%, which was lower than that in our study. These results may be due to better penetrability of STE and STQ technique than other 2D-SWE methods. Furthermore, the detection success rate of STE and STQ were significantly improved when the thickness of spleen was greater than 30mm in our study. In patients with portal hypertension with enlarged spleen, the success rate of 2D-SWE of spleen was reported up to 96%. Therefore, STE and STQ test success rate may be higher in patients with splenomegaly.

Table 3 Spleen stiffness subgroup analysis of inter-observer reliability

Variable	Inter-observer Reliability (ICC [95% CI])
Transverse spleen diameter ⩽ 30 cm	
Spleen STE	0.520 (0.214-0.707)
Spleen STQ	0.283 (0.250-0.588)
Transverse spleen diameter > 30 cm	
Spleen STE	0.704 (0.449-0.841)
Spleen STQ	0.668 (0.367-0.826)
Distance from skin to splenic capsule ⩽ 18 mm	
Spleen STE	0.692 (0.417-0.837)
Spleen STQ	0.818 (0.650-0.905)
Distance from skin to splenic capsule >18 mm	
Spleen STE	0.468 (0.082-0.691)
Spleen STQ	0.241 (0.174-0.292)

STE, sound touch elastography; STQ, sound touch quantification; ARFI, acoustic radiation force impulse imaging.

Table 4 Normal value of shear-wave velocity (kPa) assessed by different detection methods

Detection method	*n*	Mean ± SD	95% CI
Liver stiffness measurement			
STE	242	5.92 ± 0.97	5.80-6.04
STQ	237	6.00 ± 1.06	5.87-6.13
Spleen stiffness measurement			
STE	219	15.19 ± 2.75	14.83-15.54
STQ	210	16.22 ± 3.16	15.85-16.62

STE, sound touch elastography; STQ, sound touch quantification.

The intra-observer reproducibility of spleen STE and STQ was good, but the inter-observer reproducibility was barely satisfactory. This suggests that when the spleen stiffness measurement was not consistent with clinical data, repeated measurement may be needed to confirm the spleen stiffness. It was reported in literature that the reproducibility of spleen stiffness test was poor in people with normal-sized spleen, but better in people with enlarged spleen. In this study, stratified analysis of spleen size found that the reproducibility was significantly improved when the thickness of spleen was greater than 30mm and the thickness of subcutaneous tissue was less than 18mm. Most of the subjects in this study have normal spleen size, and the reproducibility of STE and STQ detection in patients with enlarged spleen require to be further studied.

Acoustic radiation force impulse (ARFI) technique was a validated method for liver stiffness measurement. Compared with ARFI, STE and STQ showed non-inferior success rate and reproducibility of liver stiffness measurement, and even better success rate of spleen stiffness measurement. The breathing quality control mode is added in STE and STQ, which is regarded as "a star" to eliminate large breathing movements, so as to improve the stability of detection.

In this study, the reference ranges of liver were 5.80-6.04 kPa in STE and 5.87-6.13 kPa in STQ, while the reference ranges of spleen were 14.83-15.54 kPa in STE and 15.85-16.62 kPa in STQ. Previous study reported that other 2D-SWE technique measured in normal adult liver was (5.02 ± 0.97) kPa, which is slightly lower than that in this study, and the value of spleen was (20.5 ± 5.4) kPa, which is significantly higher than that of this study. Therefore, although the technical principle is similar, the measurements of different manufacturers and different instruments cannot be directly equivalent, which is also consistent with guidelines.

Our study has several limitations. First, this study only included healthy people and patients with chronic hepatitis B without any pathological results. More reliable diagnostic performance of STE and STQ remains to be further determined by pathological results. Secondly, this study only compares STE and STQ with ARFI, further studies compared with other shear wave elastography technologies are needed.

In conclusion, STE and STQ in liver and spleen stiffness measurements had a high success rate with good reproducibility, which were comparable to ARFI. The inter-observer reproducibility of spleen was barely satisfactory, but was improved when the thickness of spleen was greater than 30mm. The reference ranges of STE and STQ in liver and spleen measurements were also derived based on 251 healthy adults.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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