A Noninvasive Method—Shear-Wave Elastography Compared With Transient Elastography in Evaluation of Liver Fibrosis in Patients With Chronic Hepatitis B

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Abstract: The aim of our study was to investigate the efficiency and feasibility of shear-wave elastography (sound touch elastography [STE], sound touch quantification [STQ]) compared with transient elastography (FibroScan) assessment in noninvasively and quantitatively identifying the degree of liver fibrosis. A total of 158 patients with chronic hepatitis B were included, and all accepted STE, STQ, and FibroScan assessments. Young's modulus (kPa) of STE, STQ, and FibroScan were evaluated, and the diagnostic performance of the 3 techniques on liver fibrosis stage was compared. The final diagnosis was based on histological findings from liver biopsy. Of all these patients, 36 patients were categorized as G/S < 2, and 122 were as G/S ≥ 2 according to Scheuer G/S scoring system. STE_{mean} and STQ_{mean} measurements were positively correlated with liver fibrosis stage with high correlation (r = 0.852 and r = 0.803, respectively). Receiver operating characteristic analysis of STE, STQ, and FibroScan revealed that the areas under the curve of STE and STQ were markedly increased compared with that of FibroScan when differentiating early stage of liver fibrosis (S1, S2). It was concluded that shear-wave elastography (STE, STQ, and FibroScan) performs well in evaluation of liver fibrosis in patients with chronic hepatitis B, and the efficacies of STE and STQ are better than that of FibroScan.

Key Words: chronic hepatitis B, liver fibrosis, liver stiffness, noninvasive, shear-wave elastography

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Hepatitis B virus (HBV) infection is a common cause of liver fibrosis in China. Hepatitis B virus repeatedly causes degeneration and necrosis of hepatic cells, fibrosis, and nodular hyperplasia in liver, which ultimately leads to liver cirrhosis, hepatic carcinoma, and even hepatic failure.[1,2] For patients with HBV infection, early stage of liver cirrhosis or fibrosis is reversible if they accepted early treatment[3]; thus, early diagnosis and evaluation of liver fibrosis are very important that it helps improve the effectiveness of therapy and clinical outcomes.

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Ultrasound elastography is a widely accepted noninvasive technique for objectively assessing the stiffness of liver tissue in recent years. The altered stiffness is usually the result of the deformation of tissue structures caused by chronic liver damages, which was characterized by an increase in extracellular matrix produced by fibroblast-like cells. Generally, the stiffness or elasticity of the liver indicates the degree of liver fibrosis. However, it was reported in some studies that the diagnostic efficacy of liver fibrosis and cirrhosis was not improved by conventional ultrasound examination combined with 2-dimensional shear-wave elastography (SWE).[4] Shear-wave elastography is a relatively new technique needing more investigations before they could be widely used in clinic,[5] whereas transient elastography (TE) is a relatively mature shear-wave vibroacoustic technique.[6] In this study, we applied 3 types of ultrasound-based elastography techniques: TE (FibroScan), point shear-wave speed measurement (STQ), 2D shear wave speed imaging elastography (STE) in evaluation of liver fibrosis in patients with HBV infection, in order to identify the efficiency and feasibility of these elastography techniques noninvasively and quantitatively determining the degree of liver fibrosis.

MATERIALS AND METHODS

Patients

A total of 278 consecutive patients with chronic hepatitis B (CHB) who were scheduled for liver biopsy in our department from January 1, 2017, to July 30, 2017, were prospectively and continuously enrolled in this study. The exclusion criteria were as follows: (1) the other liver diseases including drug-induced liver injury, autoimmune hepatitis, alcoholic hepatitis, and so on; (2) infection with hepatitis A virus, hepatitis C virus, Epstein-Barr virus, human herpesvirus, and so on; (3) serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was 5 times higher than the reference range; (4) moderate to severe fat liver; (5) alcohol abuse, diabetes, and obesity; (6) heart, brain and renal disorder; and (7) gestation and lactation. Finally, 158 patients were included in our analysis. This study was approved by the institutional review board of our hospital, and written informed consent was obtained from all the patients.

Image Acquisition

Shear-wave elastography was performed by 2 experienced radiologists. Resona 7 (Mindray, Shenzhen, China) ultrasound diagnostic equipment with a convex array probe (L5-1)

was applied in the point shear wave elastography (STQ) and 2D shear wave elastography (STE). Transient elastography was performed with the M or L transducer by using the FibroScan device (Echosens, Paris, France), and then Young's modulus (kPa) was recorded. After an overnight fast, patients were examined in the dorsal decubitus position with the right arm elevated above the head for optimal intercostal access. The patients were asked to hold deep breath for 3 to 4 seconds when the measurements were performed. Conventional B-mode ultrasound was first performed, followed by the STE and STQ analysis. A region of interest (ROI) was placed beneath the Glisson capsule by 1.5 to 2.0 cm, where there were no large bile ducts and vessels to avoid reverberation artifacts and increased subcapsular stiffness (Figs. 1A, B).

Ultrasound-Guided Percutaneous Liver Biopsy

Patients were kept at the same position with the right arm elevated above the head. Ultrasound selected the same area used for SWE evaluation as the biopsy area, avoiding major vessels. All liver biopsies were performed with local anesthesia (1% lidocaine). After the site was sterilely prepared and draped, the needle was inserted under direct ultrasound guidance to ensure a safe routine, and then 2 to 3 pieces of the liver sample were obtained for each patient. The biopsy needles used were Bard Magnum (Cook Medical, Bloomington, Ind). After the last sample was taken, the needle was removed, and pressure was applied with a bellyband. After applying pressure, ultrasound images were saved to document any immediate hematomas. The liver samples were immersed in 10% buffered formalin and embedded in paraffin, followed by hematoxylin-eosin and Masson staining. The histopathology analysis was done by an experienced pathologist, and the final diagnosis was approved by another experienced pathologist. Scheuer scoring system was used for pathological analysis of liver fibrosis and necroinflammatory activity.[7]

Statistical Analysis

All tests and calculations were performed with Statistical Program for Social Sciences 20.0 software (SPSS, Chicago, Ill). Descriptive variables are presented as mean ± SD. Categorical variables are described as proportions. χ^2 Test and Fisher exact test were applied in comparison of categorical variables. An independent 2-sample t test was used to compare the size of nodules between 2 independent groups. Correlation analysis between elastography techniques and liver fibrosis stages was performed by using Spearman correlation test. The reproducibility was investigated with the intraclass correlation coefficient (ICC) of reliability analysis and 95% confidence interval (CI) (ICC >0.75 indicates excellent reliability). Receiver operating characteristic curves and area under the curve (AUC) were used to compare the diagnostic efficiencies of STE, STQ, and FibroScan. Sensitivity and specificity were calculated under diagnostic testing. Cutoff values were obtained at the point with the maximum AUC. Delong test was used to obtain the significance of AUC. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 158 patients were included in this study, among which there were 63 female and 95 male patients with a mean age of 38.55 ± 18.20 years. According to the Scheuer G/S scoring system, 36 patients were categorized as G/S < 2 (group 1), and 122 were as G/S ≥ 2 (group 2). There were no significant differences in regard to the sex and age between the 2 groups ($P > 0.05$). Laboratory tests showed that serum ALT, AST, γ-glutamyltransferase, alkaline phosphatase, total bilirubin, and albumin were similar between the 2 groups ($P > 0.05$) (Table 1).

Relationship Between SWEs and Liver Fibrosis Stages

Intraobserver agreement between 2 radiologists was 0.95 (95% CI, 0.89–0.98). Intraobserver agreement showed an ICC of 0.95 for the measurements of liver fibrosis (Fig. 2), which indicated a high agreement between the 2 observers. Table 2 shows STE, STQ, and FibroScan measurements of each liver fibrosis stage (S0–S4), indicating that stiffness (kPa) of liver increased when liver fibrosis stage was higher. The maximum STE, STQ, and FibroScan measurements were found in S4 stage, whereas the minimum measurements were in S0. Table 3 analyzes the correlation degree of SWEs and liver fibrosis stage and shows that E1 (STE_{mean}), Q1 (STQ_{mean}), and Q3 (STQ_{min}) were correlated with liver fibrosis stage, respectively ($r = 0.852$, $r = 0.803$, $r = 0.305$). E1 and Q1 measurements were found to be positively correlated with higher liver fibrosis stage with high correlations, whereas

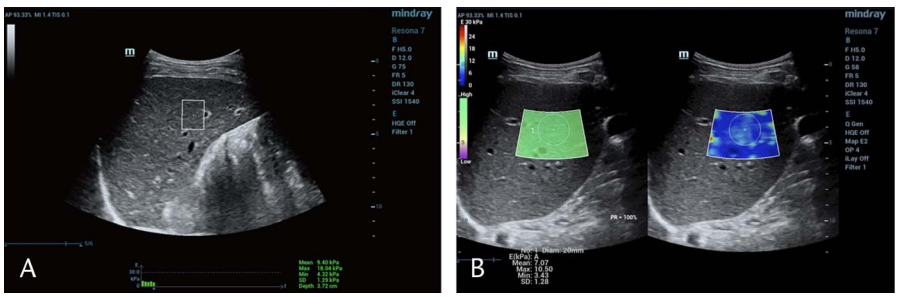

FIGURE 1. Image acquisition using STE and STQ. A, Two-dimensional gray-scale image was obtained, and then STQ measurements were performed 5 times with final SD less than 2.0 as the quality control while avoiding large blood vessels and bile ducts. B, Images were obtained when uniform color filled more than 90% of sampling area and reliability map is greater than 95% under reliability map. Quantitative measurement was performed in the ROI with the probe perpendicular to the skin after a reliable image was obtained.

TABLE 1. Characteristics of Patients

	Scheuer G/S < 2 n = 36	Scheuer G/S ≥ 2 n = 122	*P*
Demographics			
Age, mean ± SD, y	36.44 ± 15.63	40.71 ± 20.80	0.066
Sex			
Female, % (n)	41.66 (15)	39.31 (48)	0.055
Male, % (n)	58.34 (21)	60.69 (74)	
Laboratory tests			
ALT, mean ± SD, IU/L	44.64 ± 9.21	63.78 ± 32.11	0.060
AST, mean ± SD, IU/L	30.20 ± 8.12	50.33 ± 19.22	0.146
γ-Glutamyltransferase, mean ± SD, IU/L	43.00 ± 22.19	50.05 ± 29.27	0.120
Alkaline phosphatase, mean ± SD, IU/L	60.59 ± 27.14	74.65 ± 36.44	0.063
Total bilirubin, mean ± SD, mol/L	69.35 ± 16.10	63.02 ± 23.87	0.197
Albumin, mean ± SD, g/L	43.89 ± 10.11	44.51 ± 15.23	0.058

Q3 measurement was positively correlated with higher liver fibrosis stage with intermediate correlation.

Performance of SWEs in Identifying Liver Fibrosis Stage

The diagnostic performances and cutoff values of STE, STQ, and FibroScan in identification of liver fibrosis stage are presented in Table 4. STE and STQ had higher diagnostic specificity in identification of S ≥ 1 (87.1%, 87.2% vs 69.6%), S ≥ 2 (91.1%, 68.9% vs 55.6%), S ≥ 3(91.1%, 93.1% vs 85.7%), and S ≥ 4 (95.6%, 96.7% vs 85.7%) and also higher diagnostic sensitivity in identifying S ≥ 4 (89.3%, 89.3% vs 85.7%), but lower diagnostic sensitivity for S ≥ 1 (78.0%, 75.6% vs 82.9%) compared with FibroScan. Receiver operating characteristic curves and AUCs of STE_{mean}, STQ_{mean}, and $FibroScan_{mean}$ in identifying different liver fibrosis stage are

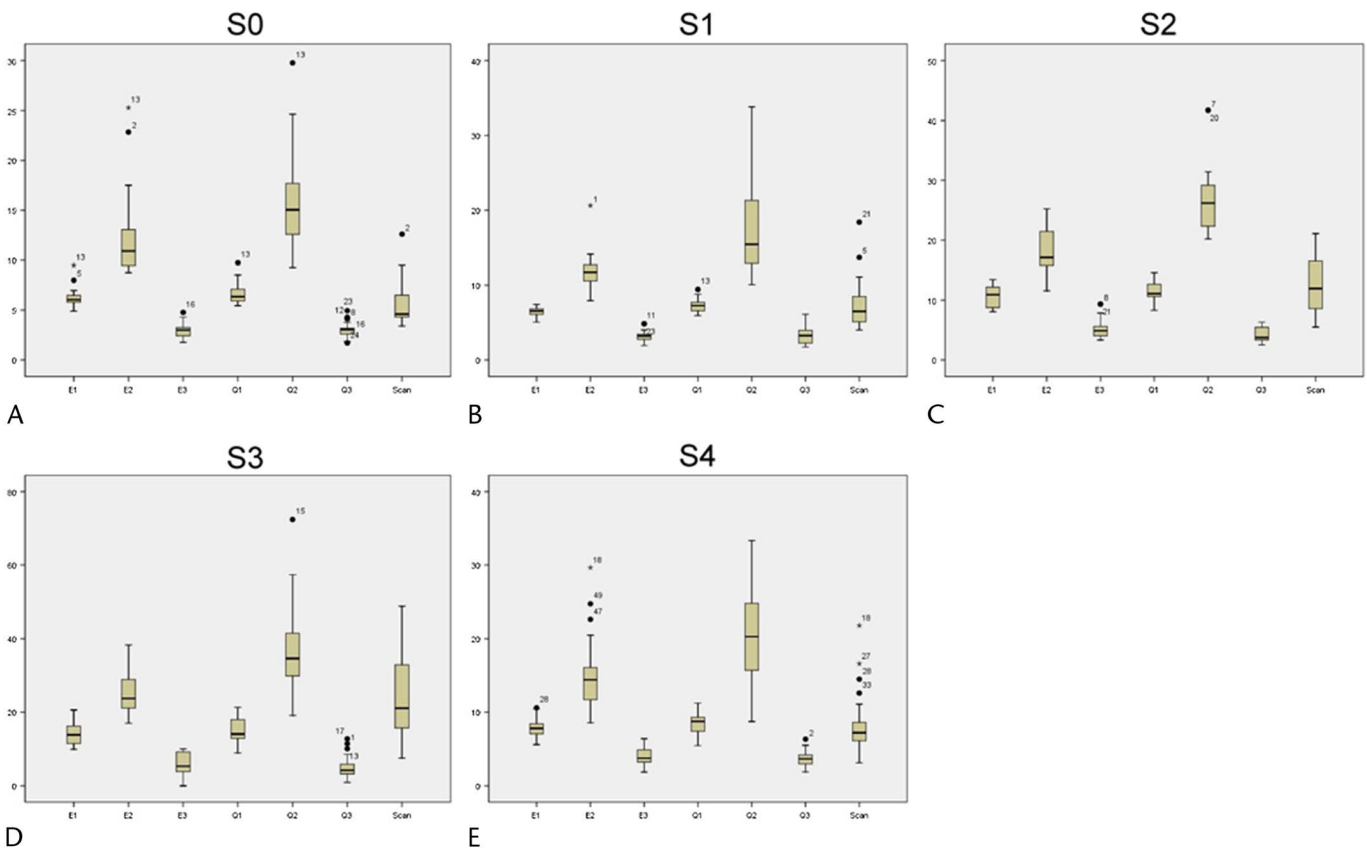

FIGURE 2. Box-and-whisker plot of SWEs at each fibrosis stage. Box-and-whisker plot of STE (E1, E2, E3), STQ (Q1, Q2, Q3), and FibroScan at each fibrosis stage—S0 (A), S1 (B), S2 (C), S3 (D), and S4 (E)—shows the interquartile range (central box), median (thick lines), and range (thin lines) of liver stiffness.

TABLE 2. STE, STQ, and FibroScan Measurements of Each Liver Fibrosis Stage

	S0	S1	S2	S3	S4
kPa/S Degree	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)
E1	6.04 (5.75–6.60)	6.53 (6.08–6.84)	7.84 (7.05–8.49)	10.57 (9.17–12.29)	13.55 (10.61–15.97)
E2	10.91 (9.38–13.41)	11.61 (10.4–12.74)	14.65 (11.78–16.75)	19.62 (15.95–22.25)	24.19 (21.48–31.36)
E3	3.00 (2.42–3.32)	3.21 (2.47–3.45)	3.62 (3.26–4.79)	4.75 (3.87–6.28)	5. 00 (3.53–7.25)
Q1	6.35 (5.92–7.12)	7.05 (6.50–7.58)	8.74 (7.50–9.44)	11.38 (10.23–12.63)	14.01 (12.34–16.74)
Q2	15.04 (12.47–17.89)	15.43 (12.76–21.36)	20.61 (15.72–25.09)	26.39 (23.7–30.31)	34.63 (30.47–41.48)
Q3	3.04 (2.58–3.25)	3.17 (2.20–3.90)	3.64 (2.96–4.18)	3.59 (3.09–5.42)	4.26 (2.32–6.70)
FibroScan	4.60 (4.25–6.90)	6.5 (5.10–8.70)	7.2 (6.10–8.70)	11.95 (7.98–17.65)	21.05 (15.20–33.00)

E1 = STE_{mean}, E2 = STE_{max}, E3 = STE_{min}, Q1 = STQ_{mean}, Q2 = STQ_{max}, Q3 = STQ_{min}, S degree = Scheuer score.

shown in Figure 3. Areas under the curve of STE_{mean} and STQ_{mean} were significantly larger than that of FibroScan in identification of S ≥ 1(0.898, 0.878 vs 0.739), S ≥ 2(0.936, 0.888 vs 0.753), S ≥ 3(0.972, 0.957 vs 0.870), and S ≥ 4(0.968, 0.955 vs 0.907).

DISCUSSION

Hepatitis B virus infection causes aggregation of inflammatory cells in liver, injury of hepatic cells, and collagen deposition in extracellular matrix by inducing host immune responses and reactions. The progression from HBV infection to liver cirrhosis and even hepatic carcinoma is through a series of morphological changes. Most of the patients with CHB are diagnosed with liver fibrosis or cirrhosis in the advanced stage, as they are often asymptomatic in the early stage. However, CHB patients who start the course of treatment in the advanced stage are found to be with poor prognosis. The early diagnosis and intervention would be of great importance for CHB patients that it decreases the possibility of unfavorable clinical outcome.[8] The current methods in evaluation of liver fibrosis include clinical symptoms, serologic examination, imaging, tissue biopsy, and so on. Although the serum biomarkers reflect the liver function and also the systematic changes of the patients, they are easily influenced by the extrinsic factors and are with low diagnostic specificity, especially in CHB patients.[9–12] Liver biopsy for pathological diagnosis is an invasive method that has high cost and low reproducibility.[13] Conventional ultrasound, computed tomography, and magnetic resonance imaging are not efficient in identifying the early stage of liver fibrosis. The advent of SWE increases diagnostic accuracy of liver fibrosis.[14,15] A higher elasticity (Young's modulus) reflects lower tissue stiffness.[16] The current elastography techniques for evaluation of liver fibrosis include TE, point SWE, 2D-SWE, and magnetic resonance elastography.[17] Among them, ultrasound elastography is cheaper, more convenient, and more reproducible than magnetic resonance elastography.

In this study, point shear wave elastography (pSWE, STQ) and 2D shear wave elastography (2D-SWE, STE) were conducted with the Mindray Resona 7 ultrasound system (Mindray), which has never been compared with TE before. This was the first time comparing STE and STQ with FibroScan, which was widely used in diagnosing liver fibrosis. In STQ examination, multiple measurements of shear-wave elasticity imaging were acquired in real-time mode under gray-scale mode. In STE examination, a multiwave imaging platform was used to apply ultrahigh-speed ultrasound wave that could track the shear-wave propagation paths in different depths of the tissue. The shear-wave propagation efficiency could be largely improved, and negative biological effects could be avoided by STE. In addition, the intraobserver reproducibility of SWE in evaluation of the liver was reported to be excellent.[18] Thus, improved resolutions and high accuracy of these images could be ensured.

In this study, 3 types of ultrasound-based SWEs, including TE (FibroScan), point shear wave elastography (STQ), 2D shear wave elastography (STE), were applied in the evaluation of liver fibrosis in patients with HBV infection. In the STQ and STE quantification, we select a 20 (length) × 15-mm (width) area and a circle (diameter 20 mm) for measurements, respectively. The selected area for quantification was larger than that in the previous studies,[19,20] yielding a better accuracy in our study. There were fewer vessels and bile ducts in S5–S6 segments, where they were less influenced by breath and artery pulse, making them the most appropriate and safety areas for biopsy and measurements. The success rate of TE (97.3%) was smaller than STE (100%) and STQ (100%), because the former was more easily impacted by weighted patients and those with thick subcutaneous adipose tissues. STE and STQ measurements maintained a better consistency between different operators as they were more reproducible and adjustable.

TABLE 3. Correlation Analysis of STE, STQ, and FibroScan With Liver Fibrosis Stage

	E1	E2	E3	Q1	Q2	Q3	FibroScan
Correlation coefficient	0.852*	0.678	0.511	0.803*	0.666	0.305†	0.640
P	0.000	0.000	0.000	0.000	0.000	0.000	0.000

E1 = STE_{mean}, E2 = STE_{max}, E3 = STE_{min}, Q1 = STQ_{mean}, Q2 = STQ_{max}, Q3 = STQ_{min}.

*High correlation.

†Intermediate correlation.

TABLE 4. Cutoff Value, Diagnostic Sensitivity, and Specificity of STE, STQ, and FibroScan at Each Liver Fibrosis Stage

		E1	E2	E3	Q1	Q2	Q3	FibroScan
	Cutoff, kPa	6.82	10.91	3.27	7.32	18.65	3.20	5.75
S ≥ 1	Sensitivity, %	78.0	85.4	70.7	75.6	72.0	65.9	82.9
	Specificity, %	87.1	56.6	73.9	87.2	87.1	78.3	69.6
	Cutoff, kPa	7.04	14.4	3.29	6.94	3.83	3.36	5.85
S ≥ 2	Sensitivity, %	76.1	50.0	71.7	84.8	89.1	56.5	80.4
	Specificity, %	91.1	88.9	68.9	46.7	44.4	68.9	55.6
	Cutoff, kPa	9.58	18.88	3.69	10.96	29.81	4.57	11.8
S ≥ 3	Sensitivity, %	100.0	94.4	83.3	94.4	77.8	50.0	94.4
	Specificity, %	91.1	81.1	62.4	92.1	93.1	86.1	85.7
	Cutoff, kPa	9.83	1.00	3.69	10.43	24.43	5.04	10.25
S = 4	Sensitivity, %	89.3	89.3	85.7	89.3	82.1	42.9	85.7
	Specificity, %	95.6	83.5	68.9	96.7	81.3	94.5	85.7

The degree of liver fibrosis increased as the disease progresses, and Young's modulus value measured by FibroScan, STE, and STQ gradually increased as well. In the previous study,[21–23] FibroScan was reported to get higher accuracy in diagnosing advanced liver fibrosis stage (S3 and S4), whereas our study showed that FibroScan performed a higher sensitivity in identifying S1. However, in the present study, STE and STQ were more accuracy than FibroScan in diagnosing liver fibrosis stage (S1–S4). Transient elastography was more likely to be influenced by obesity or ascites of the patients,[24] whereas STE and STQ were much more stable and repeatable[25]; thus, STE and STQ created the opportunity for accurate assessment of liver fibrosis. STE, STQ, and FibroScan measurements were highly correlated with liver fibrosis stage, respectively. A larger Young's modulus indicated a higher liver fibrosis stage, which may be ascribed to the pathological progression of liver fibrosis. Liver elasticity measurements were reproducible, operator independent, and well correlated to fibrosis grade in this study. The value of TE, point shear wave elastography, and 2D shear wave elastography seems to be varied in different studies.[26–28]

There are still some limitations in our study. Patients' body height and weight, the thickness of subcutaneous adipose tissues, and the depth of the ROI were not considered in this study. Whether these factors influence our measurements in

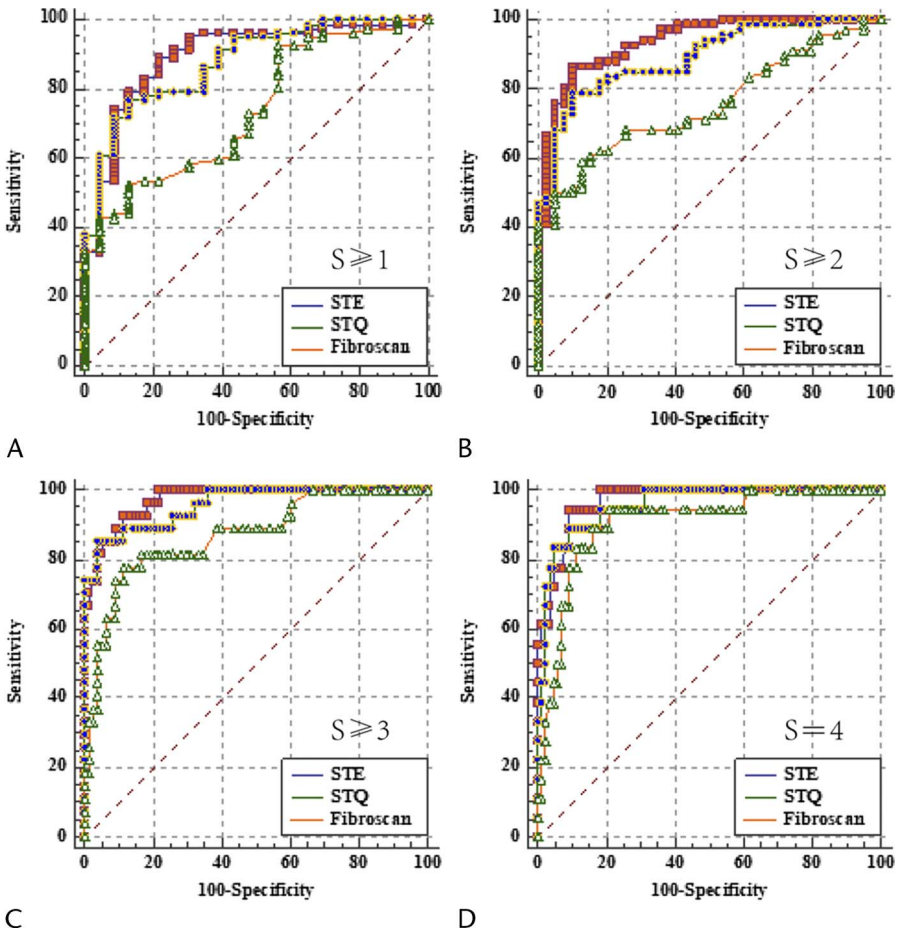

FIGURE 3. Performance of STE, STQ, and FibroScan in assessing liver fibrosis stage. Receiver operating characteristic curves of STE_{mean}, STQ_{mean}, and $FibroScan_{mean}$ in identifying S ≥ 1 (A), S ≥ 2 (B), S ≥ 3 (C), S = 4 (D) stage. Area under the curve and 95% CI: (A) 0.898 (0.823–0.948), 0.878 (0.799–0.934), 0.739 (0.644–0.820); (B) 0.936 (0.870–0.974), 0.888 (0.812–0.941), 0.753 (0.659–0.832); (C) 0.972 (0.919–0.994), 0.957 (0.898–0.987), 0.870 (0.791–0.928); (D) 0.968 (0.914–0.993), 0.955 (0.896–0.986), 0.907 (0.834–0.955).

the quantification still needs to be explored in the future study. In addition, the association of Young's modulus analysis and the degree of fatty degeneration in the liver were not identified in the present study, which deserves to be discussed in the following study. Moreover, the sample volume could be expanded in the future.

CONCLUSIONS

Shear-wave elastography (STE, STQ, and FibroScan) performs well in evaluation of liver fibrosis in patients with CHB, and the efficacies of STE and STQ are better than those of FibroScan. The mean value of STE measurements is an effective indicator in noninvasive evaluation of liver fibrosis in patients with CHB, which would be a potential guidance of treatment in clinical setting.

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