Comparison of Sound Touch Elastography, Sound Touch Quantify, and 4 Serum Fibrosis Indexes for the Diagnosis of Liver Fibrosis in Patients With Chronic Hepatitis B

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Abstract: The aim of this research was to compare the use of shear wave elastography (sound touch elastography [STE] and sound touch quantify [STQ]) and serum liver fibrosis indexes in the evaluation and staging of chronic hepatitis B (CHB) liver fibrosis. Sound touch elastography is a form of 2-dimensional shear wave elastography, and STQ is a form of point shear wave elastography. Between June 2018 and March 2019, 122 patients with CHB were assessed using STE and STQ. Serum liver biomarkers tests were undertaken, and liver biopsy was performed, and these were used to assign a pathological stage based on the Scheuer scoring system. A receiver operating characteristic curve was used to analyze the diagnostic value of noninvasive methods for evaluating and staging liver fibrosis. The cutoff values of STE for liver fibrosis stages S2 to S4 were 8.85, 9.97, and 10.29 kPa, respectively, and the areas under the receiver operating characteristic (AUCs) curve were 0.703, 0.821, and 0.900, respectively. The cutoff values of STQ for liver fibrosis stages S2 to S4 were 11.31, 13.81, and 20.60 kPa, respectively, and the AUCs were 0.674, 0.807, and 0.893, respectively. The AUCs of STE and STQ in diagnosing fibrosis stage were significantly higher than those of liver serum biomarkers ($P < 0.05$). The AUCs for the ability of the aspartate transaminase-to-platelet ratio index, the fibrosis index based on the 4 factors, the King score, and the Forns index to diagnose S2 fibrosis were 0.502, 0.624, 0.542, and 0.616, respectively, and the AUCs for their ability to diagnose S4 fibrosis were 0.856, 0.861, 0.883, and 0.823, respectively. Both STE and STQ are noninvasive methods for the assessment of liver fibrosis in CHB patients, with better diagnostic performances than those of 4 serum fibrosis indexes.

Key Words: sound touch elastography, sound touch quantify, serum indexes, chronic hepatitis B, liver stiffness

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In China, chronic hepatitis B (CHB) is the primary cause of liver-related morbidity and mortality.[1] Liver fibrosis is the main pathological feature of CHB and is an important stage in the development of cirrhosis. The prognosis and management of chronic liver disease depends largely on the stage of liver fibrosis. Liver fibrosis or early cirrhosis is reversible if CHB patients accept early or active treatment. Thus, the timely and accurate assessment of liver fibrosis is very important for CHB patients.[1,2] Currently, liver biopsy is still the "gold standard" for ascertaining the stage of liver fibrosis. However, this test has limitations, including its sampling variability and its potential to increase the probability of bleeding in patients. Therefore, liver biopsy, which is an invasive procedure, is not an ideal method for the repeated staging of liver fibrosis.[3,4]

In recent years, to overcome the limitations of liver biopsy, researchers have been trying to find noninvasive techniques for the assessment of liver fibrosis, such as elastography for detecting liver stiffness (LS), and the use of serum liver biomarkers.[4] Serum indexes such as the aspartate transaminase-to-platelet ratio index (APRI),[5] the fibrosis index based on 4 factors (FIB-4),[6] the King score,[7] and the Forns index[8] are noninvasive methods for the evaluation and staging of liver fibrosis. However, studies on serum biomarkers have been more common in patients with chronic hepatitis C than CHB, and the effectiveness of biomarkers in the evaluation of fibrosis in CHB remains controversial.[1,9,10]

A main feature of liver fibrosis is the abnormal increase in the extracellular matrix produced by liver fibroblast-like cells, resulting in increased LS.[11] Ultrasound elastography is a noninvasive technique in which tissue elasticity or stiffness is measured to determine the stage of liver fibrosis.[12–14] Shear wave elastography technology has advanced rapidly. Two-dimensional shear wave elastography and point shear wave elastography both induce a shear wave based on an acoustic radiation force impulse, and Young modulus is calculated according to the speed of the shear wave, which is reflective of LS.[14–16] Sound touch elastography (STE) and sound touch quantify (STQ) are both relatively new tests with the advantage of producing faster images using unique scanning technology. Both STE and STQ use ultrawide beam tracking detection technology to detect the propagation of shear waves in the region of interest (ROI) with ultrafast focus. The speed of shear wave at each position in the ROI is calculated in real time, and then the elastic parameter distribution image for STE, or the elastic parameter statistical result for STQ, in the ROI is obtained.[14] Both STE and STQ are forms of shear wave elastography technology; the difference between them is that STQ measures the Young modulus of tissue more simply, whereas STE can display an intuitive color-coded elastic image and can accurately quantify the tissue stiffness in the ROI.[14,17] In our study, both technologies were installed in the Mindray

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Resona 7 ultrasound system (Mindray, Shenzhen, China). Liver stiffness measurements (LSMs) were performed under the guidance of 2-dimensional grayscale images. In China, the main cause of chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma is the hepatitis B virus, and accurate staging of fibrosis in these patients is important.[3,17]

So far, few studies have compared STE and STQ for the staging of liver fibrosis in CHB patients,[17] and these tests have never been compared with serum biomarkers before. In this prospective study, we investigated the value of STE and STQ in the assessment of liver fibrosis stage in patients with CHB and compared these tests with 4 serum fibrosis indexes.

MATERIALS AND METHODS

Patients

During the period from June 2018 to March 2019, 122 patients with CHB in our hospital were prospectively enrolled in this study (90 men, 32 women; mean age, 34.62 ± 7.85 years; range, 20–58 years). All patients successfully underwent STE and STQ measurements, and LS values were obtained for each. Serum biochemical tests were undertaken on the day of elastography examination, including platelet count (PLT), alanine aminotransferase (ALT), albumin, α-fetoprotein levels, aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), cholesterol, indirect bilirubin, direct bilirubin, total bilirubin, international normalized ratio (INR), and hepatitis B virus DNA. The inclusion criteria for this study were as follows: (1) Chinese citizens 18 years or older and (2) HBsAg positive for more than half a year, without any antiviral treatment. The exclusion criteria were as follows: (1) non-CHB liver disease, (2) malignant space-occupying lesions of the liver, (3) patient after liver transplantation, and (4) pregnant women. The ethics committee of our hospital approved this study, and all patients signed an informed consent form.

LS Measurement

Resona 7 (Mindray) ultrasound diagnostic equipment with a convex array probe (SC6-1U, 1–6 MHz) positioned in the right lobe of the liver was used for LSMs. The ROI (diameter, 2 cm) was placed within the STE sampling box and the STQ sampling box, which had sizes of 4 × 3 and 1.5 × 1.0 cm, respectively. The patients fasted for at least 6 hours before examination. The patient was placed in the supine position for examination, and their right arms were raised above the head to obtain optimal intercostal access. First, a conventional B-mode ultrasound image was obtained, followed by STE and STQ imaging. The sampling box was placed under the liver capsule, within 1 to 2 cm of the right hepatic lobe (segments 5 or 6), avoiding bile ducts and vessels, and patients were asked to hold their breath for 3 to 5 seconds while the examination was being performed. Liver stiffness values were measured when the images were stabilized, and the mean LSM in the ROI was obtained, expressed in Young modulus (Fig. 1). Obtaining 5 such LSMs, with a success rate of ≥60% and a reliability index of more than 95% for each measurement, was considered successful.[1,3]

Ultrasound-Guided Liver Biopsy and Histopathology

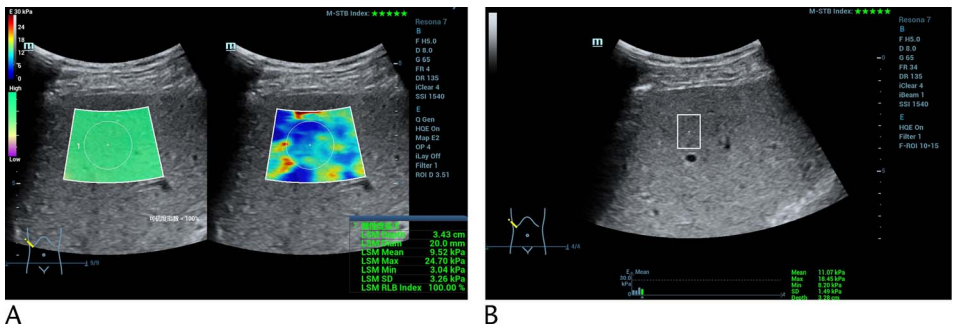
All patients underwent ultrasound-guided liver biopsy (16-gauge needle, suction technique) from the right hepatic lobe on the day after elastography examination. The requirements for each puncture specimen were the inclusion of more than 6 portal tracts and a sample length of greater than 10 mm. The degree of liver fibrosis and inflammation were grouped using the Scheuer scoring system.[18,19]

Serum Liver Fibrosis Indexes

On the same day as the STE and STQ measurements, blood parameters were obtained from all patients after at least 8 hours of fasting. Four serum fibrosis indexes were selected for this study, their calculation methods are as follows: (1) APRI = [(AST/ULN) × 100]/PLT (10^9/L), the upper limit of normal (ULN) was considered to be 40 IU/L in this study; (2) FIB-4 = Age (years) × AST]/[PLT (10^9/L) × $ALT^{1/2}$]; (3) King score = Age (years) × AST × INR/PLT (10^9/L); and (4) Forns index = 7.811–3.131 × ln[PLT (10^9/L)] + 0.781 × ln [GGT] + 3.467 × ln[Age (years)] − 0.014 × cholesterol (mg/dL), in this study, the unit of cholesterol is mmol/L, and the calculation method is 1 mg/dL = 1 mmol/L × 38.67.[20]

Statistical Analysis

SPSS software (version 22.0; SPSS, Chicago, Illinois) was used for the analysis of all results. Variable normality



A B

FIGURE 1. Shear wave elastography (STE, STQ) measurements (2-dimensional grayscale images were obtained) of the right liver lobe of the same patient with CHB-induced liver fibrosis stage S1. The mean LSMs as calculated by STE and STQ were 9.52 ± 3.26 kPa (A) and 11.07 ± 1.49 kPa (B), respectively.

analysis was undertaken using the Shapiro-Wilk test. The *t* test or Mann-Whitney *U* test was used to compare quantitative variables. Liver stiffness values for each liver fibrosis stage were compared using the 1-way analysis of variance analysis. The Spearman correlation test was used to analyze the correlation between noninvasive testing methods and pathological fibrosis stages. A univariate analysis of the factors affecting LS as measured via STE and STQ was undertaken. Receiver operator characteristic curves were used to measure the diagnostic performance of the noninvasive methods, and the Delong test was used to compare the areas under the curves (AUCs). The cutoff values for substantial fibrosis (S2), severe fibrosis (S3), and cirrhosis (S4) were defined according to the highest Youden index. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated for diagnostic testing. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

The baseline characteristics of the 122 patients with CHB enrolled in this study are shown in Table 1. The success rate of the STE and STQ measurements was 100%. Compared with women, men had significantly higher LSM values as measured by STE, ALT, and GGT, and patient age was significantly lower for the men in the study. There were no statistically significant differences in body mass index (BMI), AST, platelet count, cholesterol, INR, and LSM values on STQ between men and women (all, $P > 0.05$).

Spearman Correlation Between Noninvasive Methods and Stages of Liver Fibrosis

The correlation coefficients between STE and STQ values and the stages of liver fibrosis were 0.619 and 0.579, respectively (all, $P < 0.001$), which were higher than those of the 4 serum fibrosis indexes. Box plot diagrams showed that as the liver fibrosis stage increased, the LS values as measured by STE and STQ also increased, and LSM values measured by STQ were higher than those measured by STE at each stage of fibrosis (Fig. 2). However, the correlation coefficients between the 4 serum fibrosis indexes and fibrosis stage were lower than 0.5.

When comparing between the stages of liver fibrosis, there were significant differences in LSM values as measured by STE versus STQ ($F = 13.354$, 21.303, respectively; all, $P < 0.001$), and the difference in age was not statistically significant ($F = 0.268$, $P > 0.05$; Table 2).

Factors Affecting LSMs on STE and STQ

With univariate analysis, factors such as fibrosis stage, inflammation grade, age, BMI, AST, ALT, GGT, INR, and platelet count were shown to correlate with LSM ($P < 0.05$). It was then shown via multivariate analysis that fibrosis stage was the only factor affecting the LSM on STE and STQ ($P < 0.05$).

Performances of STE, STQ, and 4 Serum Fibrosis Indexes in the Evaluation and Staging of Fibrosis

Receiver operating characteristic curve analysis showed the AUCs for STE, STQ, and the 4 serum fibrosis indexes in ascertaining the stage of liver fibrosis (Table 3, Fig. 3). The AUCs of STE in patients with stage S2–S4 fibrosis were 0.703, 0.821,

TABLE 1. Characteristics of 122 Patients With CHB

	All Patients (n = 122)	Men (n = 90)	Women (n = 32)	*P*
Age, y	34.62 ± 7.85	33.56 ± 7.58	37.59 ± 7.97	0.015
BMI, kg/m^2	23.47 ± 4.72	23.36 ± 4.24	23.81 ± 6.11	0.542
Laboratory tests				
ALT, IU/L	168.32 ± 176.36	182.46 ± 167.65	125.20 ± 199.02	0.007
AST, IU/L	91.95 ± 109.52	93.56 ± 109.27	86.80 ± 113.01	0.446
GGT, IU/L	75.44 ± 114.17	85.84 ± 129.77	45.25 ± 31.86	0.010
Platelet count, 10^9/L	205.76 ± 62.47	203.31 ± 63.76	214.16 ± 54.66	0.128
Cholesterol, mg/dL	174.79 ± 38.67	177.11 ± 42.92	167.05 ± 21.66	0.731
INR	1.01 ± 0.07	1.01 ± 0.08	1.00 ± 0.05	0.622
LSMs, kPa				
STE measurements	10.53 ± 3.49	10.77 ± 3.19	9.74 ± 4.30	0.019
STQ measurements	12.53 ± 4.68	12.65 ± 4.51	12.17 ± 5.28	0.488
Scheuer fibrosis stage				
S0–1	66 (54.10%)	48 (72.73%)	18 (27.27%)	
S2	21 (17.21%)	18 (85.71%)	3 (14.29%)	
S3	20 (16.39%)	15 (75.00%)	5 (25.00%)	
S4	15 (12.30%)	9 (60.00%)	6 (40.00%)	
Scheuer inflammation grade				
G1	17 (13.93%)	12 (70.59%)	5 (29.41%)	
G2	60 (49.18%)	43 (71.67%)	17 (23.33%)	
G3	30 (24.59%)	22 (73.33%)	8 (26.67%)	
G4	15 (12.30%)	11 (73.33%)	4 (26.67%)	

Data are mean ± SD or number of patients.

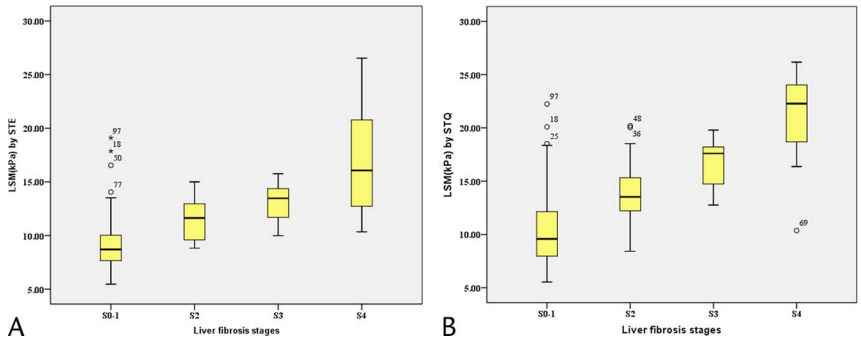


FIGURE 2. Box plot showing LSMs by shear wave elastography and fibrosis stages using the Scheuer scoring system based on liver biopsy. Box plots for STE (A) and STQ (B) at each fibrosis stage show the interquartile range (central box), median (thick lines), and range (thin lines) of LS. * and 0 indicate outliers.

and 0.900, respectively, and the corresponding cutoff values were 8.85 kPa (sensitivity, 75.2%; specificity, 75.7%), 9.97 kPa (sensitivity, 90.0%; specificity, 79.6%), and 10.29 kPa (sensitivity, 80.0%; specificity, 87.4%), respectively. The AUCs for STQ in patients with stage S2–S4 fibrosis were 0.674, 0.807, and 0.893, respectively, and the corresponding cutoff values were 11.31 kPa (sensitivity, 81.0%; specificity, 60.5%), 13.81 kPa (sensitivity, 87.5%; specificity, 72.3%), and 20.60 kPa (sensitivity, 71.4%; specificity, 88.9%), respectively.

The AUCs for STE and STQ in diagnosing stages S2 and S4 fibrosis were significantly greater than those of the liver fibrosis indexes for the same stages ($P < 0.05$). The AUCs for the APRI, FIB-4, King score, and Forns index were 0.502, 0.624, 0.542, and 0.616, respectively, for stage S2 fibrosis. The AUCs for the same tests were 0.856, 0.861, 0.883, and 0.823, respectively, for stage S4 fibrosis.

DISCUSSION

In this study, we evaluated the performance of 2 techniques (STE and STQ) for the noninvasive diagnosis of liver fibrosis. We then compared the performances of these techniques with those of 4 serum fibrosis indexes. To the best of our knowledge, this is the first study that compares 3 noninvasive methods (STE, STQ, and serum biomarkers) in terms of their ability to ascertain the stage of liver fibrosis. In recent years, ultrasound elastography technology for the evaluation of liver fibrosis has developed rapidly, with the advantage of being a noninvasive, real-time, and easy procedure. Elastography can provide new information on LS parameters and is a new way in which ultrasound can be used for diagnostic purposes.[3,12,13] Transient elastography is widely used in the diagnosis of liver fibrosis, but the success rate of the LSMs was more easily affected by some patient factors, such as obesity or ascites.[17,21–23] In our study, STE and STQ were applied in the evaluation of liver fibrosis in 122 patients with CHB. The success rate of LSMs made by STE and STQ was 100%, which is consistent with that reported by a previous study.[17]

TABLE 2. LSMs by STE and STQ in Different Liver Fibrosis Stages in Patients With CHB

Fibrosis Stage	Age, y	STE, kPa	STQ, kPa
S0–1	33.95 ± 7.65	9.22 ± 2.56	10.68 ± 3.70
S2	34.67 ± 7.62	11.46 ± 2.02	14.07 ± 3.34
S3	35.75 ± 8.86	13.10 ± 2.03	16.71 ± 2.40
S4	36.14 ± 10.30	17.14 ± 5.85	20.61 ± 5.53
F	0.268	13.354	21.303
P	0.848	<0.001	<0.001

Data are mean ± SD.

In our study, as liver fibrosis stage increased, LS values on STE and STQ measurement also increased. Higher LS values therefore indicated a higher liver fibrosis stage.[15,17,24] The Spearman correlation test showed that the correlation coefficient between STE values and the stage of liver fibrosis was 0.619 ($P < 0.001$). The same was true of STQ values ($r = 0.579$, $P < 0.001$). Xia et al[17] also showed that the correlation coefficients between the mean LS values on STE and STQ and liver fibrosis stage were 0.852, and 0.803, respectively, suggesting that STE and STQ LS values were highly consistent with liver fibrosis stage. However, the relationship between serum liver fibrosis indexes and liver fibrosis stage was limited, with a correlation coefficient of less than 0.5. Zhuang et al[19] and Liu et al[20] also showed that the correlation between serum biomarkers and histological fibrosis stage was lower than that of 2-dimensional shear wave elastography.

In this study, using liver biopsy as the standard test for liver fibrosis, we found that the AUCs of STE and STQ in diagnosing stages S2, S3, and S4 of liver fibrosis were greater than 0.67, 0.80, and 0.89, respectively. The diagnostic performances of STE and STQ were both significantly better than those of serum biomarkers. However, the AUCs of STE and STQ were lower in our study than in a previous study.[17] In the previous study, the AUCs of STE and STQ were greater than 0.88, 0.95, and 0.95 for the diagnosis of fibrosis stages S2, S3, and S4, respectively, which may be due to differences in the research populations.[17] In our study, the distribution of the pathological staging of liver fibrosis in CHB patients was unbalanced, which may have led to selection bias. We also analyzed the performance of 4 serum indexes in diagnosing severe fibrosis (S2) and cirrhosis (S4). For these, the AUCs of the serum indexes were lower than those of STE and STQ. Most previous studies have found that serum biomarkers were not effective in evaluating liver fibrosis, possibly due to the influence of factors that were unrelated to the liver or the diagnostic value of the biomarkers.[1,19,20]

TABLE 3. Predictive Values of Noninvasive Methods in Diagnosing Different Liver Fibrosis Stages

	AUROC	Cutoff, kPa	Se, %	Sp, %	PPV, %	NPV, %
STE						
≥S2	0.703 (0.602–0.804)	8.85	75.2	75.7	77.5	78.3
≥S3	0.821 (0.723–0.919)	9.97	90.0	79.6	81.2	76.4
S4	0.900 (0.801–0.999)	10.29	80.0	87.4	85.1	77.9
STQ						
≥S2	0.674 (0.567–0.781)	11.31	81.0	60.5	81.1	78.4
≥S3	0.807 (0.715–0.899)	13.81	87.5	72.3	67.4	75.4
S4	0.893 (0.749–1.000)	20.60	71.4	88.9	88.7	67.5
APRI						
≥S2	0.502 (0.348–0.657)		52.4	69.1	45.6	76.8
S4	0.856 (0.732–0.981)		71.4	92.6	65.1	55.7
FIB-4						
≥S2	0.624 (0.484–0.764)		81.0	46.9	66.8	84.9
S4	0.861 (0.664–1.000)		85.7	89.5	76.4	74.2
King score						
≥S2	0.542 (0.383–0.702)		57.1	70.4	50.2	65.7
S4	0.883 (0.741–1.000)		85.7	92.6	76.8	77.8
Forns index						
≥S2	0.616 (0.486–0.746)		81.0	56.8	66.6	77.2
S4	0.823 (0.651–0.996)		85.7	74.7	76.8	77.3

Date in parentheses are 95% confidence intervals.

AUROC, area under the receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

We also analyzed factors related to the measurement of LS by STE and STQ, such as fibrosis stage, inflammation grade, age, BMI, AST, ALT, GGT, INR, and platelet count. Our results showed that liver fibrosis stage was the only factor that correlated with LSMs ($P < 0.05$), a result that was consistent with that of a previous study.[20] However, the results of the study by Jia et al[1] showed that inflammation activity was an independent factor affecting LSMs, regardless of fibrosis stage. The reason for this difference might be that inflammation activity was graded according to the METAVIR scoring system by Jia et al, whereas the Scheuer scoring system was used in our study.

Our study encountered certain limitations. The effect that hepatic steatosis may have on LSMs was not considered in our study, and the relationship between hepatic steatosis and LSMs was not assessed. However, the results of previous studies have shown that hepatic steatosis has little or no effect on LSMs.[1,25–27] However, this still needs to be explored in future studies. Furthermore, the sample size in our study was limited, and a larger sample size should be included in future studies.

CONCLUSIONS

Sound touch elastography and STQ are 2 new noninvasive techniques for the staging of liver fibrosis. The diagnostic performance of these new techniques was found to be superior to 4 serum liver fibrosis indexes, especially for the diagnosis of severe fibrosis (S2) and cirrhosis (S4). Of the 2 elastography techniques studied, STE was more effective than STQ for the evaluation of the stage of liver fibrosis in patients with CHB.

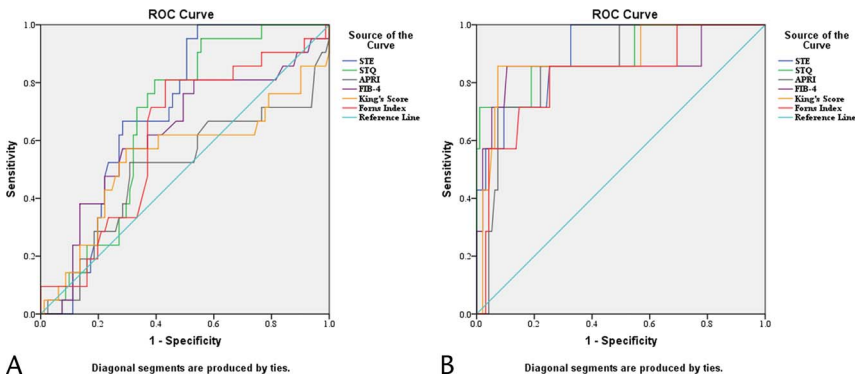


FIGURE 3. Receiver operating characteristic curves for noninvasive methods for diagnosing of substantial fibrosis (A) and cirrhosis (B) in patients with CHB.

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