Diagnostic Performance of Shear Wave Elastography in the Noninvasive Evaluation of Liver Inflammation of Chronic Hepatitis B Patients

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Abstract: In the current study, we sought to delineate the elastographic characteristics and further compare the diagnostic performance of various shear wave elastography modalities in hepatitis B virus patients whose liver fibrosis stage was less than F2 by liver biopsy. We retrospectively studied the clinical and imaging data of chronic hepatitis B virus patients who underwent liver biopsy at our hospital between January 2017 and October 2017. Totally, 102 patients were eligible for the study. The mean Young modulus of sound touch elastography (STE) and sound touch quantify (STQ) gradually increased as inflammation grade of the liver rose from G0 to G3. Spearman rank correlation analysis revealed that the mean Young modulus of STE and STQ significantly correlated with hepatic inflammation grade ($r = 0.341$, $P < 0.05$). The area under the receiver operating characteristic curve (AUC) was the highest for the mean Young modulus of STE (AUC = 0.740; $P = 0.015$) followed by that of STQ (AUC = 0.684; $P = 0.063$) for G ≥ 2 hepatic inflammation and the AUC was the highest for the mean Young modulus of STE (AUC = 0.920; $P = 0.000$) followed by that of STQ (AUC = 0.910; $P = 0.000$) for G ≥ 3 hepatic inflammation. The current study demonstrated that the mean Young modulus of STE and STQ could serve as a useful diagnostic marker for hepatic inflammation of hepatitis B virus patients with no apparent liver fibrosis.

Key Words: diagnosis, shear wave elastography, noninvasive evaluation, inflammation, chronic hepatitis B

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Despite the availability of a national immunization program since 1992, there are still 78 million chronic hepatitis B virus (HBV) carriers in China.[1] Furthermore, a minority of HBV hepatitis patients, even though using the best available antiviral therapy, experience repeated episodes of or sustained hepatic injury, including hepatic inflammation, that results in liver necrosis, growth of fibrous tissues, and nodular regeneration, eventually leading to changes in liver tissue stiffness.[2,3]

Shear wave elastography (SWE) offers a simple, reliable and noninvasive diagnostic modality for quantitative measurements of tissue elasticity and allows valuable assessment of intrinsic tissue properties, which is of particular value in diagnosing early inflammation, fibrosis and cirrhosis of the liver when no abnormality can be depicted at conventional B-mode ultrasonography, color Doppler, and plain computed tomography (CT) and magnetic resonance imaging (MRI).[4] Shear waves are generated using focused acoustic radiation force from a linear ultrasound array and propagate through the adjacent tissues in the transverse plane, causing shear displacements in tissue. Tissue displacement and shear wave velocities are tracked *via* fast plane wave excitation as the shear waves propagate. The velocity of these waves is related to liver tissue stiffness and can be measured as the hepatic Young modulus, expressed in kilopascals (kPa). Stiff tissues exhibit higher shear wave velocities than soft tissues. The more magnificent Young modulus is, the higher the tissue stiffness is, and the more likely tissues have morphological changes.[5] In transient elastography, due to lack of gray level ultrasound image guidance, the probe cannot avoid large vessels, bile ducts, and intrahepatic mass when exploring hepatic parenchyma. Failure of exploration also occurs in obese persons, patients with lung emphysema, ascites due to hepatic cirrhosis, and patients with a shrunken liver.[6] The Re 7 SWE (sound touch elastography [STE] and sound touch quantify [STQ]) technique can make multiple measurements of SWE images guided by ultrasonic time-motion gray-level images, and the box size of the region of interest (ROI) is adjustable. Besides, the SWE technique has an adequate ROI, thus reducing

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Availability of data and material: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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sampling bias; it can also make multiple measurements continuously while the patient holds breath, significantly increasing reliability and ease of measurement. In the current study, using the Re 7 SWE technique, we sought to delineate the elastographic characteristics and further compare the diagnostic performance of various SWE modalities in HBV patients whose liver fibrosis stage was less than F2 by liver biopsy.

PATIENTS AND METHODS

Patients

We retrospectively enrolled chronic HBV patients who underwent liver biopsy at our hospital between January 2017 and October 2017. A patient was excluded (1) if he or she had other liver diseases, such as drug-induced liver injury, alcohol-induced liver disease, autoimmune hepatitis, or infections with other hepatitis viruses, cytomegalovirus, or herpes simplex virus; (2) if his or her alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) increased more than 5 times the upper normal limit; (3) if a patient had a liver fibrosis stage ≥2 by liver biopsy; (4) if a patient had obvious heart, brain, or kidney disease, or diabetes; (5) if a patient had moderate to severe fatty liver on conventional ultrasound [echo attenuation of liver parenchyma (far field) on B-mode ultrasound.

Elastography

The Re7 ultrasound system (Mindray, China) was used SC5-1probe and the FibroScan 502 system (Echosens, France) equipped with an elastographic function was used for measuring Young modulus with M probe. The procedures were performed as described previously.[6]

The patient was fast for at least 2 hours before SWE and placed in the supine position. The intercostal space was fully exposed with the right arm in maximal abduction. The probe was placed on the skin between the ribs, and the direction of the probe was parallel to the intercostal space; measurement depth was 3 to 7 cm below the skin surface. Hepatic parenchyma, free of abundant vasculature and biliary ducts, of segment 5 or 6 of the right hepatic lobe was chosen for measurement. One ultrasonographer (X.R.) who had at least 13 years of experience in abdominal ultrasonography and performed more than 500 STE scans first carried out B-mode ultrasound measurement of the width of the central portal vein and the splenic vein, and the maximum diameter and thickness of the spleen. The ultrasonographer was blinded to patient data.

When 2D ultrasound images became apparent, the patient was asked to hold calm breath and examined under the SWE mode. Stable images with color filling in more than 90% of the frame were chosen, and the quality control mode (RLB Map added) was adopted (Fig. 1). Images with homogeneous green color filling RLB index >95% were considered successful. A circle with a diameter of 20 mm in the frame was chosen for quantification, and satisfactory images were acquired, measured, and stored. The mean of 5 measurements were considered valid with an interquartile range/median (IQR/M) <30%

The patient was further examined under the STQ mode while holding breath. A region of interest (ROI) with a box size of 20x15 mm was defined. Totally 10 measurements were made, and 5 consecutive measurements were averaged, and those with SD <2.0 were chosen and reported. The mean, maximum, and minimum of STE and STQ were determined. FibroScan was performed by an operator (BS) with more than 5 years of experience. Ten measurements were made in each patient and averaged. Only measurements with a success rate of ≥60% and an IQR/M <30% were considered valid. FibroScan values were recorded as FibroScan (kPa).

For reproducibility, a second ultrasonographer (ZN) with 2 years of experience in abdominal ultrasonography

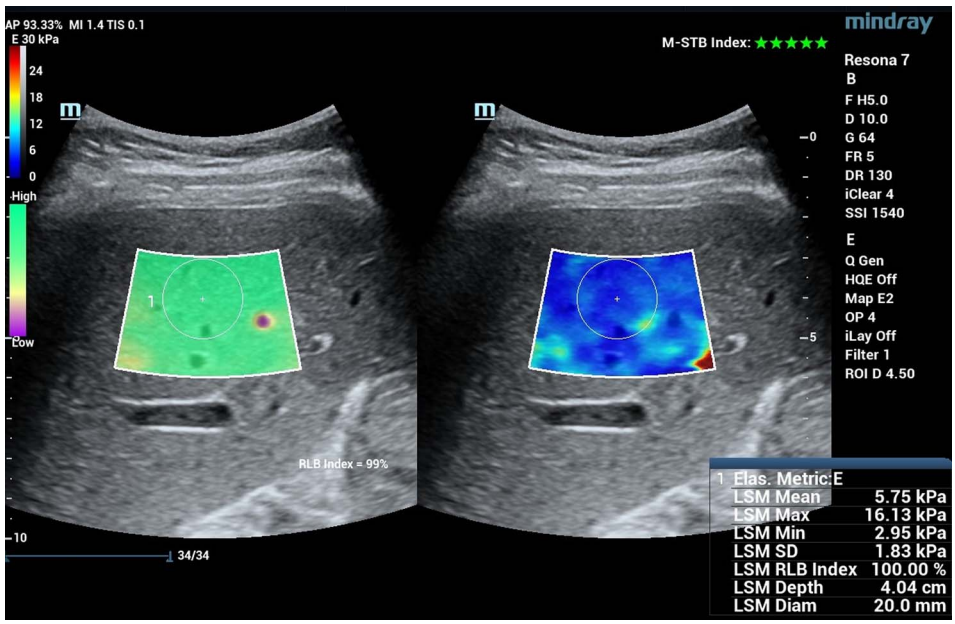

FIGURE 1. Stable images with color filling in more than 90% of the frame are chosen, and the quality control mode (RLB Map added) is adopted. Images with homogeneous green color filling RLB index >95% are considered successful.

performed the same procedures in 45 patients randomly chosen from the cohort.

Histopathologic Evaluation

Percutaneous liver biopsy was undertaken following SWE using Bard Reusable Core Biopsy System with a Bard Magnum Disposable Biopsy Core Needle(16 gauge, MN 1620). Biopsy specimens that were at least 1.5 cm in length and had a minimum of 10 intact portal tracts were eligible for evaluation. Tissue specimens were fixed in 10% neutral formaldehyde and sectioned following continuous paraffin embedding. Routine H&E and Masson staining were performed. Liver inflammation and fibrosis were determined according to Scheuer classification scheme[7] by 2 experienced pathologists (H.W. and J.X.) who were blinded to patient data and the results of SWE. G0 indicates no inflammation; G1, mild inflammation; G2, moderate inflammation; G3, moderate-to-severe inflammation; G4, severe inflammation. F0 represents no fibrosis; F1, portal fibrosis without septa; F2, star-shaped portal fibrosis, with minimal septa; F3, portal fibrosis with numerous septa, but no pseudo lobe formation; F4, portal fibrosis with numerous septa and pseudo lobe formation.

Statistical Analysis

Normally distributed data were expressed in mean ± standard deviations, and non-normally distributed data were expressed in median (IQR). Mean STE, STQ and FibroScan were compared using the DeLong method with the MedCalc software MedCalc Software Ltd (Ostend, Belgium). Correlation between variables was analyzed using Spearman rank correlation ($r < 0.4$ suggested a low correlation, $0.4\ r < 0.7$ indicated moderate correlation and $0.7\ r < 1$ represented high correlation). The intraclass correlation coefficient (ICC) was used for determining agreement among continuous variables. Agreement was classified as poor (ICC, 0.00–0.40), fair to good (ICC, 0.40–0.75), or excellent (ICC, > 0.75).

A receiver operating characteristic (ROC) curve was calculated, and the area under the ROC curve (AUC) was used to evaluate test accuracy, and the discrimination value was determined by Youden Index (sensitivity + specificity − 1). The diagnostic threshold was determined using the highest threshold of Youden index, and sensitivity and specificity were computed using this threshold.

All of the statistical tests were 2-sided, and a P value of 0.05 or less was considered statistically significant. All data analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Patient Demographics and Baseline Variables

The study flowchart is shown in Figure 2. A total of 387 chronic HBV patients underwent liver biopsy at our hospital during the study period. One hundred two patients were eligible for the study, including 69 men and 33 women, and their mean age 42.23 ± 10.24 years. Ten (9.8%) patients had no inflammation of the liver (G0), and 24 (23.5%) had mild inflammation (G1). Furthermore, moderate inflammation (G2) was present in 57 (55.9%) patients and moderate-to-severe inflammation (G3) in 11 (10.8%) patients. No patient had severe inflammation (G4) of the liver. Patients who had a liver fibrosis stage of 2 or greater were excluded from the study.

Operator Characteristics

The success rate of liver stiffness measurement by transient elastography, point SWE, and STE was 98.04%, 100%, and 100%, respectively. There was no statistically significant difference in all the elastographic parameters by the 2 ultrasonographers ($P > 0.05$). Furthermore, the ICC of the 2 operators was excellent for both STE (0.945; 95% confidence interval [CI], 0.90–0.96) and STQ (0.903; 95% CI, 0.86–0.93) ($P > 0.05$). Besides, there was no statistically significant difference in inflammation grades rated by the 2 pathologists ($P > 0.05$).

Hepatic Elastographic Characteristics and Hepatic Inflammation Grade

A statistical difference was observed between mean STE and FibroScan ($P = 0.0315$), but there was no statistical difference between mean STE and STQ ($P = 0.7934$) and between mean STQ and FibroScan ($P = 0.1082$).

The mean Young modulus of STE gradually increased as inflammation grade of the liver rose from G0 to G3 (Table 1). The mean Young modulus of STE for G3 was 13.4% higher than that for G0. Consistently, the mean Young modulus of STQ steadily increased with increasing severity of hepatic inflammation. The mean Young modulus of STQ for G3 was 33.9% higher than that for G0. Moreover, the mean Young modulus of FibroScan rose progressively as hepatic inflammation increased from G0 to G3. The mean Young modulus of FibroScan for G3 was 57.7% higher than that for G0.

Our Spearman rank correlation analysis revealed that the mean Young modulus of STE significantly correlated with hepatic inflammation grade ($r = 0.341$, $P < 0.05$) (Table 2). In addition, FibroScan showed significant correlation with inflammation grade of the liver ($r = 0.305$, $P < 0.05$). The minimum Young modulus of STE and STQ also showed significant correlation with the width of the splenic vein ($r = 0.380$ and 0.305, respectively; $P < 0.05$ in both). No other correlation was demonstrated.

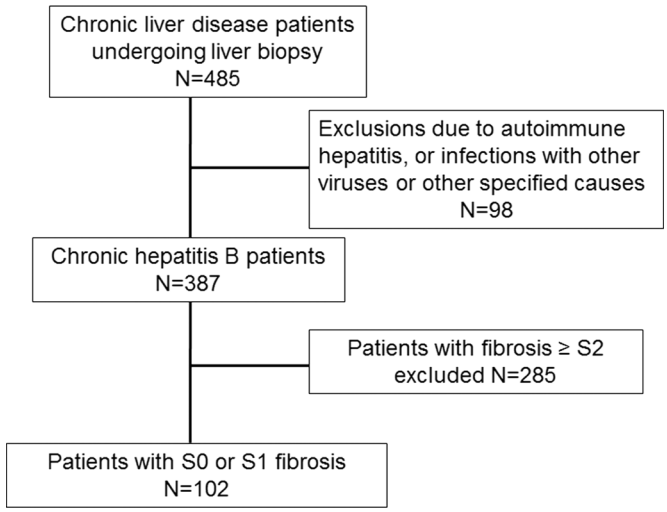

FIGURE 2. The study flowchart.

TABLE 1. Young Modulus (kPa) and Liver Inflammation Grades of the Study Patients

Grade*	G0, n = 10	G1, n = 24	G2, n = 57	G3, n = 11
STE				
Mean	6.18 ± 0.75	6.24 ± 0.97	6.62 ± 0.51	7.01 ± 0.98
Maximum	11.64 ± 2.46	12.86 ± 4.43	12.54 ± 3.99	12.69 ± 2.46
Minimum	2.73 ± 0.91	3.00 ± 0.79	3.31 ± 0.95	3.56 ± 0.96
STQ				
Mean	6.70 ± 1.05	6.91 ± 0.30	7.15 ± 1.14	8.97 ± 1.21
Maximum	16.12 ± 5.56	16.31 ± 7.20	19.64 ± 7.80	20.85 ± 3.46
Minimum	2.36 ± 0.81	3.31 ± 0.83	3.46 ± 1.20	3.75 ± 0.98
FibroScan	5.56 ± 2.01	7.82 ± 4.31	8.11 ± 3.02	8.77 ± 2.01

*Liver inflammation and fibrosis was determined according to Scheuer classification scheme (7).

G0, no inflammation; G1 mild inflammation; G2 moderate inflammation; G3 moderate-to-severe inflammation; G4 severe inflammation.

Diagnostic Performance of Elastographic Parameters in Assessing Hepatic Inflammation

We evaluated the diagnostic performance of elastographic parameters in evaluating hepatic evaluation. We found that, for patients with G ≥ 2 hepatic inflammation, the mean Young modulus of STE and FibroScan had the highest sensitivity (91.7% for both) (Table 3 and Fig. 3). Meanwhile, the maximum Young modulus of STQ had the highest specificity (91.2%), followed by the minimum Young modulus of STQ (75.0%). The AUC was the highest for the mean Young modulus of STE (AUC = 0.740; $P = 0.015$) followed by the mean Young modulus of STQ (AUC = 0.684; $P = 0.063$).

We then evaluated the diagnostic performance of elastographic parameters in patients with G ≥ 3 hepatic inflammation. The mean Young modulus of STE and STQ had the highest sensitivity (100% for both) (Table 4 and Fig. 4). Meanwhile, the maximum Young modulus of STQ had the highest specificity (86.1%) followed by the mean and minimum Young modulus of STE (80.6% for both). The AUC was the highest for the mean Young modulus of STE (AUC = 0.920; $P = 0.000$) followed by the mean Yong modulus of STQ (AUC = 0.910; $P = 0.000$).

DISCUSSION

Though the diagnostic performance of transient elastography and SWE has been well validated for liver fibrosis, the effect of hepatic inflammation on liver tissue stiffness has not been evaluated independently of liver fibrosis. In the current study, we investigated the elastographic characteristics of HBV patients who had no or mild (F1) fibrosis, thus removing the effect of obvious liver fibrosis on liver tissue stiffness and allowing assessment of the effect of hepatic inflammation on liver tissue stiffness. We showed that liver tissue stiffness on STE, STQ, and transient elastography increased as the severity of hepatic inflammation increased, and liver tissue stiffness on STE and transient elastography significantly correlated with hepatic inflammation grade.

Hepatitis B virus causes injury against hepatocytes by inducing host immune response and via inflammation, resulting in the deposition of collagen and other extracellular matrix components. The protracted and progressive course of HBV-associated liver disease manifests as changes in liver tissue morphology and stiffness. In chronic hepatitis patients, liver inflammation and hepatic fibrosis are frequently present simultaneously. Overt inflammation may worsen liver fibrosis and even lead to hepatic cirrhosis. In chronic HBV patients, in the absence of apparent hepatic fibrosis, if a liver biopsy shows hepatic inflammation grade ≥2, prompt antiviral therapy should be instituted at this reversible stage to improve the clinical outcome of chronic hepatitis.[8] Currently, hepatic inflammation is assessed clinically by serology, liver elastography, and liver tissue pathologic examination. Among them, serological changes manifest as elevations in liver transaminases and bilirubin, which are subject to influences of multiple factors and can only indirectly and nonspecifically reflect liver pathologic changes.[9,10] Liver biopsy and pathology is the gold standard for diagnosing liver inflammation, but it is invasive and subject to sampling bias. Patients are also at risk of bleeding and biliary leakage. Besides, it is expensive and has poor reproducibility.[11] Though liver fibrosis is the primary pathologic determinant of liver stiffness, liver inflammation may impact on liver tissue stiffness. However, the evidence is mostly based on studies using transient elastography with M probe.[12,13] Poynard et al[14] evaluated 1270 patients with chronic liver disease by elastography and found that inflammation had a smaller effect on liver fibrosis on SWE than transient elastography using M probe. Studies have shown a positive

TABLE 2. Correlation Coefficients Between Elastic Modulus and Other Factors

Correlation Coefficient (r)	Inflammation Grade	SPV	MPV	Sex	Age	SP1	SP2
STE							
Mean	0.341*	0.179	0.234	0.045	−0.023	0.042	0.135
Maximum	0.062	−0.122	0.228	0.261	0.037	−0.163	0.043
Minimum	0.127	0.380*	0.121	−0.180	−0.046	0.192	0.080
STQ							
Mean	0.252	0.048	0.174	0.104	0.044	−0.095	−0.077
Maximum	0.083	−0.095	0.015	0.112	0.132	−0.167	−0.142
Minimum	0.007	0.450*	0.132	−0.054	−0.019	0.221	0.293
FibroScan	0.305*	−0.098	0.110	0.176	−0.103	−0.133	0.105

*$P < 0.05$ indicates statistical difference.

MPV, width of the main portal vein; SPV, width of the splenic vein; SP1, maximum diameter of the spleen; SP2, thickness of the spleen.

TABLE 3. Diagnostic Performance of Elastographic Parameters in Patients With G ≥ 2 Hepatic Inflammation

	STE			STQ			
	Mean	**Maximum**	**Minimum**	**Mean**	**Maximum**	**Minimum**	**FibroScan**
AUC	0.740	0.586	0.592	0.684	0.505	0.590	0.594
Cutoff	6.08	11.62	3.14	7.11	20.38	3.41	4.70
Sensitivity	91.7%	66.7%	66.7%	50%	58.3%	50%	91.7%
Specificity	56.2%	59.4%	62.5%	56.2%	91.2%	75.0%	37.5%
P	0.015*	0.385	0.350	0.063	0.958	0.363	0.343

*$P < 0.05$ indicates statistical difference.

correlation between inflammation of the liver tissue and liver tissue stiffness, and inflammation grade >2 has a noticeable effect on liver tissue stiffness.[15] However, liver fibrosis and inflammation are often present simultaneously, and the relative impact of inflammation on liver tissue elasticity should be assessed independently of fibrosis severity.[16] Theoretically, when assessing the effect of inflammation on liver tissue stiffness, the effect of hepatic fibrosis should be excluded. Clinically, a proportion of chronic HBV hepatitis patients do not have prominent liver fibrosis or do not exhibit pathologic changes of hepatic cirrhosis; in such cases, if moderate to severe inflammation is present, antiviral therapy should be promptly instituted in order to disrupt the pathologic process of liver fibrosis and cirrhosis. Therefore, accurate and prompt assessment of liver inflammation in this subset of patients is of clinical significance in guiding therapy and improving the prognosis of these patients.

We showed that the mean Young modulus of STE had an AUC of 0.740 for G ≥ 2 hepatic inflammation and 0.920 for G ≥ 3 hepatic inflammation and the mean Young modulus of STQ had an AUC of 0.684 or G ≥ 2 hepatic inflammation and 0.910 for G ≥ 3 hepatic inflammation, suggesting that liver tissue stiffness on STE and STQ may provide a sensitive and specific diagnostic marker for hepatic inflammation.

The current study followed the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommendations for performing SWE and chose a circular area 2 cm in diameter and a box 20 X 15 mm in size for STE and STQ measurement. This large sampling area improves the accuracy of measurement; furthermore, STE and STQ are easy to operative and consume 3-5 seconds for single image acquisition and are applicable to patients with ascites or obese persons. We also chose segment 5 and 6 of the right hepatic lobe where the hepatic parenchyma is free of large vasculature and biliary ducts. This allows consistency of elastography free of influences from pulsations or respiration. We report a success rate of 98.04%, 100%, and 100% for transient elastography, STQ, and STE for liver tissue stiffness. Patients in our cohort were generally in good condition, and no patients had ascites or shrunken liver, or lung emphysema, which complicate the performance of elastography.

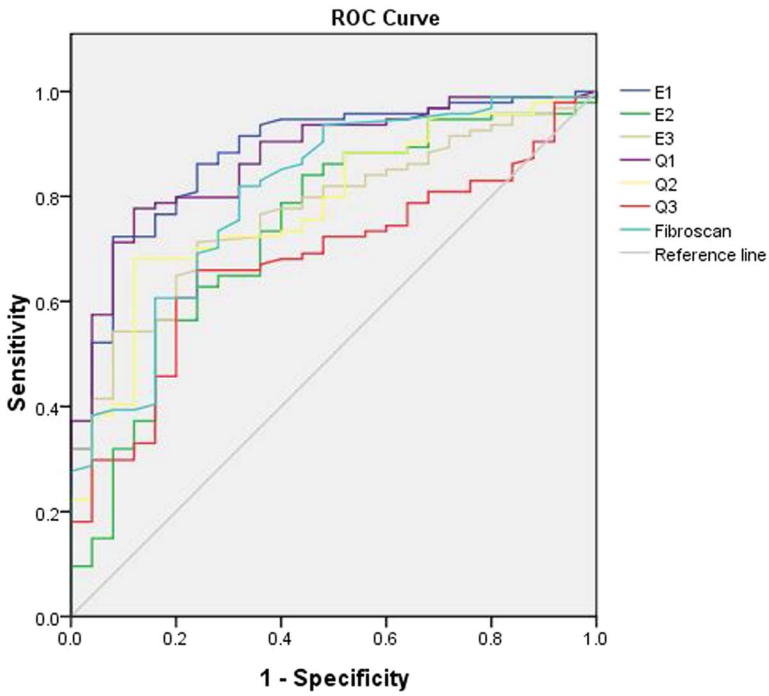

FIGURE 3. Diagnostic performance of elastographic parameters in patients with G ≥ 2 hepatic inflammation. The mean (E1), maximum (E2), and minimum (E3) of STE, and the mean (Q1), maximum (Q2), and minimum (Q3) of STQ and FibroScan are evaluated.

TABLE 4. Diagnostic Performance of Elastographic Parameters in Patients With G ≥ 3 Hepatic Inflammation

	STE			STQ			
	Mean	Maximum	Minimum	Mean	Maximum	Minimum	FibroScan
AUC	0.920	0.687	0.523	0.910	0.778	0.536	0.769
Cutoff	6.69	12.3	3.44	7.13	21.17	3.63	6.35
Sensitivity	100%	75%	37.5%	100%	62.5%	37.5%	87.5%
Specificity	80.6%	72.2%	80.6%	72.2%	86.1%	72.2%	66.7%
P	0.000*	0.100	0.843	0.000*	0.015*	0.749	0.018*

*$P < 0.05$ indicates statistical difference.

In 2 cases with failed transient elastography, the patients had thick subcutaneous tissues. The STQ and STE assisted by B-mode ultrasound images can complete the measurement by adjusting images. We also found that STQ and STE were not operator dependent with good reproducibility between different operators.

Previous studies have shown that fibrosis is the major determinant of liver tissue stiffness and inflammation is a minor determinant; however, these studies did not exclude the influence of liver fibrosis when assessing effect of inflammation on liver tissue stiffness.[16–19] This study excluded patients who had a liver fibrosis stage ≥2 by liver biopsy and only included patients with no fibrosis and F1 fibrosis, thus excluding obvious liver fibrosis as a determinant of liver tissue stiffness. Our Spearman rank correlation analysis of elastic modulus and inflammation grade of the liver revealed that the mean Young modulus of STE and FibroScan exhibited significant correlation with inflammation grade of the liver. Our findings showed that with increasing severity of inflammation of the liver, the values of elastic modulus parameters gradually increased for transient elastography, STQ, and STE, which is consistent with the pathological process of the disease and also similar to the findings by other investigators.[16–19] We found that for only the mean Young modulus of STE, STQ, and FibroScan significantly correlated with hepatic inflammation.

Furthermore, the corresponding AUC for the mean Young modulus of STE and STQ was 0.74 and 0.684, respectively. E1 has a certain degree of accuracy. The diagnostic performance of various elastic modulus parameters was in the following order: the mean Young modulus of STE > the mean Young modulus of STQ > the maximum Young modulus of STQ > FibroScan. Among them, the mean Young modulus of STE and STQ had better diagnostic performance, and the corresponding AUC was 0.920 and 0.910 while the corresponding AUC for FibroScan was only 0.769, indicating relatively limited application value of FibroScan. Therefore, the mean Young modulus of STE has excellent accuracy as a noninvasive diagnostic modality for liver tissue stiffness in HBV patients with apparent hepatic inflammation (G = 2 and G = 3). The mean Young modulus of STE and STQ have high accuracy for HBV patients with more severe hepatic inflammation (G = 3), which could provide practical guidance for assessing whether antiviral therapy has reduced the grade of hepatic inflammation.

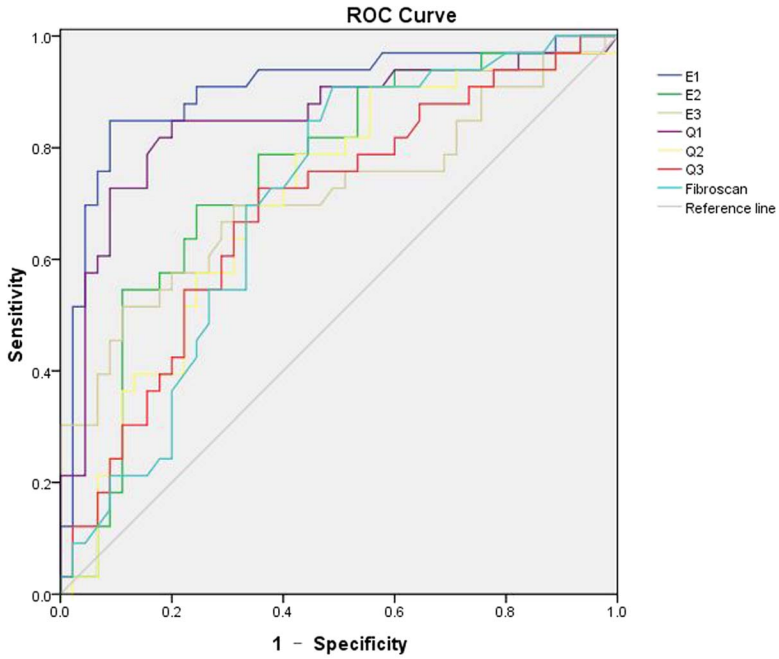

FIGURE 4. Diagnostic performance of elastographic parameters in patients with G ≥ 3 hepatic inflammation. The mean (E1), maximum (E2), and minimum (E3) of STE, and the mean (Q1), maximum (Q2), and minimum (Q3) of STQ and FibroScan are evaluated.

One of the limitations of the current study is its limited population size; it had only a small number of grade 3 hepatic inflammation patients and no grade 4 hepatic inflammation patients. Future studies that are prospective and have a larger patient population are required to confirm the findings of the current study.

CONCLUSIONS

The current study demonstrated that the mean Young modulus of STE and STQ could serve as a useful diagnostic marker for hepatic inflammation of HBV patients with no apparent liver fibrosis.

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