Staging liver fibrosis in patients with chronic hepatitis B using two-dimensional shear wave elastography based on histopathological findings: a prospective multicenter study

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Background: With the rapid development of shear wave elastography technology, the clinical application prospect of two-dimensional shear wave elastography (2D SWE) for non-invasive monitoring of liver fibrosis is extremely promising. This study aimed to evaluate the diagnostic performance of ElastQ, a noval 2D SWE method, in the staging of liver fibrosis in patients with chronic hepatitis B with histopathological results as the reference standard.

Methods: Between August 2020 and December 2021, a prospective multicenter study of 602 consecutive patients with chronic hepatitis B was conducted in 14 hospitals. All patients underwent liver biopsy and 2D SWE examination. The patients were divided into a training cohort and a validation cohort. The area under the receiver operating characteristic curve (AUROC) was calculated, and the optimal cut-off values for ElastQ were obtained.

Results: Overall, 2D SWE values showed a strong correlation with fibrosis stage (r=0.71, P<0.001). In the training cohort, the AUROCs of ElastQ for diagnosing fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 0.817 [95% confidence interval (CI): 0.777–0.853], 0.887 (95% CI: 0.852–0.915), 0.912 (95% CI: 0.881–0.937), and 0.832 (95% CI: 0.793–0.866)], respectively. In the validation cohort, the AUROCs of ElastQ for diagnosing fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 0.807 (95% CI: 0.742–0.861), 0.868 (95% CI: 0.810–0.914), 0.855 (95% CI: 0.796–0.903), and 0.851 (95% CI: 0.791–0.900), respectively. The optimal liver stiffness cut-off values for the identification of fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 5.72 kPa (sensitivity: 78%, specificity: 70%), 6.85 kPa (sensitivity: 77%, specificity: 86%), 7.43 kPa (sensitivity: 80%, specificity: 86%), and 8.03 kPa (sensitivity: 81%, specificity: 73%), respectively.

Conclusions: Two-dimensional SWE can accurately stage liver fibrosis in patients with chronic hepatitis B.

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Introduction

Chronic hepatitis B (CHB) virus infection is the main cause of liver fibrosis in China (1). Liver fibrosis can progress to liver cirrhosis, liver cancer, and liver failure. Clinical treatment strategies differ depending on the stage of liver fibrosis (2). Mild to moderate liver fibrosis can be reversed with prompt and specific treatment (3). Therefore, for patients with CHB, accurate evaluation and dynamic monitoring of the degree of liver fibrosis are of great significance in guiding clinicians to implement timely treatment and control the course of the disease (2).

Liver biopsy is recognized as the gold standard for the staging of liver fibrosis. However, liver biopsy is an invasive examination and thus has poor repeatability and low acceptance by patients (4). Therefore, noninvasive examination is preferred and has become a much debated topic in clinical research (5). Although serum markers can predict liver fibrosis to a certain extent, their predictive accuracy is mediocre, because they are not liver specific (6). Some studies in the field of medical imaging have reported that magnetic resonance elastography has a higher diagnostic performance than transient elastography (TE) in the staging of liver fibrosis; however, its high cost and low accessibility have limited its clinical utility and patient acceptance (7-9). Ultrasound elastography has gradually become the primary method for the assessment of liver stiffness due to its convenience, high speed, real-time capability, and low cost (10).

Ultrasound elastography predicts the degree of liver fibrosis by quantifying liver tissue stiffness. Two-dimensional shear wave elastography (2D SWE) is an ultrasound elastography technique which can predict the degree of liver fibrosis. Compared with TE, which has been widely reported, 2D SWE has a higher success rate and a wider area of fibrosis assessment (11-13). ElastQ, available on the Philips EPIQ system (Philips, Bothell, WA, USA), is based on the same principles as other 2D SWE imaging systems (14). Stiffness values or shear wave speed values involving the same subject vary among manufacturers due to system and engineering-dependent factors such as differences in shear wave excitation settings and reconstruction algorithms (15). Therefore, any new shear wave elastography system needs to be validated in clinical practice to establish reference thresholds.

The aim of this prospective multicenter study was to evaluate the diagnostic performance of the ElastQ in a large sample of patients with CHB compared with serum biomarkers, with histopathological findings as the reference standard, and to obtain the optimal cut-off values for fibrosis staging. We present the following article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-831/rc).

Methods

Patients and study design

Between August 2020 and December 2021, consecutive patients diagnosed with CHB virus infection were considered for enrollment in a prospective multicenter study involving 14 hospitals. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).The study was approved by West China Hospital of Sichuan University Biomedical Research Ethics Committee (approval No. 2020638), Tianjin Third Central Hospital Institutional Review Board, the Affiliated Hospital of Southwest Medical University Institutional Review Board, Beijing Youan Hospital of Capital Medical University Ethics Committee, Panzhihua Central Hospital Institutional Review Board, the First Affiliated Hospital of Xiamen University Ethics Committee, the First Affiliated Hospital of Guangxi Medical University Ethics Committee, the First People's Hospital of Yinchuan Ethics Committee, Sichuan Cancer Hospital Ethics Committee, Guizhou Provincial People's Hospital Ethics Committee, the Second People's Hospital Ethics Committee, Qinghai University Affiliated Hospital Ethics Committee, the Fourth People's Hospital of Qinghai Province Ethics Committee, and Shijiazhuang Fifth Hospital Ethics Committee. Written informed consent was obtained from all patients.

The inclusion criteria for patients were as follows: (I) aged 18 years or older; (II) had been hepatitis B surface antigen (HBsAg)-positive for more than 6 months; and (III)
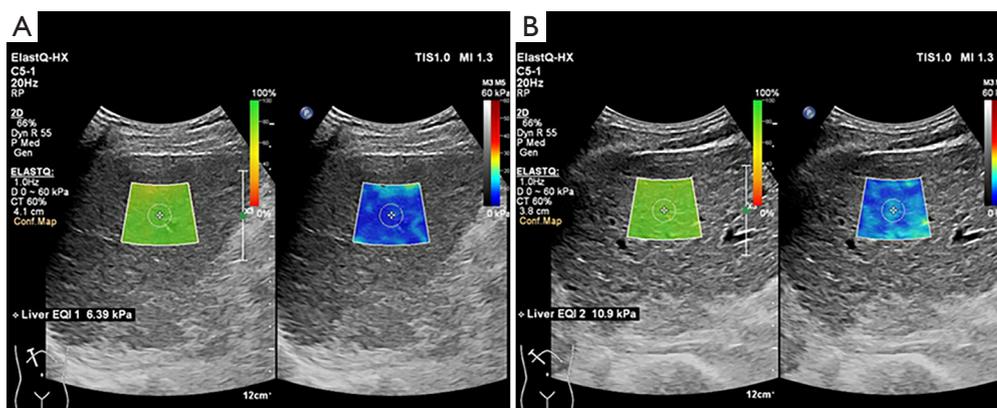
Figure 1 Two-dimensional shear wave elastography measurement interface map. (A) A 57-year-old patient diagnosed with CHB-associated liver disease with S1 fibrosis. (B) A 50-year-old patient diagnosed CHB liver disease with S4 fibrosis. In each figure, the image on the left displays the ElastQ confidence map superimposed on the B-mode image, and the image on the right displays the ElastQ stiffness map superimposed on the B-mode. A measurement circle with a diameter of 1 cm is placed in the center of the stiffness map for quantification. Stiffness value =6.39 kPa for patient with S1 and 10.9 kPa for patient with S4. CHB, chronic hepatitis B.

underwent liver biopsy after sonography. The following patients were excluded: (I) patients who had previously undergone liver transplantation; (II) patients who were pregnant or lactating; (III) patients with a body mass index (BMI) ≥30 kg/m²; (IV) patients with other hepatic diseases such as hepatic vein tumor thrombus, intrahepatic bile duct dilatation, or biliary obstruction; (V) patients who had liver biopsy specimen of inadequate quality; and (VI) patients with an unreliable liver stiffness measurement (LSM).

The sample size was determined based on the desired sensitivity and specificity. The maximum expected sensitivity and specificity were taken from previous publications (6,16-18). The power of test was set as 0.9 and the standard error as 0.05. The calculated required sample size to achieve 90% power was 562, but as a precautionary measure (5%), the sample size was set at 590.

Patients with each grade of fibrosis were randomly divided into two groups at a ratio of 7:3. Of the patients, 70% were assigned to the training cohort to determine the optimal cut-off values, and the remaining 30% became the validation cohort to validate the diagnostic performance of the cut-off values. To investigate the influence of inflammatory activity grade and alanine transaminase (ALT) levels in identifying the fibrosis stage, subgroup analysis was performed by dividing the patients into groups according to inflammatory activity grade (G1, G2, G3, and G4). However, since there were only a small number of patients with G4 (n=10), the G4 and G3 groups were combined for analysis. Additionally, patients were divided into two groups

based on ALT levels: ALT < 2 × upper limit of normal (ULN) (n=352) and ALT ≥ 2 × ULN (n=68).

Liver stiffness measurement by 2D SWE

All the patients underwent regular B-mode imaging and 2D SWE examination within 14 days before liver biopsy. The B-mode and 2D SWE examinations were performed with the EPIQ 7 ultrasound system (Philips, Bothell, WA, USA) with a C5-1 convex probe. All the ultrasound operators had more than 2 years of extensive clinical experience and were proficient in using ultrasound equipment. In addition, all had familiarized themselves with the research protocol and followed a detailed operating procedure manual. All operators were blinded to the clinical information and biopsy results of the patients.

During each ElastQ imaging examination, homogeneous liver parenchyma, without large vessels or gallbladder interference, was selected as the region of interest. The ElastQ sampling box was placed 1–2 cm below the liver capsule. During a 6-second breath hold, the operator froze the image when the color inside the ElastQ sampling box was stabilized with the side-by-side confidence map filled mostly with yellow-green color (red = confidence score 0, green = confidence score 100). The operator then employed a circular measurement caliper with a diameter of 1 cm inside the high-confidence region for stiffness quantification. The ElastQ imaging and measurement interface is shown for a fibrotic liver at S1 and a fibrotic liver at S4 in *Figure 1A,1B*,

respectively. The operator repeated the measurement five times. Between the consecutive acquisitions, the patient could maintain normal breathing. When less than two-thirds of the ElastQ confidence map was green, or when the big vessels were not avoided, the measurement was considered failed or unreliable. The quantified LSM was expressed in kilopascals (kPa). The measurement reliability for each patient was defined by the ratio of the interquartile range to the median (IQR/M). When the IQR/M was 30% or less, the patient's 2D SWE values were recorded. Measurements were considered unreliable if the IQR/M exceeded 30% (14). The mean 2D SWE value of the five measurements was calculated for further analysis.

Liver biopsy and histologic staging

Percutaneous liver biopsies were performed under ultrasound guidance. Samples of more than 15 mm in length and with more than six portal tracts were considered eligible. Needle biopsy specimens were fixed with 10% formalin. Liver biopsies were subjected to hematoxylin and eosin and histochemical trichrome staining. For pathological quality control, all pathological specimens were gathered from the 14 hospitals for central reading by 2 pathologists (with 9 and 12 years of experience). The pathologists were blinded to the patients' 2D SWE results. The fibrosis stage and inflammatory activity grade were evaluated using the Scheuer score. The liver fibrosis stages were: S0 (no fibrosis), S1 (portal fibrosis without septa), S2 (portal fibrosis and few septa), S3 (numerous septa without cirrhosis), and S4 (cirrhosis). The inflammation activity grades were: G0 (none), G1 (mild), G2 (moderate), G3 (obvious), and G4 (severe) (19).

Laboratory tests

Laboratory tests, such as liver function tests, blood counts, and serum markers for the hepatitis B virus, were performed 14 days before the liver biopsy. Each patient's platelet count (PLT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), ALT, aspartate aminotransferase (AST), total bilirubin, and direct bilirubin were recorded. Two noninvasive fibrosis scores based on patients' laboratory tests and demographic information were calculated as follows: aspartate aminotransferase-to-platelet ratio index (APRI) = [AST (upper limit of normal U/L)/platelet count ($\times 10^9$/L) $\times$ 100 and fibrosis-4 index (FIB-4) = [age (years) $\times$ AST (U/L)]/ [platelet count ($\times 10^9$/L) $\times$ ALT (U/L)$^{1/2}$] (20,21).

Statistical analysis

Statistical analyses were performed using SPSS (version 23.0, IBM, Armonk, NY, USA) and MedCalc software (version 11.2, MedCalc Software, Ostend, Belgium). Quantitative variables were expressed as medians and interquartile ranges, and categorical variables as absolute and relative frequencies. Quantitative data were compared between two groups using Student's t-test or the Mann-Whitney test, and categorical data using the χ^2 test or Fisher's test. A P value of less than 0.05 was considered statistically significant. Spearman's correlation coefficient were used to evaluate the correlations between the two groups of variables. Intraobserver variability in LSM was assessed using the intraclass correlation coefficient (ICC). An ICC of more than 0.80 was regarded as excellent agreement. The area under the receiver operating characteristic curve (AUROC) and its 95% confidence interval (CI) were used to evaluate the diagnostic performance of 2D SWE, and the Delong test was used to compare the AUROCs. The optimal cut-off values of ElastQ in ROC curve analysis were determined by maximizing the Youden index.

Results

Between August 2020 and December 2021, a total of 667 patients with CHB were recruited for 2D SWE examination. After a detailed clinical data review and 2D SWE image quality assessment, 65 patients were excluded. Of the excluded patients, 8 had an age or BMI outside the eligible ranges, and another 8 were coinfected with the hepatitis C virus. The other 49 patients were excluded due to having poor measurement quality (n=37) or an insufficient number of 2D SWE measurements (n=12); this translated to a 94.3% success rate for 2D SWE (*Figure 2*). Finally, 602 patients, with an average age of 51 years (range, 18 to 83 years), were enrolled. The patients were divided on a 70:30 basis into a training cohort (n=420) and a validation cohort (n=182). The demographic and baseline characteristics of the patients are summarized in *Table 1*. There were no significant differences in patient clinical characteristics between the training and validation cohorts (P>0.05).

The ICC for LSM by 2D SWE, based on five measurement from each patient, was 0.923 (95% CI: 0.911–0.933), indicating high reproducibility and stability of 2D SWE.
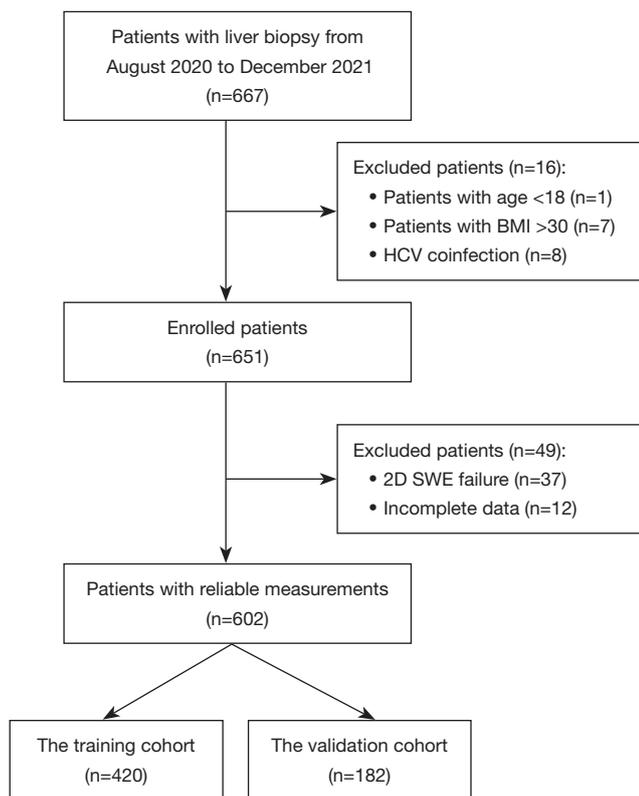
Figure 2 Patient flowchart. BMI, body mass index; HCV, hepatitis C virus; 2D SWE, two-dimensional shear wave elastography.

All 2D SWE values ranged from 3.08 kPa to 21.00 kPa. According to patients' histopathological results, the distribution of liver fibrosis stages in the training cohort was as follows: S0 (n=30, 7.1%), S1 (n=84, 20%), S2 (n=79, 18.8%), S3 (n=93, 22.1%), and S4 (n=134, 31.9%) (*Table 1* and *Figure 3*). Overall, 72.8% of patients had significant fibrosis (≥ S2) and 31.9% of patients had cirrhosis (S4). The 2D SWE values showed a strong correlation with fibrosis stage (r=0.71, P<0.001). In the training cohort, the AUROCs of ElastQ for diagnosing fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 0.817 (95% CI: 0.777–0.853), 0.887 (95% CI: 0.852–0.915), 0.912 (95% CI: 0.881–0.937), and 0.832 (95% CI: 0.793–0.866), respectively. The optimal liver stiffness cut-off values for predicting fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 5.72 kPa (sensitivity: 78%, specificity: 70%), 6.85 kPa (sensitivity: 77%, specificity: 86%), 7.43 kPa (sensitivity: 80%, specificity: 86%), and 8.03 kPa (sensitivity, 81%; specificity: 73%), respectively (*Table 2*).

Next, the diagnostic performance of the cut-off values

was assessed in the validation cohort. The AUROCs of ElastQ for diagnosing fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 0.807 (95% CI: 0.742–0.861), 0.868 (95% CI: 0.810–0.914), 0.855 (95% CI: 0.796–0.903), and 0.851 (95% CI: 0.791–0.900), respectively. The diagnostic performance of the cut-off values in the training cohort and validation cohort is shown in *Table 3*.

The comparison of the diagnostic performance of 2D SWE, the APRI, and the FIB-4 is shown in *Figure 4* and reported in *Table 2*. In the correlation analysis with liver fibrosis stage, 2D SWE showed a significantly stronger correlation than APRI or FIB-4 (r=0.719 *vs.* r=0.44 *vs.* r=0.521, respectively, P<0.001). Additionally, 2D SWE had higher AUROCs than both APRI and FIB-4 for all liver fibrosis stages (≥S1: 0.82 *vs.* 0.73 *vs.* 0.75, respectively, ≥S2: 0.89 *vs.* 0.78 *vs.* 0.82, respectively, ≥S3: 0.91 *vs.* 0.75 *vs.* 0.78, respectively, and S4: 0.83 *vs.* 0.67 *vs.* 0.73, respectively, P<0.05 for all).

The distribution of inflammatory activity grades in the study cohort was G1 (n=120, 28.6%), G2 (n=180, 42.9%), G3 (n=110, 26.2%), and G4 (n=10, 2.4%). A moderate correlation of LSM with inflammation grade was observed (r=0.528, P<0.001). In the diagnosis of fibrosis stage S4, the AUROC in the low-activity group (G1) was higher than those in the moderate-activity group (G2) and the high-activity group (G3–4) (0.921 *vs.* 0.786 *vs.* 0.749, respectively; P<0.05). The correlation between ALT and LSM was weak (r=0.14, P<0.05). In the diagnosis of fibrosis stages ≥S3 and S4, the AUROC in the normal ALT level group (ALT < 2 × ULN, n=352) was higher than that in the elevated ALT level group (ALT ≥ 2 × ULN, n=68) (*Table 4*).

Discussion

This large prospective multicenter study primarily evaluated the diagnostic performance of a novel 2D SWE elastography system (ElastQ) for liver fibrosis staging and determined the optimal diagnostic cut-off values in patients with CHB. Using histopathological results as the reference standard, our study showed that ElastQ was convenient to operate and demonstrated stable results. Furthermore, its diagnostic performance was significantly superior to that of serum markers (FIB-4 and APRI).

Our study presents several unique advantages. First, the proportion of patients was uniform across liver fibrosis stages, which reduced the effects of potential bias on the statistical results. Second, we strictly excluded patients with medical conditions or diseases that might affect liver

Table 1 Demographics and baseline characteristics of the patients

Characteristics	Reference value	Training cohort	Validation cohort	P value
No. of patients	NA	420 (69.8)	182 (30.2)	
Age (years)	NA	53 [40.3–61]	51 [43–58]	0.501
Sex				
Male	NA	316 (75.2)	138 (75.8)	
Female	NA	104 (24.8)	44 (24.2)	
BMI (kg/m²)	NA	23.6 [21.6–26]	22.9 [20.8–25]	0.324
PLT (×10⁹/L)	100–300	152 [105–210]	145 [99–182.3]	0.138
AST (U/L)	<40	31.5 [23–54.8]	36 [23–76.3]	0.090
ALT (U/L)	<50	36 [22–70]	44 [25–125.5]	0.147
GGT (U/L)	<60	35 [20–66]	41 [24–74]	0.649
ALP (U/L)	51–160	82 [66.3–102]	80 [63–104]	0.936
Total bilirubin (μmol/L)	5.0–28.0	15.1 [11.3–19.7]	14.8 [11.1–21.3]	0.952
Direct bilirubin (μmol/L)	<8.8	3.7 [2.4–5.7]	4.3 [2.8–7.3]	0.753
Scheuer fibrosis stage				
S0	NA	30 (7.1)	12 (6.6)	
S1	NA	84 (20.0)	35 (19.2)	
S2	NA	79 (18.8)	33 (18.1)	
S3	NA	93 (22.1)	45 (24.7)	
S4	NA	134 (31.9)	57 (31.3)	
Inflammation grade				
G1	NA	120 (28.6)	44 (24.2)	
G2	NA	180 (42.9)	91 (50.0)	
G3	NA	110 (26.2)	41 (22.5)	
G4	NA	10 (2.4)	6 (3.3)	

Qualitative variables are in n (%), and quantitative variables are median [interquartile range]. NA, not available; BMI, body mass index; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase.

stiffness and collected pathological specimens for central reading to ensure the reliability of our results. Third, to the best of our knowledge, this is the first multicenter prospective report on ElastQ with a large sample size.

Many studies have reported that TE has great potential for diagnosing fibrosis stage and is recommended as a noninvasive technique in guidelines (22). However, an increasing number of studies suggest that 2D SWE has many advantages over TE (23-26). Poynard *et al.* (24) reported that 2D SWE had a higher success rate than TE in patients with obesity and ascites (86% *vs.* 55%,

P=0.04) and that it produced more reliable results. The ICC in our study was higher than those reported by Joo *et al.* (25) for point shear wave elastography and Ronot *et al.* (26) for TE (0.923 *vs.* 0.848 *vs.* 0.85), showing 2D SWE to have good repeatability. The ElastQ imaging system used in this study provides side-by-side and concurrent confidence and stiffness maps. The quality index presented in the confidence map can guide the user to dynamically monitor the acquisition performance and make reliable measurements.

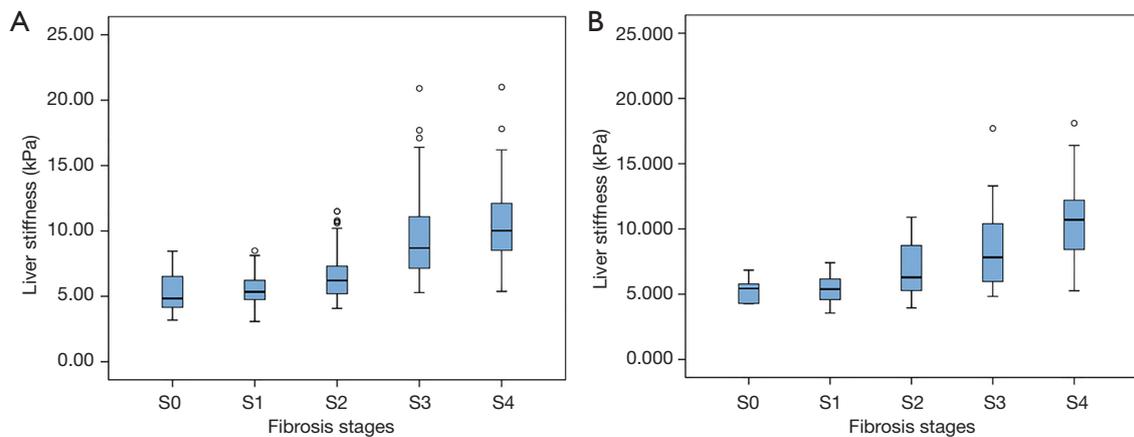In this study, the optimal cut-off values for identifying

Figure 3 Box plot of two-dimensional shear wave elastography values assessed by ElastQ for different stages of histological fibrosis (A) in the training cohort and (B) in the validation cohort.

Table 2 Comparison of the diagnostic performance of two-dimensional shear wave elastography, aspartate aminotransferase-to-platelet ratio index, and fibrosis-4 index in the training cohort

Fibrosis stage	AUROC	P value	Cut-off value	Sensitivity	Specificity	PPV (%)	NPV (%)
≥S1							
2D SWE	0.817	<0.001	>5.69 kPa	0.78	0.7	97	20
APRI	0.725	<0.001	>0.43	0.64	0.77	97	14
FIB-4	0.75	<0.001	>1.53	0.66	0.83	98	16
≥S2							
2D SWE	0.887	<0.001	>6.85 kPa	0.77	0.86	94	58
APRI	0.782	<0.001	>0.37	0.82	0.64	86	57
FIB-4	0.824	<0.001	>1.57	0.76	0.78	90	54
≥S3							
2D SWE	0.912	<0.001	>7.43 kPa	0.8	0.86	87	79
APRI	0.746	<0.001	>0.42	0.82	0.59	70	74
FIB-4	0.78	<0.001	>1.6	0.79	0.65	73	72
S4							
2D SWE	0.832	<0.001	>8.02 kPa	0.81	0.73	59	89
APRI	0.674	<0.001	>0.42	0.85	0.52	43	87
FIB-4	0.725	<0.001	>1.57	0.89	0.52	47	91

AUROC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; 2D SWE, two-dimensional shear wave elastography; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index.

Table 3 Comparison of diagnostic performance between the training and validation cohorts

Fibrosis stage	AUROC	P value	Cut-off value (kPa)	Sensitivity	Specificity	PPV (%)	NPV (%)
≥S1							
Training cohort	0.817		>5.69	0.78	0.7	97	20
Validation cohort	0.807	>0.05	>5.69	0.72	0.75	98	16
≥S2							
Training cohort	0.887		>6.85	0.77	0.86	94	58
Validation cohort	0.868	>0.05	>6.85	0.68	0.94	97	51
≥S3							
Training cohort	0.912		>7.43	0.8	0.86	87	79
Validation cohort	0.855	>0.05	>7.43	0.73	0.84	85	71
S4							
Training cohort	0.832		>8.02	0.81	0.73	59	89
Validation cohort	0.851	>0.05	>8.02	0.82	0.74	60	90

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

fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were 5.72 kPa, 6.85 kPa, 7.43 kPa, and 8.03 kPa, respectively. Our previous study reported that the optimal cut-off values of elastography point quantification (ElastPQ) in identifying fibrosis stages ≥S1, ≥S2, ≥S3, and S4 were ≥5.8 kPa, ≥6.8 kPa, ≥9.1 kPa, and ≥10.3 kPa, respectively (6). The cut-off values obtained in this study are closer to each other. In this analysis, the maximum 2D SWE value of ElastQ was 21 kPa, while the maximum value of ElastPQ was 38 kPa (6). A likely explanation for this difference is that the 2D SWE value measured by ElastQ is more stable than that measured by ElastPQ. The closeness of cut-off values impacts on clinical practice. Therefore, we recommend that the number of measurements obtained must be five. Also, when measuring liver stiffness, it is important to ensure that the confidence score is in the range of 90 to 100. Credible and stable results can only be achieved through strict compliance with operational norms. Moreover, our study included more patients with significant fibrosis and cirrhosis. That is because cirrhosis (S4) accounts for a larger proportion of patients in larger hospitals, while smaller hospitals have a higher proportion of no fibrosis or mild fibrosis (S0–2). This difference is related to the psychology of the patient's choice of institution and the local treatment mechanism. Therefore, the results of our study are more generalizable to groups of patients with a high prevalence of fibrosis, such as those in the infection department and those undergoing liver surgery. Furthermore, the characteristics

of different ultrasound machines should also be taken into consideration for system-dependent SWE measurements (27), and it should be re-emphasized that the cut-off values recommended for different elastography systems are not interchangeable (28).

Our study also found that the diagnostic performance of APRI and FIB-4 was inferior to that of 2D SWE, which is consistent with previous research findings (6,29-31). Serum markers have a poor real-time performance; if the disease changes, the changes in serum marker values will be delayed (32). However, 2D SWE can directly measure the stiffness of the liver (33), and it can therefore predict the stage of liver fibrosis with high accuracy.

Consistent with the elastography guidelines (2), our study showed good correlations between different inflammation grades and LSM (r=0.528, P<0.001). In the diagnosis of fibrosis stage S4, the diagnostic performance of LSM in the low-activity group (G1) was better than that in the moderate-activity (G2) and high-activity (G3–4) groups. In our study, the correlation between ALT and LSM was weak (r=0.14, P<0.05). Wu *et al.* (34) have reported that they used 1 × ULN of ALT as the grouping cut-off point, and the difference in diagnostic performance between the two groups was moderate (P=0.45). In the guidelines for hepatitis diagnosis and treatment, liver function damage or hepatitis virus activity is considered for patients with an ALT level of 2 × ULN or above (35). Therefore, we used 2 × ULN as the grouping cut-off point. Our study showed

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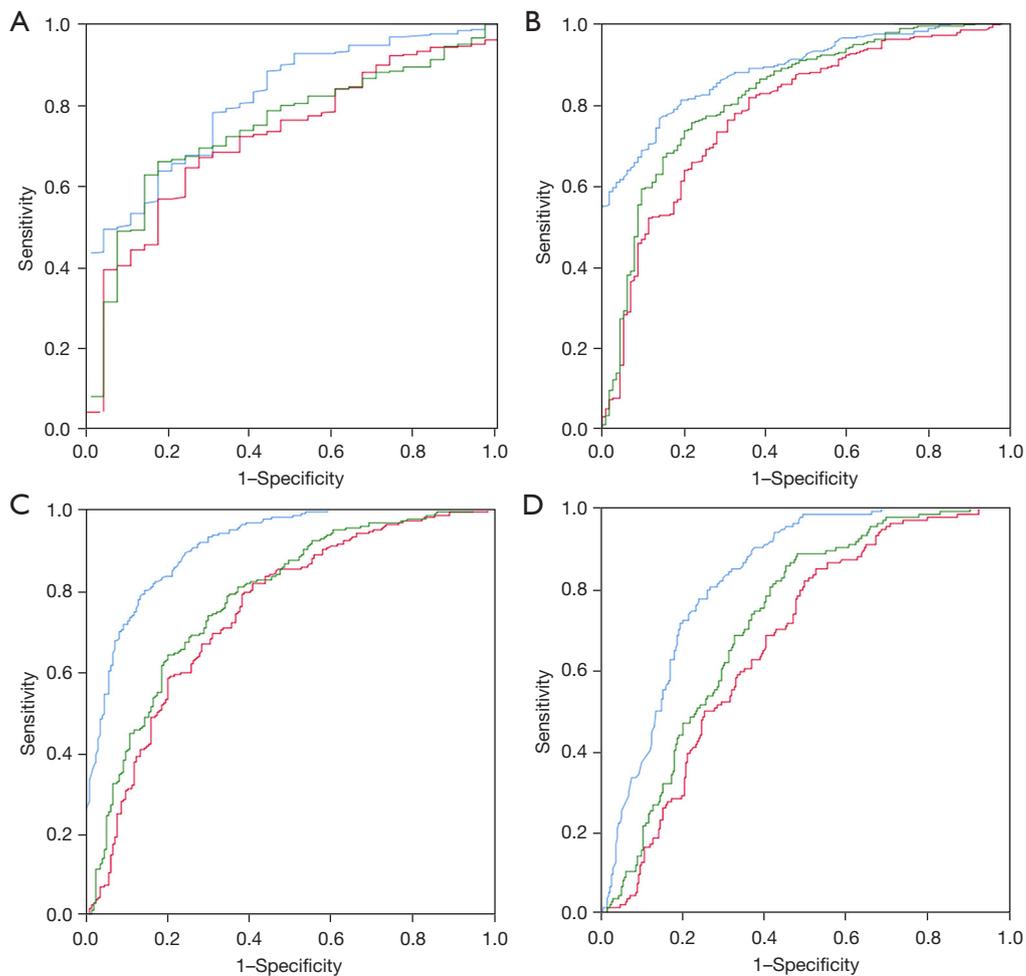
Figure 4 Receiver operating characteristic curves of liver stiffness (blue line), the aspartate aminotransferase-to-platelet ratio index (green line), and the fibrosis-4 index (red line) for different liver fibrosis stages in the training cohort. (A) ≥S1, (B) ≥S2, (C) ≥S3, and (D) S4.

Table 4 Influence of inflammation grade and alanine aminotransferase level on the area under the receiver operating characteristic curve of two-dimensional shear wave elastography

Variable	≥S1	≥S2	≥S3	S4
Inflammation stage				
G1 (n=120)	0.689 (0.598, 0.771)	0.863 (0.788, 0.919)	0.908 (0.842, 0.953)	0.921 (0.857, 0.962)
G2 (n=180)	0.673 (0.600, 0.741)	0.84 (0.778, 0.890)	0.907 (0.855, 0.945)	0.786 (0.719, 0.843)
G3–4 (n=120)	0.764 (0.678, 0.837)	0.879 (0.807, 0.932)	0.866 (0.792, 0.921)	0.749 (0.662, 0.824)
P value	>0.05	>0.05	>0.05	<0.05
ALT level				
ALT ≤ 2 × ULN (n=352)	0.81 (0.74, 0.88)	0.891 (0.86, 0.92)	0.924 (0.90, 0.95)	0.87 (0.83, 0.91)
ALT > 2 × ULN (n=68)	0.803 (0.56, 1.00)	0.781 (0.65, 0.91)	0.816 (0.71, 0.92)	0.63 (0.49, 0.76)
P value	0.968	0.111	0.049	0.001

Data in parentheses are 95% confidence intervals. ALT, alanine aminotransferase; ULN, upper limit of normal.

that when the ALT level was below 2 × ULN, the diagnostic performance of LSM was higher (P<0.001) and the 2D SWE values were more reliable. These results confirmed the inflammation activity grade and ALT level to be important confounding factors in the diagnosis of fibrosis stage (33,36).

There were several limitations in our study. First, the proportions of patients with different fibrosis grades were not uniform, and patients with cirrhosis (S4, 31.9%) accounted for a relatively large proportion of the study population. Therefore, that may affect the generalization of truncation value. Second, our study included few patients with severe inflammation and, as such, patients with obvious inflammation (G3) and severe inflammation (G4) were not analyzed separately. Third, with the development of standardized treatment for CHB, an increasing number of patients are treated with long-term antiviral therapy. However, antiviral therapy was not found to be an independent risk factor for predicting the grade of liver fibrosis in univariate logistic regression (P>0.05). Therefore, we did not discuss the impact of antiviral therapy in depth in this study. Further studies are needed to explore the dynamics of LSM in patients on antiviral therapy. Finally, to avoid the influence of abdominal wall thickness on LSM, we excluded patients with a BMI higher than 30. This exclusion criterion was intended to prevent the influence of fatty liver, but it also limited the generalizability of the results of this study (37).

Conclusions

In conclusion, 2D SWE performed well in the diagnosis and staging of liver fibrosis, with convenient operation and stable results. It is expected to become an alternative method for the noninvasive assessment of the degree of liver fibrosis in the future.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-831/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-831/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by West China Hospital of Sichuan University Biomedical Research Ethics Committee (No. 2020638), Tianjin Third Central Hospital Institutional Review Board, Affiliated Hospital of Southwest Medical University Institutional Review Board, Beijing Youan Hospital of Capital Medical University Ethics Committee, Panzhihua Central Hospital Institutional Review Board, First Affiliated Hospital of Xiamen University Ethics Committee, the First Affiliated Hospital of Guangxi Medical University Ethics Committee, First People's Hospital of Yinchuan Ethics Committee, Sichuan Cancer Hospital Ethics Committee, Guizhou Provincial People's Hospital Ethics Committee, the Second People's Hospital Ethics Committee, Qinghai University Affiliated Hospital Ethics Committee, Fourth People's Hospital of Qinghai Province Ethics Committee, and Shijiazhuang Fifth Hospital Ethics Committee. All patients gave their written informed consent.

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