

Evaluating the Diagnostic Performance of Sound Touch Elastography, Visco-elastography, and Sound Attenuation in Chronic Liver Diseases Detection

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Objectives: This study aims to explore the diagnostic effectiveness of sound touch elastography (STE), visco-elastography, and ultrasound attenuation analysis (USAT) in some chronic liver diseases (CLDs).

Materials and Methods: From February 1st to September 30th, 2023, participants underwent multiple examinations on the same day, including sound touch elastography (STE), visco-elastography, ultrasound attenuation analysis (USAT), FibroScan-VCTE, and FibroScan-CAP. Statistical analysis utilized t-tests and rank sum tests to compare differences between the hepatic fibrosis and non-hepatic fibrosis groups, the hepatocellular injury state and non-hepatocellular injury state groups, and the fatty liver and non-fatty liver groups. The ROC curve of sound touch elastography, visco-elastography, and ultrasound attenuation analysis was calculated to obtain cut-off values, area under the curve, and corresponding sensitivity and specificity values.

Results: This study comprised 310 patients, with age, height, alanine aminotransferase, ultrasound attenuation analysis, and FibroScan-CAP identified as significant variables for liver fibrosis, hepatocellular injury state, and non-alcoholic fatty liver disease. The determined cut-off values for sound touch elastography, visco-elastography, and ultrasound attenuation analysis were 8.09 (7.30-9.17), 1.62 (1.49-1.74), and 0.68 (0.59-0.68), respectively. Based on these cut-off values, preliminary diagnoses can be made for seven different types of chronic liver diseases.

Conclusion: The combination of sound touch elastography, visco-elastography, and ultrasound attenuation analysis demonstrates strong reliability for early screening and diagnosis of chronic liver diseases, encompassing liver fibrosis, non-alcoholic fatty liver, and hepatocellular injury state.

Key words: Ultrasonography; Liver diseases; Chronic hepatocellular injury state; Viscoelasticity

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As the causes of chronic liver disease become increasingly varied, it has emerged as a disease with high global prevalence [1-4]. Epidemiological

data from 2019 indicate that there were 2.59 million patients with liver disease worldwide, with nearly three-quarters of these cases being chronic liver disease

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(CLDs) [5]. Research indicates that hepatitis B, hepatitis C, and non-alcoholic fatty liver disease are the primary causes of chronic liver disease [6]. Whether through viral infections or lipid infiltration damaging the liver cells chronically these factors are highly likely to lead to the terminal progression of chronic liver disease—cirrhosis, which is associated with numerous adverse events, including esophageal and gastric variceal bleeding, hepatic encephalopathy, the hepatorenal syndrome and liver cancer [7-9]. Consequently, the diagnosis and monitoring of chronic liver disease have become critical areas of focus.

Liver fibrosis, viral hepatitis, and non-alcoholic fatty liver disease are principal contributors to the onset and progression of CLDs [10]. The multifactorial nature of CLDs often demands the extensive expertise of clinicians for accurate differentiation and diagnosis. Diagnosing conditions such as viral hepatitis typically involves serological and virological testing, along with imaging examinations, which are complex and time-consuming [1]. Additionally, definitive diagnosis of liver fibrosis and NAFLD often requires liver biopsy, which is variable, invasive, and expensive [11]. Alternatively, magnetic resonance imaging (MRI) can accurately quantify liver fat content, offering an objective, accurate, and safe method, but the associated high cost and time consumption [12]. Consequently, ultrasound has emerged as the preferred modality for assessing various chronic liver diseases due to its efficiency, non-invasiveness, low cost, and absence of radiation. However, conventional grayscale ultrasound may not suffice for the diagnostic needs of diverse chronic liver conditions.

Recent advancements in ultrasound technology have shown that Ultrasound Attenuation Spectroscopy (USAT) can quantitatively analyze liver fat content and aid in diagnosing fatty liver, as evidenced in studies [13,14]. Similarly, shear wave elastography (STE) has been effective in diagnosing and grading liver fibrosis [15-17]. These techniques suggest a potential for non-invasive diagnostics in CLDs [18]. Furthermore, visco-elastography, as a novel ultrasound technique, utilizes visual imaging to measure tissue shear waves for quantifying viscoelasticity [19]. It scans and captures potential changes in liver cells during the hepatocellular injury state, allowing for quantitative analysis that can be used to determine the activity of hepatitis [19], and it has been utilized to assess the hepatocellular injury state [20]. However, there is no research yet focused on combining the three ultrasound technologies—STE, visco-elastography, and USAT—to diagnose certain complex factors of chronic liver disease.

Therefore, the primary aim of this study is to evaluate the preliminary diagnostic efficacy of combining

STE, visco-elastography, and USAT technologies for certain CLDs. Additionally, the study aims to identify other possible indicators for the auxiliary diagnosis of CLDs.

Materials and Methods

Statement of ethics

This study was executed in strict adherence to the principles outlined in the Declaration of Helsinki (2013 revision) and received approval from the Ethics Committee of Shenzhen People's Hospital. Furthermore, all participants were fully informed about the research objectives and procedures and provided their written informed consent.

Patient selection

This study continuously collected data from 310 patients suspected of having CLDs from February 1st to September 30th in 2023 in Shenzhen People's Hospital. Chronic liver disease was defined as a spectrum of disorders characterized by persistent liver injury, inflammation, and/or fibrosis [21]. Etiologies included, but were not limited to, viral hepatitis, autoimmune liver diseases, and metabolic dysfunction-associated steatotic liver disease. While the spectrum of CLDs is broad, this study specifically focused on disease onset and progression driven primarily by liver fibrosis, hepatocellular injury, and non-alcoholic fatty liver disease (NAFLD). Given these disease factors, multiple global consensus and guidelines endorse FibroScan as the reference standard for assessing fatty liver and liver fibrosis, offering a non-invasive diagnostic approach specifically for NAFLD [12,22-24]. Consequently, this study employs FibroScan VCTE and FibroScan CAP as the reference standards for evaluating liver fibrosis and NAFLD, respectively. Moreover, prior research indicates that elevated alanine aminotransferase (ALT) levels are a crucial early marker for liver disease assessment [25]. Thus, in this study, participants were classified based on serum ALT levels using a threshold of > 40 U/L as a biochemical criterion for identifying liver injury.

This study included two cohorts: patients with suspected or confirmed CLD and normal control participants:

For the CLD Cohort Inclusion criteria: (1) Patients with elevated ALT in liver function serological examination [25]; (2) The presence of immunoglobulin (Ig) M in the serum is positive for HAV for more than 4 months; (3) HbsAg positive for more than 6 months; (4) HCV RNA positive for 6 months [26]; (5) According to patients with non-alcoholic liver disease as defined in the EASL-EASD-EASO Clinical Practice Guidelines for

the management of non-alcoholic fatty liver disease [27]; (6) FibroScan VCTE ≥ 12.4 kPa; (7) Completion of STE, visco-elastography, USAT, FibroScan-VCTE, and FibroScan-CAP examinations on the same day; (8) Over 18 years old; (9) Complete serological examination information. Collect age, gender, height and weight of participants.

For the Normal Control cohort Participants were included if they met all the following criteria: (1) No known history of any chronic liver disease (viral, autoimmune, metabolic, or alcoholic), and normal liver biochemistry (ALT, AST, GGT, ALP, and bilirubin within laboratory reference ranges); (2) No history of excessive alcohol consumption (defined as daily alcohol intake < 30 g for men and < 20 g for women); (3) Absence of liver steatosis, significant fibrosis, or focal lesions on routine abdominal ultrasound performed prior to enrollment. Fulfillment of all Procedural Criteria listed above (points 6-8).

Exclusion Criteria (applied to all screened participants): (1) Presence of a liver tumor or history of liver transplantation; (2) Unsuccessful STE, visco-elastography and USAT measurements; (3) Patients excessive drinking (daily alcohol consumption ≥ 30 g for men and ≥ 20 g for women); (4) Inability or unwillingness to provide informed consent.

Operators and medical equipment

The gray-ultrasound, STE, visco-elastography, USAT, FibroScan-CAP, and FibroScan-VCTE examinations were executed by a proficient individual with two decades of experience in detecting liver ultrasound. The individual (FJ-Dong) has five years of experience in carrying out FibroScan-VCTE and visco-elastography examinations and three years in STE examinations. STE, visco-elastography and USAT were carried out utilizing the Resona 7 system (Mindray Medical Solutions, probe SC6-1U, Shenzhen, China). FibroScan-CAP and FibroScan-VCTE were performed by the FibroScan Handy (Echosens, probe M and XL, Paris, France).

Examination protocol

The participants fasted for 8 hours or more and have a good level of consciousness and being able to cooperate with the ultrasound doctor during the examination. Place the subject in a supine position behind their back and raise their right hand to the top of their head. Perform ultrasound examination of STE, visco-elastography, and USAT in the patient's right liver lobe, capturing clear two-dimensional liver images and avoiding duct echoes as much as possible. The order of the three ultrasound-based techniques—STE, visco-elastography, and USAT—was randomized for each participant using

a computer-generated sequence. This was done to prevent any systematic bias that might arise from a fixed examination order.

STE measures the speed of laterally propagating shear waves induced by an acoustic radiation force impulse. This speed is converted to liver stiffness, which primarily reflects the degree of fibrosis [28]. Visco-E extends the concept by analyzing the shear wave dispersion and attenuation. It quantifies not only stiffness but also tissue viscosity, a parameter suggested to be influenced by both fibrosis and inflammatory activity [19,29]. STE and visco-elastography are used for abdominal probes with frequencies of 2-5 MHz. The inspection progress is performed while the patient is lying flat and holding their breath for 3-5 seconds. According to the M-STB index, the detection requirements are divided into 1-5 star levels, and the conditions that meet the measurement results are above 4 stars. The visco-elastography sampling frame is placed 1cm below the right liver capsule to avoid intrahepatic duct structures. Select a circular quantitative detection area to display the average elastic modulus in kPa. Each measurement was repeated three times, and the average value was recorded. The subsequent offline analysis of stored STE and visco-elastography images was performed by an independent assessor who was blinded to patient identity, clinical data, and results from other techniques (USAT, FibroScan). The units of results for STE and visco-elastography are kPa, and Pa·s respectively [30,31].

USAT estimates the attenuation coefficient of the ultrasound beam as it passes through the liver parenchyma. This parameter correlates with hepatic steatosis, as lipid droplets scatter and attenuate ultrasound energy [32]. During the USAT examination, position the sampling box in liver segments S5 and S6, ensuring it is clear of the gallbladder, bile ducts, and blood vessels. Instruct the patient to hold their breath for 3-5 seconds to stabilize the image. Optimal results are achieved when the sampling box is filled with more than 90% color. If the color fill is less than 80%, adjust the area of interest accordingly. Measure the USAT value and calculate the average from three readings. The analysis of USAT data was also conducted by an assessor blinded to other imaging and clinical results. The results are reported in decibels per centimeter per megahertz (dB/cm/MHz) [30].

For FibroScan-VCTE and FibroScan-CAP, the expert measured the intercostal space at either the anterior axillary line or midaxillary line until they obtained at least 10 valid individual measurements, and take the average value. The FibroScan analyst was blinded to the results of the STE, visco-elastography, and USAT examina-

tions. The units of results for VCTE and CAP are kPa and dB/m, respectively [33].

Measurement reproducibility analysis

To assess the immediate reproducibility and internal consistency of the ultrasound-based measurements, a key metric for evaluating operator variability and technical reliability, we analyzed the three consecutive measurements acquired for each technique (STE, Visco-elastography, USAT) during the single examination session. This approach evaluates the test-retest reliability under stable, real-world clinical conditions. Reproducibility was quantified using the intraclass correlation coefficient (ICC). ICC values were interpreted as follows: < 0.50, poor; 0.50-0.75, moderate; 0.75-0.90, good; and > 0.90, excellent.

Definition of the reference standard

In this study, the diagnostic performance of the novel ultrasound techniques (STE, visco-elastography, USAT) was evaluated against an established non-invasive reference standard. The classification of liver fibrosis and steatosis was based exclusively on the measurements from FibroScan (VCTE and CAP), using the device's validated cut-off values: liver stiffness (by VCTE): normal: < 7.3 kPa; hepatic fibrosis: $\geq$ 7.3 kPa and < 12.4 kPa; cirrhosis: $\geq$ 12.4 kPa. Hepatic steatosis (by CAP): normal: < 238 dB/m; fatty liver: $\geq$ 238 dB/m. The use of FibroScan as the reference standard is justified by its widespread clinical acceptance and robust validation against liver histology [18,24,34].

Sensitivity analysis of ALT threshold for visco-elastography

To address the potential for misclassification bias inherent in using a single ALT threshold, a sensitivity analysis was performed. The diagnostic performance of visco-elastography was re-evaluated using established sex-specific upper limits of normal (Male: > 30 U/L, Female: > 19 U/L) for ALT, as recommended by clinical guidelines [35,36]. When applying this more rigorous classification, the AUC of visco-elastography for identifying biochemical liver injury was 0.72 (95% CI: 0.66-0.77), compared to an AUC of 0.81 (95% CI: 0.76-0.86) under the original criterion (ALT > 40 U/L). This change in AUC (Δ AUC = 0.09) and the consistent, fair-to-good performance across both thresholds indicate that the association between visco-elastography and liver injury is robust. Crucially, this variation demonstrates that the technique is sensitive to the precise definition of hepatocellular injury, suggesting that it captures pathophysiological processes that are intrinsically linked to the gradation of biochemical damage. The detailed per-

formance metrics under both classification criteria are summarized in table S1.

Sample size consideration

This study was a retrospective, exploratory diagnostic research. The sample size was determined by the total number of consecutive patients who completed all target examinations (STE, visco-elastography, USAT, and FibroScan series) within the predefined enrollment period (February 1st to September 30th, 2023), resulting in 310 eligible patients. As this was not a prospective study with a pre-specified primary hypothesis, a formal sample size calculation was not performed prior to data collection. However, to assess the statistical precision afforded by our cohort for key diagnostic assessments, a post-hoc estimation was conducted. Taking the evaluation of STE for significant fibrosis ($F \geq 2$, using FibroScan-VCTE as the reference) as an example: among the 310 patients, 85 were classified as having significant fibrosis. Based on literature reporting diagnostic sensitivity around 85% for point shear wave elastography (technically analogous to STE) [37], the 95% confidence interval half-width (margin of error) for sensitivity estimation in our study is approximately $\pm 7.6\%$. For specificity (based on 225 non-fibrotic patients and an assumed specificity of 80%), the margin of error is approximately $\pm 5.2\%$. This level of precision was deemed acceptable for an exploratory study aiming to provide initial evidence.

Statistical analysis

Statistical analysis is performed by R version 4.2.2 (<https://www.r-project.org>). The GraphPad Prism is used for data processing and displaying variable distribution in graphical form. The statistical significance is set to a p-value below 0.05. Use Bayesian models for multiple imputation of missing data. In order to compare whether there are differences within the groups of VCTE $\geq$ 7.3 kPa and VCTE < 7.3 kPa, t-test or rank sum test is determined based on the normal or non-normal distribution of the data. Interval data is represented as a median with lower and upper quartiles. In order to find the cut-off values of STE, visco-elastography, and USAT based on the critical values of VCTE, ALT, and CAP, the parametric and non-parametric receiver operating characteristic (ROC) curve, area under the curve (AUC), and corresponding sensitivity, specificity, accuracy was calculated.

Results

Participation information

There were 207 were male and 103 were female from

participants, with a median age of 42.5 years (interquartile range [IQR]: 34.25–52 years). Table 1 presents the specific clinical attributes of the participants, categorized into hepatic fibrosis and non-hepatic fibrosis groups. Using a standard threshold of $P < 0.05$, statistical significance was found in age ($P < 0.01$), sex ($P = 0.02$), height ($P < 0.01$), weight ($P < 0.01$), ALT ($P < 0.01$), STE mean values ($P < 0.01$), Visco-elastography mean values ($P < 0.01$), USAT mean values ($P < 0.01$), FibroScan-VCTE ($P < 0.01$), and FibroScan-CAP ($P < 0.01$).

Additional baseline tables were also stratified by hepatocellular injury state and non-alcoholic fatty liver disease, with clinical features outlined in table S2 and table S3. For hepatocellular injury state, age ($P < 0.01$), sex ($P = 0.02$), height ($P < 0.01$), weight ($P < 0.01$), ALT ($P < 0.01$), STE mean values ($P < 0.01$), visco-elastography mean values ($P < 0.01$), USAT mean values ($P < 0.01$), FibroScan-CAP ($P = 0.01$), and FibroScan-VCTE ($P < 0.01$) were statistically significant. In the non-alcoholic fatty liver disease group, sex ($P = 0.02$), height ($P < 0.01$), weight ($P < 0.01$), ALT ($P < 0.01$), visco-elastography mean values ($P = 0.01$), USAT ($P < 0.01$), and FibroScan-CAP ($P < 0.01$) showed statistical significance. When integrating the three groups, age, height, ALT, USAT, and FibroScan-CAP were identified as the statistically significant variables.

Measurement reproducibility

The internal reproducibility of STE, visco-elastography, and USAT measurements, assessed from three consecutive measurements obtained during the examination,

was found to be excellent (see table S4). The ICC values for STE, visco-elastography, and USAT were 0.96 (95% CI: 0.94–0.99), 0.93 (95% CI: 0.91–0.95), and 0.95 (95% CI: 0.91–0.97), respectively. These results indicate a very high level of consistency and low variability in the measurements obtained by the same operator under stable conditions.

The cut-off values of STE, visco-elastography, and USAT and their diagnostic efficacy for CLDs

The cut-off values for STE, visco-elastography, and USAT, along with the corresponding AUC, sensitivity, specificity, and accuracy, are detailed in table 2. The AUC values of each model show that the three techniques have good diagnostic efficacy for various liver disease states: STE for liver fibrosis (AUC: 0.82, 95% CI: 0.76–0.87), visco-elastography for hepatocellular injury state (AUC: 0.81, 95% CI: 0.76–0.86), and USAT for NAFLD (AUC: 0.82, 95% CI: 0.77–0.87), the ROC for STE, visco-elastography, and USAT were shown in figure 1. To provide a comprehensive diagnostic assessment, we integrated the findings from the three ultrasound techniques. Each participant was classified as positive or negative for three relevant features based on the validated cut-offs: liver fibrosis (STE ≥ 8.09 kPa), hepatocellular injury state (visco-elastography ≥ 1.62 Pa·s), and NAFLD (USAT ≥ 0.68 dB/cm/MHz). The combination of these three binary classifications yielded seven distinct diagnostic scenarios, as illustrated in figure 2 and figure 3. The scenarios are as follows: 1) isolated liver fibrosis; 2) liver fibrosis combined with NAFLD; 3) liver fibrosis combined with hepatocellular injury;

Table 1 Clinical characteristics of CLDs participants based on liver fibrosis

Variables	Total (n = 310)	Non Fibrosis (n = 225)	Fibrosis (n = 85)	P value
Age ^c	42.5 (34.25, 52)	44 (36, 53)	38 (32, 49)	< 0.01
Sex ^a				0.02
F	103 (33)	84 (37)	19 (22)	
M	207 (67)	141 (63)	66 (78)	
Height ^c (cm)	168 (160, 172.75)	166 (160, 171)	171 (165, 175)	< 0.01
Weight ^c (Kg)	65.5 (58.62, 75)	64 (58, 72.5)	72 (62.5, 80)	< 0.01
HCV patient ^a	30 (10)	21 (9)	9 (11)	0.91
HBV patient ^a	143 (46)	109 (48)	34 (40)	0.23
ALT ^c (U/L)	27 (19, 43.75)	22 (17, 28)	69 (52, 117)	< 0.01
STE ^c (kPa)	7.47 (6.52, 9)	7.23 (6.38, 8.47)	8.63 (7.12, 11.05)	< 0.01
Visco-elastography ^c (Pa·s)	1.6 (1.42, 1.84)	1.53 (1.31, 1.72)	1.85 (1.68, 2.13)	< 0.01
USAT ^c (dB/cm/MHz)	0.62 (0.52, 0.73)	0.6 (0.52, 0.71)	0.68 (0.54, 0.86)	< 0.01
FibroScan-CAP ^b (dB/m)	241.59 $\pm$ 58.43	235.96 $\pm$ 53.68	256.49 $\pm$ 67.55	< 0.01
FibroScan-VCTE ^c (kPa)	5.4 (4.3, 7.38)	5.1 (4.2, 6.85)	6.5 (5, 9.7)	< 0.01

Except where indicated, data are medians, with IQRs in parentheses. HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; STE, sound touch elastography; USAT, ultrasound attenuation analysis; CAP, controlled attenuation parameter; VCTE, vibration-controlled transient elastography; ^a Disordered classification variables are shown by percentage; ^b Normally distributed numerical variables are shown by mean $\pm$ standard deviation; ^c Non-normally distributed numerical variables are shown by median (first quartile, third quartile).

Table 2 The diagnosis performance of CLDs

	Cut-off (95%CI)	AUC (95%CI)	Specificity (%)	Sensitivity (%)	Accuracy (%)
STE mean	8.09 (7.30-9.17)	0.82 (0.76-0.87)	76.42	74.07	75.81
Visco-E mean	1.62 (1.48-1.74)	0.81 (0.76-0.86)	63.56	83.53	69.03
USAT mean	0.68 (0.58-0.68)	0.82 (0.77-0.87)	90.14	58.93	73.23

CI: confidence interval; STE, sound touch elastography; USAT, ultrasound attenuation analysis.

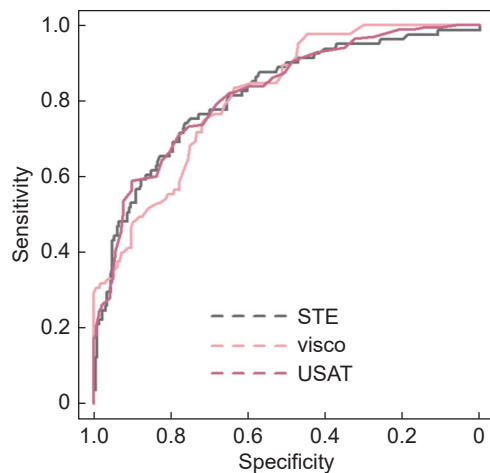


Figure 1 The diagnostic performance of STE, visco-elastography and USAT for CLDs. ROC curve for detecting STE, visco-elastography, USAT cut-off values based on the FibroScan-VCTE, ALT, FibroScan-CAP level. The area under the curve: 0.82, 0.81, 0.82 respectively.

4) liver fibrosis with NAFLD and hepatocellular injury;
5) isolated NAFLD; 6) NAFLD combined with hepato-

cellular injury; and 7) isolated hepatocellular injury state.

Discussion

CLDs are characterized by high incidence and mortality rates. The complex and varied pathogenesis of CLDs poses significant challenges for clinical diagnosis and treatment. This study employed three advanced ultrasound technologies—STE, Viscoelastic imaging, and USAT—to establish cut-off values aimed at distinguishing CLDs with mixed etiologies, such as liver fibrosis, hepatocellular injury state, and NAFLD. The findings revealed that age, height, ALT levels, USAT values, and FibroScan CAP scores are crucial predictive variables across three chronic liver disease subgroups: fibrosis versus non-fibrosis, hepatocellular injury state versus non-hepatocellular injury state, and NAFLD versus non-NAFLD. This underscores the significance of these variables as important predictors in the manage-

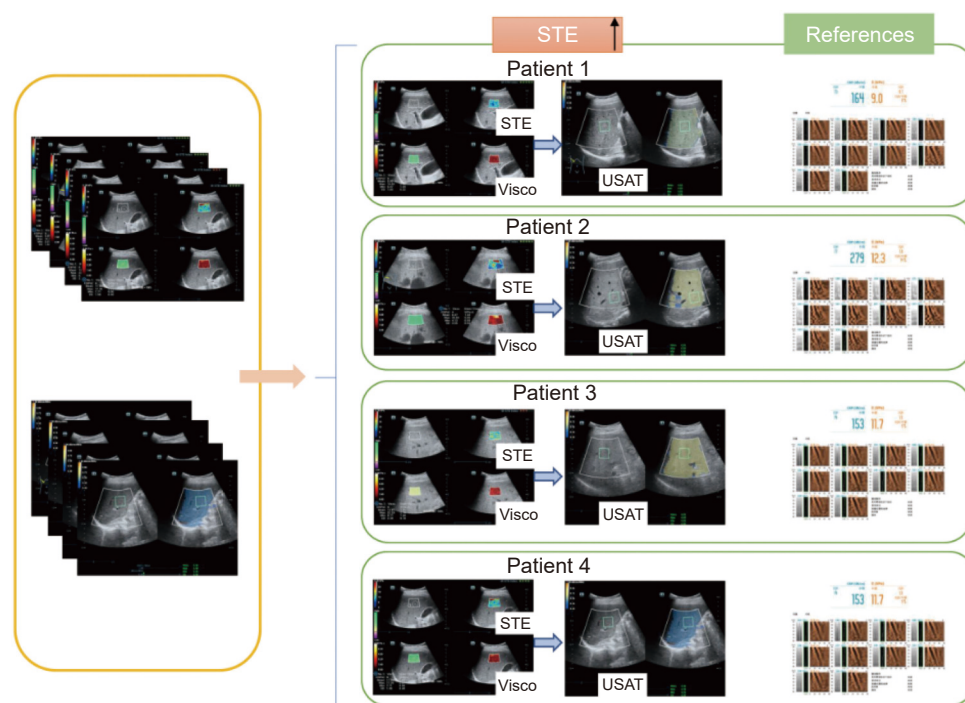


Figure 2 Diagnostic flowchart of the cases, grouped according to STE. The first column shows the results of STE and visco-elastography, the second column shows the results of USAT, and the third column shows the results of FibroScan-VCTE and CAP. Patient 1, elevated STE (9.85), normal visco (1.52), normal USAT (0.62) → liver fibrosis; Patient 2, elevated STE (8.47), normal visco (1.43), elevated USAT (0.7) → liver fibrosis combined with non-alcoholic fatty liver; Patient 3, elevated STE (13.01), elevated visco (1.91), elevated USAT (0.82) → liver fibrosis combined non-alcoholic fatty liver in the hepatocellular injury state; Patient 4, elevated STE (11.83), elevated visco (1.68), normal USAT (0.46) → liver fibrosis in the hepatocellular injury state.

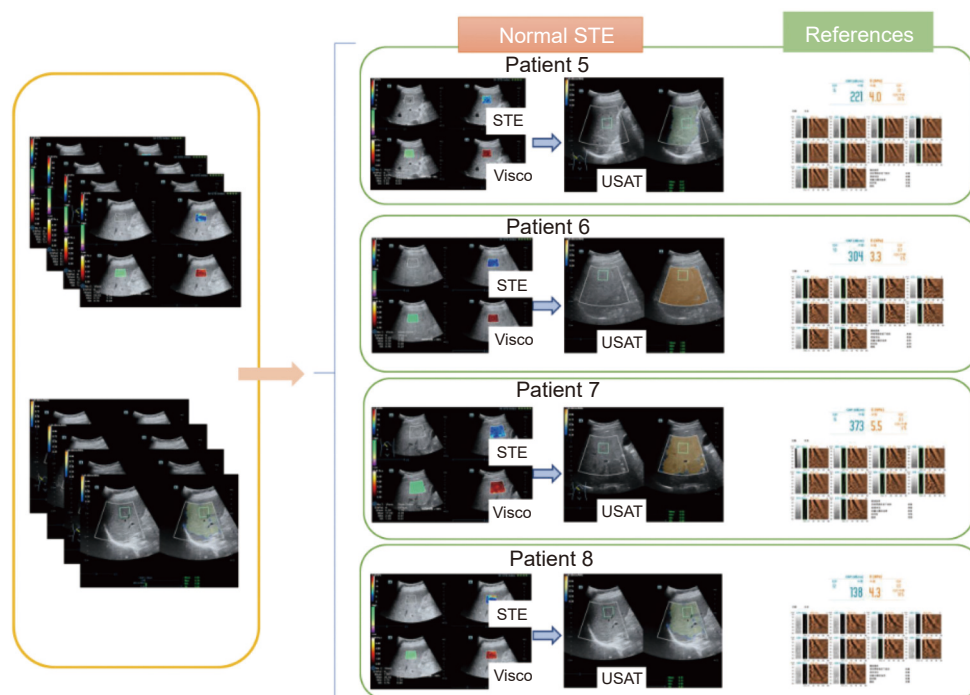


Figure 3 Diagnostic flowchart of the cases, grouped according to STE. The first column shows the results of STE and visco-elastography, the second column shows the results of USAT, and the third column shows the results of FibroScan-VCTE and CAP. Patient 5, normal STE (8.02), normal visco (1.4), normal USAT (0.6)→normal participant; Patient 6, normal STE (5.53), normal visco (1.42), elevated USAT (1)→simple non-alcoholic fatty liver; Patient 7, normal STE (6.52), elevated visco (1.73), elevated USAT (0.93)→non-alcoholic fatty liver in the hepatocellular injury state; Patient 8, normal STE (7.64), elevated visco (2.11), normal USAT (0.63)→simple hepatocellular injury state.

ment of chronic liver disease.

Based on the reference standards for CLDs caused by different etiologies such as liver fibrosis, hepatocellular injury state, and NAFLD, we constructed three ROC curves and determined the cut-off values for each: the cut-off STE value was 8.09 (95% CI: 7.30-9.17), the cut-off USAT value was 1.62 (95% CI: 1.49-1.74), and the cut-off Visco-elastography value was 0.68 (95% CI: 0.58-0.68). This study demonstrates that STE has superior diagnostic efficacy for liver fibrosis, consistent with other researchers' findings [38], establishing STE as an effective method for diagnosing and staging liver fibrosis. However, according to the guidelines by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), STE is deemed unsuitable for conditions like inflammation and acute hepatitis [39]. Visco-elastography overcomes this limitation, providing valuable insights for assessing the hepatocellular injury state. Our findings indicate that visco-elastography can significantly differentiate patients with normal and elevated ALT levels, achieving an AUC of 0.81. FibroScan-CAP is emphasized as a non-invasive tool using ultrasound technology to estimate liver fat content, offering advantages over liver biopsy due to its lower sampling error and performance unaffected by liver fibrosis [40,41]. Similarly, USAT imaging is considered a non-invasive technique that assesses liver fat content

by restoring the sound speed and attenuation information in ultrasound signals from different liver locations. Previous studies have validated the effectiveness of USAT in detecting NAFLD liver steatosis, with an AUC of 0.89 [42]. Although the AUC for USAT in this study is slightly lower at 0.82, it still confirms the diagnostic value of USAT for pure NAFLD.

It is worth noting that a pivotal insight from this study is derived from the sensitivity analysis, which revealed that the diagnostic performance of visco-elastography was modulated by the stringency of the ALT threshold used to define liver injury (Table S1). We posit that this observed sensitivity is not a methodological shortfall but rather a robust validation of its biological plausibility. Unlike STE, which primarily reflects the static, collagen-based architecture of hepatic fibrosis, the viscoelastic properties measured by this novel technique are hypothesized to capture the dynamic tissue microenvironment altered by active necroinflammation.

From a pathophysiological perspective, active hepatocellular injury is characterized by a cascade of events including cellular swelling (ballooning), inflammatory cell infiltration, and extracellular matrix edema [43]. These processes directly alter the intrinsic mechanical properties of the liver parenchyma, increasing its viscosity and altering its stress-relaxation behavior—properties that visco-elastography is uniquely designed to

quantify [44,45]. The finding that its diagnostic accuracy is sensitive to the gradation of biochemical injury, as refined by sex-specific ALT thresholds, provides compelling evidence that the technique is tracking these specific activity-driven pathological changes. This functional correlation, distinguishing it from structural modalities like STE or USAT, strongly supports the potential of visco-elastography as a future tool for non-invasive monitoring of disease activity and treatment response in chronic liver diseases.

Thus, this study explores the preliminary diagnostic efficacy of three new ultrasound technologies—STE, visco-elastography, and USAT—for diagnosing CLDs with complex etiologies, highlighting their high diagnostic performance for liver fibrosis, hepatocellular injury state, and NAFLD, with respective AUC values of 0.82, 0.81, and 0.82. The innovation of this study lies in using ultrasound imaging to assess liver conditions within the context of liver fibrosis, hepatocellular injury state, and NAFLD.

This study constructed the multiparametric ultrasound framework that defines seven phenotypic scenarios of CLD. This stratification carries significant clinical implications for personalized patient management. For instance, identifying isolated steatosis primarily guides lifestyle modification, while detecting steatosis with concurrent biochemical injury raises strong suspicion for underlying steatohepatitis (MASH), indicating a need for further assessment to consider pharmacotherapy or trial enrollment. The identification of fibrosis in any combination elevates prognostic concern, triggering requirements for surveillance of complications such as portal hypertension and hepatocellular carcinoma. Crucially, the triple-positive phenotype pinpoints high-risk patients with biochemical injury on a background of fibrosis and steatosis, who merit the most intensive evaluation and intervention. Thus, by moving beyond isolated metrics, this integrative approach facilitates nuanced risk stratification and guides subsequent clinical decision-making, effectively bridging the gap between multiparametric measurement and individualized patient care pathways. By integrating these three technologies, the study proposes a relatively comprehensive early screening method for CLDs, potentially reducing the incidence of misdiagnosis and assisting clinicians in more efficiently diagnosing different etiologies of CLDs. Moreover, combining these three technologies into a single ultrasound device enhances the convenience of examinations and optimizes the use of medical resources during the procedures.

The cost-effectiveness of visco-elastography compared to existing modalities is a crucial consideration for its clinical translation. While this study did not perform

a formal economic analysis, several factors suggest its potential for favorable cost-utility. Unlike magnetic resonance elastography (MRE) [46], which requires dedicated hardware and is resource-intensive, Visco-elastography is implemented on a standard ultrasound system, potentially leveraging existing hospital infrastructure and reducing capital expenditure. Compared to the widely used FibroScan (VCTE), visco-elastography offers the added value of simultaneously assessing viscosity, a marker of inflammatory activity, alongside stiffness, within a single examination. This could reduce the need for separate tests to stage fibrosis and grade activity, streamlining patient workflow. However, this potential advantage must be weighed against the current need for specialized software and operator expertise. Future studies incorporating direct cost-benefit analyses and assessing the impact on clinical decision-making pathways are warranted to definitively establish its economic value.

Regarding the present study design, the objective of this study was to explore the potential of three non-invasive techniques for the early diagnosis of CLDs. To this end, patients with decompensated cirrhosis were excluded from the cohort. Individuals with decompensated cirrhosis, particularly those presenting with portal hypertension or ascites, seldom require the aforementioned ultrasound-based non-invasive examinations for the early detection of CLDs. This exclusion was implemented to reduce technical confounders associated with elastography measurements in this investigation. Furthermore, while common metabolic confounders such as obesity and diabetes were documented, our primary analysis focused on evaluating the unadjusted performance of the imaging parameters. Future studies with larger cohorts are necessary to determine whether these factors modify the optimal diagnostic thresholds and to validate the proposed cut-off values in broader patient populations, including those with compensated advanced CLDs.

In addition to these design-focused considerations, several important limitations of this study should be acknowledged. First, the sample size was moderate. While the precision for the primary diagnostic assessments (e.g., STE for fibrosis) was acceptable, the study was not powered for independent hypothesis testing in every subgroup of the seven theoretical clinical scenarios (e.g., ‘fibrosis + steatosis + injury’). In addition, the findings related to these combined scenarios should be considered preliminary and descriptive, and their definitive diagnostic value requires further validation in larger, prospective studies. Secondly, this study employed FibroScan as the non-invasive reference standard, a pragmatic and methodologically sound approach that is well-established in the comparative evaluation of emerging imaging technologies [47]. However, Fibroscan does

not provide the same histopathological detail, and liver biopsy remains the most valuable gold standard in clinical settings, and future studies will still require histopathological liver biopsies to further validate the effectiveness and accuracy of the ultrasound techniques explored in this research. The third, an additional recognized limitation of ultrasound-based techniques, including visco-elastography, is their variable performance in patients with obesity. Increased subcutaneous adipose tissue can attenuate ultrasound signal penetration, potentially compromising measurement reliability. Our study, limited by sample size, did not conduct a BMI-based subgroup analysis. Future validation in larger cohorts must specifically assess the technique's accuracy in obese populations (e.g., BMI > 30 kg/m²). Finally, in this study, the use of a single operator, while controlling variability, may limit generalizability to less experienced settings. And recruitment from a tertiary center may over-represent advanced disease, affecting the extrapolation of our results to community populations. Future multi-center studies are needed for broader validation.

Conclusion

Therefore, STE, visco-elastography, and USAT demonstrate good diagnostic efficacy for seven different types of CLDs, and the combined utilize of these three techniques can assist clinicians in the early diagnosis and assessment of CLDs with complex etiologies. This establishes a foundation for the early screening of CLDs and highlights the potential of these non-invasive ultrasound techniques in clinical settings. However, this study also underscores the necessity for further research to refine the diagnostic process and enhance the ability to accurately distinguish specific types of CLDs.

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Authors' contributions

Study concept and design: SM, ZD. Data extraction: ZH. Data analysis and interpretation: SM, MW, JX. Manuscript preparation: SM. Manuscript review: HZ, FD. Manuscript editing: SM. All authors approved the final manuscript for submission.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was executed in strict adherence to the principles outlined in the Declaration of Helsinki (2013 revision). This continuously collected study was approved by the Institutional Review Board of the Shenzhen People's Hospital, specifically the Medical Ethics Committee of Shenzhen People's Hospital. The need for informed consent was obtained by the Institutional Review Board of Shenzhen People's Hospital, specifically by the Medical Ethics Committee of Shenzhen People's Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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