Original Article

The diagnostic value of novel ultrasound attenuation analysis in detecting liver steatosis identified by the controlled attenuation parameter: a diagnostic accuracy study

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Background: Ultrasound attenuation analysis (USAT) is a type of novel ultrasound attenuation imaging that can be used to detect hepatic steatosis based on the attenuation coefficient. We sought to evaluate the diagnostic accuracy for assessing the severity of liver steatosis by USAT using the controlled attenuation parameter (CAP) as a reference in patients with non-alcoholic fatty liver diseases (NAFLD) and chronic hepatitis B (CHB) infections.

Methods: In total, 326 consecutive subjects with or without chronic liver diseases were enrolled in this study who underwent CAP examination and USAT to evaluate hepatic steatosis from October 2022 to November 2022 at The Fourth Affiliated Hospital of Zhejiang University School of Medicine. Hepatic steatosis stage (S) was determined by CAP according to the following cut-off values recommended by the manufacturer: S ≥ S1 (≥11%, mild): 238 dB/m; S ≥ S2 (≥34%, moderate): 259 dB/m; and S ≥ S3 (≥67%, severe): 292 dB/m, and thus the optimal cut-off values for the USAT were acquired. The area under the receiver operating characteristic curves (AUROCs) for the categories of steatosis were used to measure the diagnostic accuracy of USAT.

Results: A total of 296 patients were recruited, including 101 (34.1%) patients with NAFLD, 172 (58.1%) with CHB and the remainder were healthy control subjects (7.8%). We used the CAP as the reference standard and found that the USAT increased gradually as the stage of steatosis increased (P<0.001). A strong positive correlation was found between USAT and CAP (r=0.787, P<0.001). In the whole population, the AUROCs of the USAT for S ≥ S1, S ≥ S2 and S ≥ 3 were 0.89, 0.90, and 0.90, respectively, and the cut-off values according to the Youden index for S ≥ S1, S ≥ S2, and S ≥ 3 were 0.62, 0.66, and 0.72 dB/cm/MHz, respectively. Our study showed that the USAT had a good ability to detect hepatic steatosis in NAFLD and CHB patients.

Conclusions: USAT had a strong association with CAP and a good diagnostic capability in the detection

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of hepatic steatosis, which appears to be a promising tool for the non-invasive detection and quantification of hepatic steatosis.

Keywords: Non-alcoholic fatty liver diseases (NAFLD); chronic hepatitis B infections; ultrasound attenuation analysis (USAT); controlled attenuation parameter (CAP); hepatic steatosis

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Introduction

Hepatic steatosis is a frequent feature of chronic liver diseases with multiple etiologies. The prevalence of hepatic steatosis is rising globally, and it is significantly linked to obesity and metabolic syndrome. The main cause of hepatic steatosis is non-alcoholic fatty liver disease (NAFLD), but it can also be caused by chronic hepatitis B (CHB) infections. NAFLD is becoming the leading cause of chronic liver diseases, and has an estimated global prevalence of 30% in the general public and a prevalence of 80% in morbidly obese individuals (1). CHB is a significant public health problem affecting over 290 million people worldwide (2,3), and it often co-occurs with hepatic steatosis. Simple steatosis is benign; however, regardless of whether simple steatosis is caused by NAFLD or CHB, it may predispose individuals to fatty steatohepatitis, cirrhosis, liver failure, and ultimately hepatocellular carcinoma (4,5). Due to the added health burden, rising mortality risk, and potential need for liver transplantation, the severity of liver steatosis requires urgent attention (6,7).

Steatosis frequently goes undetected in the early stages, and serious abnormalities, such as jaundice and ascites, do not present until cirrhosis develops. Currently, there is a lack of specific pharmacotherapy for steatosis; however, individuals with hepatic steatosis should be able to be identified efficiently and affordably and steatosis should be able to be evaluated accurately in a way that is non-invasive and readily available. This would also help clinicians to make informed decisions and identify those at great risk of clinical progression.

The gold standard for evaluating hepatic steatosis continues to be liver biopsy. Due to several factors, including the invasive nature, the possibility of sampling errors, and a lack of sufficient patient follow-up, liver biopsy cannot be used as the routine examination given the large-scale population suffering from hepatic steatosis (8). Thus, non-invasive methods for the diagnosis of steatosis, especially those that use imaging techniques, need to be developed.

FibroScan was initially intended to be used to determine liver stiffness measurements (LSMs) using vibration controlled transient elastography. In recent years, the controlled attenuation parameter (CAP), which makes use of the characteristic of considerable attenuation of ultrasound waves when passing through fatty liver tissue, was developed by FibroScan to quantify the degree of hepatic steatosis concurrently when performing LSMs (9,10). Numerous investigations have proven its excellent diagnostic efficacy in identifying hepatic steatosis in people with chronic liver diseases caused by a variety of etiologies (11,12). Compared to liver biopsy, magnetic resonance imaging (MRI) and computed tomography (CT), the CAP offers the benefits of non-invasive quantification, easy operation, instant results, and low costs.

The guidelines of the Asia-Pacific Working Party on Non-Alcoholic Fatty Liver Disease recommend that the CAP be used as a screening tool for NAFLD, as well as for evaluating progress in response to lifestyle interventions and weight loss (13). However, as the CAP is calculated

Highlight box

Key findings
- USAT shows good diagnostic value in evaluating the severity of hepatic steatosis.

What is known and what is new?
- CAP was accepted as a useful tool available in quantifying hepatic steatosis;
- USAT is a neoteric non-invasive quantitative technique implemented in traditional ultrasound machines. USAT had a strong association with CAP and a good diagnostic capability in the detection of hepatic steatosis

What is the implication, and what should change now?
- USAT could be a useful tool in identifying liver steatosis in the future as its good diagnostic accuracy.

based on one-dimensional ultrasound signals obtained by a single array probe, it is unable to capture visual structural information for the liver, and the data is easily affected by the liver sampling position or section. Thus, the repeatability and accuracy of the quantitative measurement need to be further refined (14). A compound quantitative technique that can provide visual structural information for the liver and two-dimensional acoustic attenuation results for the liver is urgently needed in clinical settings.

Recently, a neoteric ultrasound attenuation analysis (USAT) modality from Mindray Corporation was invented as a non-invasive quantitative method. This modality uses the attenuation coefficient to diagnose hepatic steatosis. The amplitude of ultrasonic waves decreases with depth due to the attenuation that occurs during body propagation. Under the guidance of two-dimensional gray-scale sonography, the USAT detects the mean ultrasonic attenuation coefficients in the liver tissue at the region of interest (ROI). It also automatically avoids structures that affect the measurement accuracy, such as blood vessels, biliary ducts, and intrahepatic masses. The USAT enables the quantitative evaluation of the degree of hepatic steatosis, which is also helpful for disease follow-up. Also, USAT can be realized in traditional ultrasound machines with no extra equipment specialized in detecting steatosis. These advantages make it accurate and efficient at measuring the degree of steatosis.

NAFLD and CHB are two representative diseases of chronic liver diseases worldwide. Hepatic steatosis is easily observed in histopathological results. Due to the many histologically determined studies based on the CAP (15,16), we chose to examine the USAT using the CAP as the standard rather than liver histology results. In addition to the ethical aspects of invasiveness, the CAP has a better sampling error than histology techniques. We sought to explore the diagnostic value of the attenuation coefficient determined by the USAT in evaluating the degree of hepatic steatosis by comparing it to the CAP in patients with NAFLD and CHB. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5821/rc).

Methods

Subjects

This was a single-center cross-sectional study. From October 1st, 2022 to November 5th, 2022, a prospective consecutive study was conducted at The Fourth Affiliated Hospital of Zhejiang University School of Medicine. The study population comprised 326 consecutive subjects with or without chronic liver diseases, who were assessed for liver steatosis on the same day by both the USAT and CAP. We also recorded the patients' information, including their age, gender, weight height, previous medical history, and alcohol consumption. Body mass index (BMI) was computed by dividing the body weight (kilograms) by the square of the height (meters). The patients' laboratory data for hepatitis B [hepatitis B surface antigen (HBsAg), anti-HBs, hepatitis B core antigen (HBcAg), anti-HBc, and hepatitis B e antigen (HBeAg)] were also collected.

To be eligible for inclusion in this study, patients had to meet the following inclusion criteria, the patients had to be aged ≥18 years and have the capacity to give informed consent. Patients scheduled to undergo a FibroScan examination for suspected of diffuse liver diseases (usually as a result of imaging modalities or abnormal liver enzymes) were recruited for the test group. As per the 2018 practice guidelines of the American Association for the Study of Liver Diseases, a diagnosis of NAFLD was made if there was evidence of hepatic steatosis liver based on imaging or histology results, no other causes of steatosis, no significant alcohol consumption (i.e., an ethanol intake of <21 standard drinks per week for men and <14 standard drinks per week for women), and no co-existing chronic liver disease (17). A diagnosis of chronic hepatitis B virus (HBV) infection was made if the patient tested positive for the HBsAg for >6 months.

To strengthen the reliability of the cut-off values, healthy control subjects, comprising hospital staff members who underwent routine annual health check-ups, were included in the study. Only those with normal laboratory values and no history of liver diseases or those who were not receiving any medical treatments were enrolled.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a hepatitis virus other than the HBV, or other chronic liver diseases, including alcoholic liver disease or cholestatic liver disease; (II) had undergone liver surgery, such as a liver transplant or a partial hepatectomy; and/or (III) had other serious extra-hepatic diseases, such as chronic heart failure, chronic obstructive pulmonary diseases, and chronic kidney diseases.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Fourth Affiliated

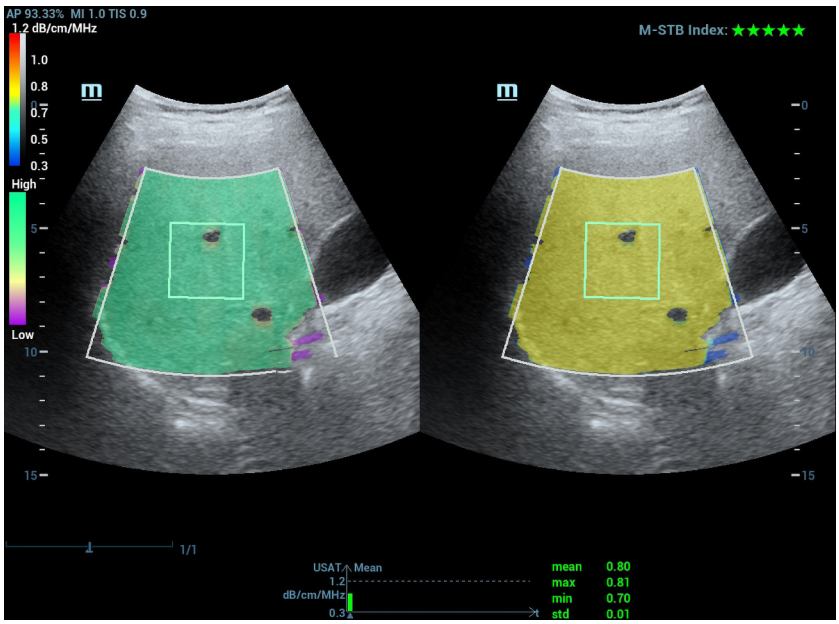

Figure 1 Actual measurement screen of an USAT. USAT, ultrasound attenuation analysis; std, standard deviation; AP, acoustic power; MI, mechanical index; M-STB, motion-stability.

Hospital of Zhejiang University School of Medicine (No. K2022153). Informed consent was obtained from each individual before inclusion.

USAT

USAT was measured by a newly developed ultrasound machine with a SC6-1U phased array probe (Mindray R9, China). The USAT examination was performed by an experienced radiologist in accordance with the manufacturer's instructions, who was blind to the patients' clinical diagnoses and CAP data. All the examinations were performed after the patients had fasted for >8 hours. To widen the intercostal space and create the appropriate scanning window for the test, the patients were positioned lying on their backs with their right upper extremity on their head. First, the B-mode ultrasound was scanned to fix a suitable position in liver segment V/VI. Second, the USAT mode was activated and the ROI was placed at a position about 5 cm below the liver capsule. A sizable, color-coded attenuation distribution map was generated automatically, in which areas with serious calculation errors (such as blood vessels and the gall bladder) were intelligently filtered out. After modifying the measurement box, which was a square with a side length of 2 cm, the operator pressed the "UPDATE" button. Third, to obtain the attenuation coefficient measurements, the best image was selected using the credibility map as per the instructions (*Figure 1*). Using the same chosen liver images for 5 successive measurements, the results were automatically saved in the system. The median value of the 5 measurements taken in a uniform region of the liver parenchyma and having an interquartile range/median (IQR/M) of <0.30 were defined as effective and successful USAT measurements. The USAT values are expressed in dB/cm/MHz. The USAT technology is explained in detail in the Mindray whitepaper. Abdominal subcutaneous fat thickness was defined as the vertical distance from the skin to the liver capsule on the same portion without applying pressure.

CAP measurement

The CAP was obtained by FibroScan equipped with M probes (Echosens, FibroScan 420, France). The inspection was carried out in accordance with the transient elastography user's manual by a certified manufacturer-trained operator who was blind to the USAT results. To ensure the precise attenuation value of the liver, the CAP was only appraised once a LSM value had been obtained. The LSMs results were based on at least 10 valid measurements, which achieves a success rate of at least 60% and an IQR/M below 30%. There are no recommendations

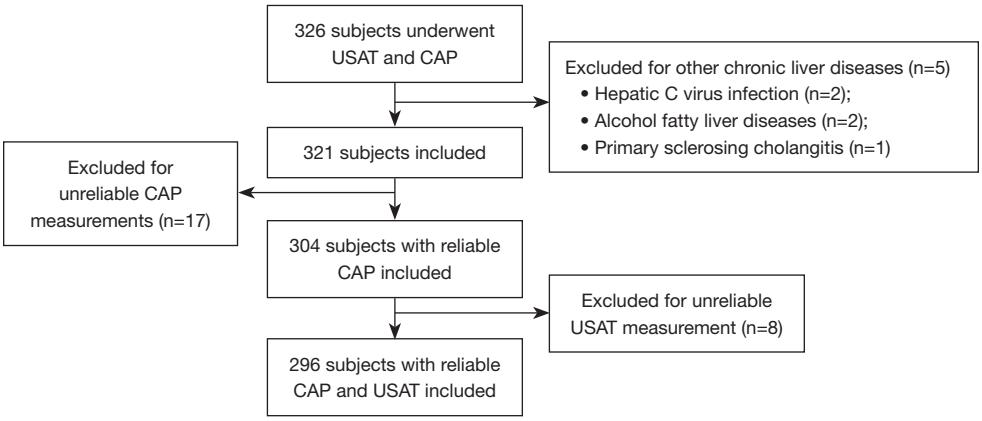

Figure 2 Study flow chart. USAT, ultrasound attenuation parameter; CAP, controlled attenuation parameter.

on how to determine successful CAP measurements. The representative CAP value, which offered a numerical quantitative evaluation of steatosis from 100 to 400 dB/m, was determined based on the median value of the valid data. To discriminate between the steatosis stages (S) using the CAP, we applied the following cut-off values provided by the manufacturer, which is obtained by taking the histological grade of steatosis as reference: S ≥ S1 (≥11%): 238 dB/m; S ≥ S2 (≥34%): 259 dB/m; S ≥ S3 (≥67%): 292 dB/m (18).

Statistical analysis

Power of the study and sample size estimation: A total sample size of 257 subjects achieves 90% power to detect the expected AUROC values from 0.85 to 0.90 using PASS software (copyright 2017, NCSS, LLC).

The statistical analysis was performed using SPSS software version 25.0 (IBM Statistics), MedCalc 20.022 (MedCalc Software, Ostend, Belgium) and R software 4.2.0. The continuous numerical variables are presented as the mean ± standard deviation or the median according to their distribution, and the categorical variables are presented as the number and proportion of patients. The normality of the continuous variable distributions was tested using the Shapiro-Wilk test. The significance of the differences between the groups was analyzed using a one-way analysis of variance, Chi-square test, and Kruskal-Wallis test adjusted by the *post-hoc* Bonferroni test. Spearman's rank correlation coefficients were used to assess the associations between the USAT and the other parameters. A multivariable linear regression analysis was performed to explore the potential predictors of the USAT. We conducted a receiver operating curve (ROC) analysis to evaluate the performance and thresholds. The cut-off values of the USAT were established based on maximize the Youden index, with fixed sensitivity and specificity values of 90%. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated using cutoffs obtained by ROC curves. P values <0.05 were considered statistically significant.

Results

Patient characteristics

A total of 326 subjects were enrolled in our study, and 30 subjects were excluded (see *Figure 2*). The data of 296 participants were included in the final analysis (see *Table 1*). The patients comprised 230 men and 66 women with a mean age of 26.2 years. The patients had a mean BMI of 40.4 kg/m^2, and 62.2% of the patients were obese (i.e., had a BMI ≥25 kg/m^2). Of the patients, 172 were diagnosed with CHB infection (58.1%), 101 patients were diagnosed with NAFLD (34.1%), and the remainder were healthy control subjects (7.8%). The mean USAT value was 0.7 dB/cm/MHz. No significant adverse events happened in our process of test, such as hypotension and syncope.

The incidence of hepatic steatosis based on the CAP

Hepatic steatosis was present in 256 of the 296 subjects (86.5%). Among the patients, 13.5%, 18.6%, 36.5%, and 31.4% were diagnosed with S0, S1, S2, and S3 hepatic steatosis, respectively. Among the 101 patients with NAFLD diagnosed by ultrasound, 2 (2%) patients had S0 hepatic

Table 1 Characteristics of the study cohort

Characteristics	Patient distribution (n=296)
Gender	
Male	230 (77.7)
Female	66 (22.3)
Age (years)	26.2±3.5
BMI (kg/m^2)	40.4±11.3
BMI <25 (kg/m^2)	112 (37.8)
BMI ≥25 (kg/m^2)	184 (62.2)
Distance from the skin to the liver capsule (cm)	1.9±0.4
Etiology of hepatic steatosis	
Chronic hepatic B infection	172 (58.1)
NAFLD	101 (34.1)
Health controls	23 (7.8)
Steatosis stage using the CAP	
S0	40 (13.5)
S1	55 (18.6)
S2	108 (36.5)
S3	93 (31.4)
USAT (dB/cm/MHz)	0.7±0.1

The continuous numerical variables are presented as the mean ± standard deviation or the median according to their distribution, and the categorical variables are presented as the number and proportion of patients. n, number; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; CAP, controlled attenuation parameter; USAT, ultrasound attenuation analysis.

Table 2 Spearman correlation analysis associated with the USAT

Variable	r	P
Gender	–1.112	0.054
Age	–0.004	0.946
BMI	0.348	<0.001*
CAP	0.787	<0.001*
Distance from the skin to the liver capsule	0.334	<0.001*

*, P<0.05. r, Spearman correlation coefficient; USAT, ultrasound attenuation analysis; BMI, body mass index; CAP, controlled attenuation parameter.

steatosis, 17 (16.8%) had S1hepatic steatosis, 37 (36.6%) had S2 hepatic steatosis, and 45/101 (44.6%) had S3 hepatic steatosis. In relation to the patients with CHB infection, only 9.3% of had S0 hepatic steatosis; most of the patients (41.2%) had S2 hepatic steatosis, while 21.5% and 27.9% had S1 and S3 hepatic steatosis, respectively. Notably, the NAFLD patients were more likely to suffer from severe hepatic steatosis than the CHB patients. Hepatic steatosis was easily observed in the CHB patients surprisingly.

Correlations between the USAT and different parameters

As *Table 2* shows, the correlation coefficients of the USAT with the BMI and the distance from skin to liver were 0.348 and 0.334, respectively, which represents mild correlations (P<0.001 for both). However, the USAT and CAP were closely correlated (r=0.787, P<0.001). The USAT was not correlated to sex or age. In the multiple linear regression analysis (dependent variable: USAT), only the CAP was found to be independently correlated with the USAT (P<0.001), and the USAT was not affected by the BMI and the distance from the skin to the liver capsule.

Assessment of steatosis using the USAT compared to the CAP

In this study, we sought to explore the diagnostic performance of the USAT, which is a novel quantitative method for diagnosing hepatic steatosis. *Figure 3* shows the distribution of the USAT values according to the CAP steatosis stage. The median USAT values for S0, S1, S2, and S3 were 0.52, 0.57, 0.68, and 0.84 dB/cm/MHz, respectively, indicating a stepwise rise in hepatic steatosis coupled with a worsening of the condition (P<0.001). The Kruskal-Wallis test adjusted by the *post-hoc* Bonferroni test showed that the USAT differed significantly among S1, S2, and S3, but not between S0 and S1 (P=0.392 between S0 and S1, otherwise P<0.001).

Figure 4 shows the AUROCs, and *Table 3* shows the diagnostic performance of the CAP cut-off values optimized using Youden index, a sensitivity of 90% and a specificity of 90% for the detection of hepatic steatosis of S ≥ S1, S ≥ S2, S ≥ 3. The AUROCs indicated quite high discrimination across all hepatic steatosis stages. The AUROC of the USAT for the prediction of ≥ S1 was 0.89 [95% confidence

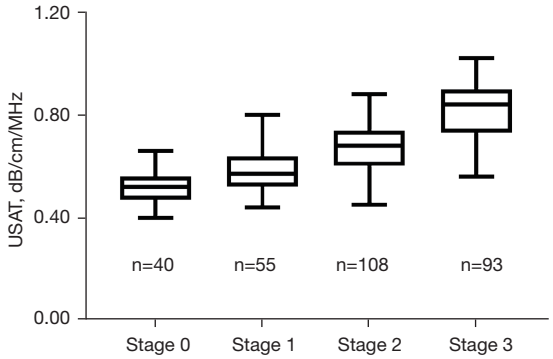

Figure 3 Correlation between the stage of hepatic steatosis based on the CAP and USAT values in the total subjects. (Kruskal-Wallis test P=0.392 between CAP in stage 0 and CAP in stage 1, P<0.001 otherwise). CAP, controlled attenuation parameter; USAT, ultrasound attenuation analysis.

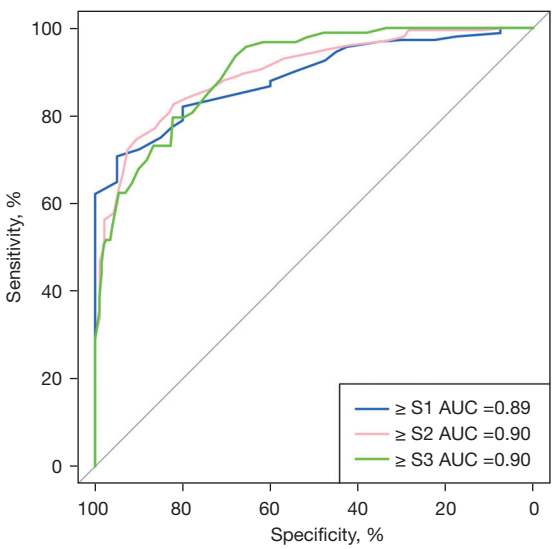

Figure 4 ROC curves of the USAT for diagnosing different grades of hepatic steatosis. The AUROCs of USAT for diagnosing hepatic steatosis grade ≥1 (blue line), ≥2 (red line) and ≥3 (green line) were 0.89 (95% CI: 0.85–0.92), 0.90 (95% CI: 0.86–0.93) and 0.90 (95% CI: 0.87–0.94), respectively. The dots indicate the cut-off levels. AUC, area under the curve; USAT, ultrasound attenuation analysis; AUROC, area under the ROC curves; ATI, attenuation imaging; CI, confidence interval; ROC, receiver operating characteristic.

interval (CI): 0.85–0.92] with a sensitivity of 0.71 (95% CI: 0.65–0.76) and a specificity of 0.95 (95% CI: 0.83–0.99) at the cut-off value of 0.62 dB/cm/MHz, which was selected by maximizing Youden's index. The AUROC of the USAT for a diagnosis of ≥ S2 was 0.90 (95% CI: 0.86–0.93) with sensitivity of 0.75 (95% CI: 0.68–0.81) and a specificity of 0.91 (95% CI: 0.83–0.96) at the threshold of 0.66 dB/cm/MHz, which was selected using Youden's index. The AUROC of S ≥3 was 0.90 (95% CI: 0.87–0.94) with a sensitivity of 0.80 (95% CI: 0.70–0.87) and a specificity of 0.82 (95% CI: 0.76–0.87) at the threshold of 0.72 dB/cm/MHz, which was selected using Youden's Index.

In general, the diagnostic performance of the USAT corresponded well to that of the CAP, which provides strong evidence that the USAT is a promising model. We also determined that a threshold of USAT >0.66 dB/cm/MHz could be used to rule in hepatic steatosis, and a threshold of USAT <0.43 dB/cm/MHz could be used to rule out hepatic steatosis.

Effects of etiologies on the diagnostic accuracy of the USAT

We analyzed whether etiologies affected the AUROCs of the USAT, and found that the performance of the USAT in the NAFLD patients was slightly better than the performance of the USAT in the CHB patients with AUROC values of 0.90 (95% CI: 0.84–0.95) for S ≥ S1, 0.96 (95% CI: 0.90–0.98) for S ≥ S2, and 0.93 (95% CI: 0.86–0.97) for S ≥3 (*Table 4*). However, the USAT displayed credible diagnostic performance in both the NAFLD patients and the CHB patients, which suggests that the USAT can be used to diagnose hepatic steatosis.

Discussion

We explored the association of the CAP and the USAT, which is an innovative ultrasound technique, in a cohort of patients undergoing CAP to investigate suspected hepatic steatosis. To our knowledge, this is the first study to examine the diagnostic performance of the USAT in NAFLD and CHB patients. In our study, the feasibility of the USAT was 97.5%, which was higher than that of the CAP. We also evaluated the correlations between the USAT and the patients' clinical data, the USAT and the CAP. In addition, our study provided optimized cut-off values for grading steatosis for use in the clinical context (using the Youden index with 90% sensitivity or 90% specificity). We discovered that the USAT was an effective non-invasive method that could be used to quantify hepatic steatosis in NAFLD and CHB patients and even in the entire population, and it could be used as a reliable test to assess steatosis in regions with insufficient medical funds and resources.

Table 3 Diagnostic performance of the USAT in determining steatosis stage as measured by the CAP in the whole population

Related parameters	Diagnostic test	S ≥ S1	S ≥ S2	S ≥ S3
AUROC (95% CI)	–	0.89 (0.85–0.92)	0.90 (0.86–0.93)	0.90 (0.87–0.94)
Prevalence	–	0.87	0.68	0.31
Youden index	Cut-off (dB/cm/MHz)	0.62	0.66	0.72
	Sensitivity (95% CI)	0.71 (0.65–0.76)	0.75 (0.68–0.81)	0.80 (0.70–0.87)
	Specificity (95% CI)	0.95 (0.83–0.99)	0.91 (0.83–0.96)	0.82 (0.76–0.87)
	PPV (95% CI)	0.99 (0.96–1.00)	0.94 (0.90–0.97)	0.67 (0.60–0.74)
	NPV (95% CI)	0.34 (0.29–0.38)	0.63 (0.57–0.68)	0.90 (0.85–0.93)
	LR+ (95% CI)	14.14 (3.65–54.72)	7.88 (4.21–14.74)	4.49 (3.28–6.14)
	LR– (95% CI)	0.31 (0.25–0.38)	0.28 (0.22–0.36)	0.25 (0.17–0.37)
Sensitivity =0.90	Cut-off (dB/cm/MHz)	0.52	0.57	0.68
	Sensitivity (95% CI)	0.90 (0.86–0.93)	0.90 (0.85–0.93)	0.90 (0.80–0.94)
	Specificity (95% CI)	0.55 (0.39–0.71)	0.66 (0.56–0.76)	0.70 (0.65–0.78)
	PPV (95% CI)	0.93 (0.90–0.95)	0.85 (0.81–0.88)	0.59 (0.53–0.64)
	NPV (95% CI)	0.46 (0.35–0.57)	0.75 (0.66–0.82)	0.93 (0.88–0.96)
	LR+ (95% CI)	2.00 (1.41–2.82)	2.66 (2.00–3.54)	3.09 (2.45–3.88)
	LR– (95% CI)	0.18 (0.12–0.29)	0.16 (0.10–0.24)	0.17 (0.09–0.29)
Specificity =0.90	Cut-off (dB/cm/MHz)	0.61	0.66	0.76
	Sensitivity (95% CI)	0.73 (0.66–0.78)	0.75 (0.68–0.81)	0.68 (0.57–0.77)
	Specificity (95% CI)	0.90 (0.76–0.97)	0.90 (0.83–0.96)	0.90 (0.85–0.94)
	PPV (95% CI)	0.98 (0.95–0.99)	0.94 (0.90–0.97)	0.76 (0.67–0.83)
	NPV (95% CI)	0.34 (0.29–0.39)	0.63 (0.57–0.68)	0.86 (0.82–0.89)
	LR+ (95% CI)	7.23 (2.84–18.37)	7.88 (4.21–14.74)	6.88 (4.43–10.67)
	LR– (95% CI)	0.31 (0.25–0.39)	0.28 (0.22–0.36)	0.36 (0.27–0.48)

Hepatic steatosis stage according to CAP: S ≥ S1 means CAP >238 (dB/m), S ≥ S2 means CAP >259 (dB/m), S ≥ S3 means CAP >292 (dB/m). USAT, ultrasound attenuation analysis; CAP, controlled attenuation parameter; AUROC, area under the ROC curve; LP+, positive likelihood ratio; LR–, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

Table 4 AUROCs for diagnosing hepatic steatosis with different etiologies

Steatosis stage	AUROC (95% CI) for NAFLD	AUROC (95% CI) for CHB
S ≥ S1	0.90 (0.84–0.95)	0.89 (0.84–0.93)
S ≥ S2	0.96 (0.90–0.98)	0.88 (0.82–0.92)
S ≥ S3	0.93 (0.86–0.97)	0.90 (0.85–0.94)

AUROC, area under receiver operating characteristic curve; CI, confidence interval; NAFLD, non-alcoholic fatty liver diseases; CHB, chronic hepatitis B; ROC, receiver operating characteristic.

Previous studies have confirmed that liver steatosis, a common characteristic of NAFLD and chronic hepatitis caused by the hepatitis C virus or the HBV, have been associated with fibrosis and the progression of liver diseases (19,20). Thus, it is significant to process steatosis test and warrant early interventions to prevent disease progression.

Abdominal ultrasound is considered the first modality for use in persons suspected of hepatic steatosis. However, when hepatic fatty infiltration is <20%, its diagnostic ability is poor. Moreover, it is operator dependent and unable to properly quantify steatosis, which restricts its clinical utility in detecting fatty liver disorders (8).

CT can roughly assess hepatic steatosis based on measurements of attenuation values of liver parenchyma, the difference between hepatic and splenic attenuation (CT_{L-S}), and the liver-to-spleen attenuation ratio ($CT_{L/S}$). According to Choi *et al.*, who used the cut-off values of –6.9 Hounsfield units (HU) for CT_{L-S} and 0.89 for $CT_{L/S}$, the sensitivity and specificity rates of diagnosing moderate to severe steatosis were 70.59%, 90.54% (CT_{L-S}), and 76.47%, and 90.54% ($CT_{L/S}$), respectively (21). However, as CT emits radiation, it is not recommended for widespread use in asymptomatic people.

MRI, particularly magnetic resonance spectroscopy and MRI proton density fat fraction, is thought to be the most authoritative imaging tool for the qualitative and quantitative assessment of hepatic steatosis, and can detect as little as 5–10% liver steatosis with high accuracy and sensitivity. However, due to its high cost and limited availability, it is not ideal for routine usage in large groups of NAFLD patients, and thus has limited application in clinical settings (22,23).

The CAP is becoming more widely accepted as a useful technique for determining the amount of liver fat content when using liver biopsy as the gold standard (24,25). However, its accuracy of identifying hepatic steatosis is impaired in individuals who are overweight or obese or those with severe liver cirrhosis and ascites (14). Further, the CAP is costly and must be equipped with FibroScan, which is only capable of assessing liver stiffness and hepatic steatosis. Conversely, the USAT can perform simultaneous measurements when processing abdominal ultrasound examinations. It can also be visualized with a B-mode image, and can automatically avoid pipeline structures, thus ensuring the quality for evaluating hepatic steatosis. USAT adds a fresh functional parameter to contemporary ultrasonography. Our study confirmed that the applicability rate of the USAT (97.5%) is higher than that of the CAP (94.8%).

In the present study, the AUROCs of the attenuation coefficient based on the USAT for predicting all stages of steatosis were >0.85, which indicates that the diagnostic ability of the USAT is high. In NAFLD patients, the USAT had the highest AUROC for S ≥ S2, which showed that the USAT was best able to discriminate hepatic steatosis degrees between moderate and severe, and beneficial to proceed clinical intervention. The cut-off values for steatosis stage increased gradually from S1 to S3 when set using the Youden index as well as with high sensitivity or high specificity. Thus, the USAT can discriminate between various degrees of steatosis. Additionally, the USAT was better applying in evaluating hepatic steatosis in NAFLD than CHB patients, but the diagnostic accuracy of the USAT was not affected, as the AUROCs were both more than 0.85. It can potentially be regarded as a useful method that can be used in response to lifestyle or pharmacological or surgical interventions.

In recent years, ultrasound system manufacturers have been working on technology built into common ultrasound equipment that can be used to measure the ultrasonic beam attenuation coefficient. Bende *et al.* (26) evaluated the efficacy of the attenuation coefficient implemented on the ultrasound-guided attenuation parameter (UGAP) using the CAP as the reference approach. They discovered the cut-off values for predicting stage 1, 2, and 3 liver steatosis were 0.55 dB/cm/MHz (AUROC: 0.83), 0.66 dB/cm/MHz (AUROC: 0.90), and 0.7 dB/cm/MHz (AUROC: 0.91), respectively, and found a strong positive correlation between the UGAP and CAP values (r=0.73, P<0.0001). Our results are broadly consistent with those of Bende *et al.*, except in relation to stage 1 (AUROC 0.89 at the threshold of 0.62 dB/cm/MHz in our study *vs.* AUROC 0.83 at the threshold of 0.55 dB/cm/MHz in Bende *et al.*'s study). This difference may be due to the prevalence of patients with S ≥ S1 steatosis, which was 86.5% in our cohort and 72.8% in the cohort of Bende *et al.* Further, their sample size was smaller than ours and comprised only 179 subjects.

In a prospective study of 114 subjects potentially at risk of steatosis, Ferraioli *et al.* (27) found that the value of attenuation imaging (ATI) was not affected by age, gender, or BMI, which is in line with our results. The correlation between the CAP measurements and ATI in the study of Ferraioli *et al.* was moderate (r=0.61), but their figure was lower than ours (r=0.79). This may be because the underlying algorithm is not the same among different manufacturers of the attenuation coefficient measurement.

Our study had several limitations. First, it was a single-

center study with a relatively small sample size. However, we did focus on 2 main types of liver disease that result in steatosis. Second, we chose the CAP as the reference to examine the diagnostic accuracy of the USAT rather than the liver biopsy, which may affect the study results to some extent. However, liver biopsies are generally only performed in patients with a doubtful diagnosis or those suspected to have advanced liver disease (28). The CAP is a relatively accurate method for gauging the severity of steatosis. To further investigate and verify accuracy of USAT, we will carry out a study using the liver biopsy as the gold reference. Third, we did not include the serum biomarker of liver steatosis in our study as in common clinical practice, complete blood index results were only available for a small percentage of the participants. Further research is required to fully understand the association between the USAT and the metabolic components, as earlier studies have shown that hepatic steatosis and metabolic syndrome are closely related (9,29,30).

Conclusions

In summary, this study determined the optimized cut-off values for the USAT using the CAP as a reference and verified the high applicability/low failure rate of the USAT in a cohort of patients who were likely to have steatosis. Given its good diagnostic accuracy, the USAT could be a useful tool in identifying liver steatosis in the future.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5821/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5821/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5821/coif). JP reports that he only provides related technical consultation for Shenzhen Mindray Bio-medical Electronics Co., Ltd. when needed. The other 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 ethics committee of The Fourth Affiliated Hospital of Zhejiang University School of Medicine (No. K2022153). Informed consent was taken from each individual.

References

1. Weinstein G, Zelber-Sagi S, Preis SR, et al. Association of Nonalcoholic Fatty Liver Disease With Lower Brain Volume in Healthy Middle-aged Adults in the Framingham Study. JAMA Neurol 2018;75:97-104.
2. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018;3:383-403.
3. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.
4. Calzadilla Bertot L, Adams LA. The Natural Course of Non-Alcoholic Fatty Liver Disease. Int J Mol Sci 2016;17:774.
5. Fazel Y, Koenig AB, Sayiner M, et al. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 2016;65:1017-25.
6. Cai S, Ou Z, Liu D, et al. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with

component of metabolic syndrome. United European Gastroenterol J 2018;6:558-66.
7. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577-86.
8. Lee DH. Imaging evaluation of non-alcoholic fatty liver disease: focused on quantification. Clin Mol Hepatol 2017;23:290-301.
9. Huang Z, Ng K, Chen H, et al. Validation of Controlled Attenuation Parameter Measured by FibroScan as a Novel Surrogate Marker for the Evaluation of Metabolic Derangement. Front Endocrinol (Lausanne) 2021;12:739875.
10. Sasso M, Audière S, Kemgang A, et al. Liver Steatosis Assessed by Controlled Attenuation Parameter (CAP) Measured with the XL Probe of the FibroScan: A Pilot Study Assessing Diagnostic Accuracy. Ultrasound Med Biol 2016;42:92-103.
11. de Lédinghen V, Wong GL, Vergniol J, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2016;31:848-55.
12. Thiele M, Rausch V, Fluhr G, et al. Controlled attenuation parameter and alcoholic hepatic steatosis: Diagnostic accuracy and role of alcohol detoxification. J Hepatol 2018;68:1025-32.
13. Wong VW, Chan WK, Chitturi S, et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. J Gastroenterol Hepatol 2018;33:70-85.
14. Wilder J, Patel K. The clinical utility of FibroScan(®) as a noninvasive diagnostic test for liver disease. Med Devices (Auckl) 2014;7:107-14.
15. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66:1022-30.
16. Shen F, Zheng RD, Mi YQ, et al. Controlled attenuation parameter for non-invasive assessment of hepatic steatosis in Chinese patients. World J Gastroenterol 2014;20:4702-11.
17. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
18. Sasso M, Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010;36:1825-35.
19. Mak LY, Hui RW, Fung J, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. J Hepatol 2020;73:800-6.
20. Minakari M, Molaei M, Shalmani HM, et al. Liver steatosis in patients with chronic hepatitis B infection: host and viral risk factors. Eur J Gastroenterol Hepatol 2009;21:512-6.
21. Choi Y, Kim DK, Youn SY, et al. Unenhanced computed tomography for non-invasive diagnosis of hepatic steatosis with low tube potential protocol. Quant Imaging Med Surg 2022;12:1348-58.
22. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: Clinical trials to clinical practice. J Hepatol 2016;65:1006-16.
23. Wildman-Tobriner B, Middleton MM, Moylan CA, et al. Association Between Magnetic Resonance Imaging-Proton Density Fat Fraction and Liver Histology Features in Patients With Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis. Gastroenterology 2018;155:1428-1435.e2.
24. Jun BG, Park WY, Park EJ, et al. A prospective comparative assessment of the accuracy of the FibroScan in evaluating liver steatosis. PLoS One 2017;12:e0182784.
25. Vuppalanchi R, Siddiqui MS, Van Natta ML, et al. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. Hepatology 2018;67:134-44.
26. Bende F, Sporea I, Șirli R, et al. Ultrasound-Guided Attenuation Parameter (UGAP) for the quantification of liver steatosis using the Controlled Attenuation Parameter (CAP) as the reference method. Med Ultrason 2021;23:7-14.
27. Ferraioli G, Maiocchi L, Raciti MV, et al. Detection of Liver Steatosis With a Novel Ultrasound-Based Technique: A Pilot Study Using MRI-Derived Proton Density Fat Fraction as the Gold Standard. Clin Transl Gastroenterol 2019;10:e00081.
28. Leoni S, Tovoli F, Napoli L, et al. Current guidelines for the management of non-alcoholic fatty liver disease:

A systematic review with comparative analysis. World J Gastroenterol 2018;24:3361-73.
29. Suzuki A, Diehl AM. Nonalcoholic Steatohepatitis. Annu Rev Med 2017;68:85-98.
30. Clarke WT, Miranda J, Neidich E, et al. Metabolic syndrome and liver steatosis occur at lower body mass index in US Asian patients with chronic hepatitis B. J Viral Hepat 2019;26:1164-9.

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