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ULTRASOUND

Diagnostic performance of ultrasound attenuation imaging for assessing low-grade hepatic steatosis

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Abstract

Objectives To investigate the diagnostic performance of attenuation imaging (ATI) for the assessment of low-grade hepatic steatosis using liver biopsy as the reference standard.

Methods The study included 57 potential donor candidates for living liver transplantation who underwent ATI, transient elastography (TE), and liver biopsy for evaluation of hepatic steatosis between February 2020 and April 2020. The attenuation coefficient (AC) from ATI and the controlled attenuation parameter (CAP) from TE were measured for each participant in a random and blind manner. The histologic hepatic fat fraction (HFF) was graded (S0, < 5%; S1, 5–33%; S2, 33–66%; S3, > 66%). The accuracy of ATI for diagnosing hepatic steatosis was compared with that of CAP using ROC analysis. Correlations between AC and HFF were evaluated, and factors affecting AC were determined by linear regression analysis.

Results The median HFF was 3% (range: 0–35%), with 31 (54.4%), 24 (42.0%), and 2 (3.5%) participants being graded as S0, S1, and S2, respectively. The AUCs for the ROCs of AC and CAP for the detection of hepatic steatosis were 0.808 (95% CI: 0.682–0.900) and 0.829 (95% CI: 0.706–0.916), respectively, with the difference not being statistically significant ($p = 0.762$). AC showed 61.5% of sensitivity and 90.3% of specificity. AC was positively correlated with HFF ($p < 0.001$). HFF was the only factor significantly affecting AC.

Conclusions ATI showed moderate sensitivity and high specificity in the diagnosis and quantification of hepatic steatosis in low-grade steatosis without fibrosis. Only HFF significantly affected AC.

Key Points

- *Attenuation imaging showed moderate sensitivity and high specificity performance in the diagnosis and quantification of hepatic steatosis in low-grade steatosis without fibrosis.*
- *The diagnostic performance of the attenuation coefficient by attenuation imaging did not significantly differ from that of the controlled attenuation parameter by transient elastography in quantifying low-grade steatosis.*
- *The histopathologically determined hepatic fat fraction was the only factor significantly affecting the attenuation coefficient.*

Keywords Biopsy · Diagnostic imaging · Fatty liver · Ultrasonography

Abbreviations

AC	Attenuation coefficient
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATI	Attenuation imaging
BMI	Body mass index
CAP	Controlled attenuation parameter
HDL	High-density lipoprotein cholesterol
HFF	Hepatic fat fraction
NAFLD	Nonalcoholic fatty liver disease
TE	Transient elastography

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Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is rapidly growing worldwide because of the increased incidence of obesity and insulin resistance [1, 2], and is currently up to 30–40% [3, 4]. As hepatic steatosis may progress to cirrhosis and can be associated with adverse liver-related outcomes in patients with underlying liver disease [5–7], the detection and quantification of hepatic fat are crucial for patient management. In living donor liver transplantation, accurate fat quantification in the liver graft is important for both donor safety and successful outcomes in recipients, as steatosis affects hepatocyte function and impairs regeneration following major hepatic resection [8].

Liver biopsy is considered the gold standard for assessment of hepatic steatosis. However, besides being an invasive procedure, it is prone to sampling error and interobserver variability in the histopathology analysis [9–11]. Though in recent years, noninvasive quantification of hepatic steatosis using MRI has shown comparable accuracy to liver biopsy [3, 12, 13], the MRI approaches have drawbacks such as high cost and limited availability.

Ultrasonography (US) has been widely used as a screening tool for the general population at risk of hepatic steatosis. Of the various US-based parameters that can be used to quantify hepatic steatosis, the controlled attenuation parameter (CAP) obtained from transient elastography (TE) has been used in a number of observational studies and clinical trials [14–17]. A recent meta-analysis of individual patient data revealed the CAP to have high accuracy (AUCs, 0.83–0.89) for quantification of hepatic steatosis in comparison to histopathology [18]. However, TE is not integrated with B-mode US, and it can measure hepatic fat only at a pre-determined depth. To overcome this limitation, recently, attenuation imaging (ATI) incorporated with B-mode US has been developed [19, 20]. ATI provides measurement of the attenuation coefficient (AC) corresponding to the slope of the attenuation profile of the transmitted beam, which is determined by the media in the region of interest (ROI) after the exclusion of acoustic transmission characteristics (i.e., the influence of beam focusing and gain) unique to the probe [19, 21]. Even though several studies have demonstrated ATI to have high accuracy for the assessment of steatosis in patients with chronic liver disease [20, 22, 23], its diagnostic performance in healthy adult population with low-grade steatosis is yet to be evaluated. It would also be meaningful to investigate the diagnostic value of AC in the absence of confounding factors such as fibrosis.

Therefore, the purpose of this study was to evaluate the diagnostic performance of ATI for detection and quantification of low-grade hepatic steatosis in healthy adults, using liver biopsy as the reference standard.

Materials and methods

Participants

This work formed a sub-study of a prospective multicenter trial to determine the usefulness of 2D-shear wave elastography and attenuation imaging for the diagnosis of nonalcoholic steatohepatitis, for which the study protocol is registered at the Clinical Research Information Service (KCT0004326). This study was approved by our institutional review board, and written informed consent was obtained from all participants. Potential donor candidates for living liver transplantation who were scheduled for liver biopsy for the assessment of hepatic steatosis prior to surgery at Asan Medical Center were consecutively enrolled from February 2020 to April 2020. According to our institution's predefined protocol for liver transplantation, all donor candidates underwent pre-operative imaging workup for measurement of liver volume and evaluation of hepatic vascular and biliary anatomy, as well as a percutaneous liver biopsy to evaluate hepatic steatosis. All participants were asked to fast for at least 6 h prior to liver biopsy. On the same day as the liver biopsy, participants underwent an anthropometric examination for recording details such as body mass index (BMI), history of alcohol consumption (amount and drinking pattern), and serological analysis of parameters including liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), lipid panel (total cholesterol, high-density lipoprotein cholesterol [HDL], and triglycerides), level of platelets, and coagulation parameters (prothrombin time/international normalized ratio). A significant bleeding risk (platelets < 80 000/μL, prothrombin time international normalized ratio > 1.5) was considered a contraindication for percutaneous liver biopsy.

US examinations

Dedicated US scanners were used to perform ATI and TE examinations on the same day to acquire AC and CAP, respectively. These US examinations were performed just before the liver biopsy. One of two board-certified abdominal radiologists with expertise in US elastography measurement (J.K.J. and S.Y.K. with approximately 100 and 500 cases) performed the ATI. The TE was performed by one of the two radiologic technicians who had experience in TE (I.W.Y. and Y.B.C. with approximately 3500 cases). All operators were blinded to the results of the other US examinations and clinical information, except for the knowledge that the subjects were scheduled for a liver biopsy for liver donation. For a subset of 15 participants,

the two radiologists alternately and independently performed ATI to allow evaluation of inter-operator reproducibility. The AC values obtained by the first operator were used for the main analysis.

ATI was performed using a dedicated US scanner (Aplio i800, Canon Medical System) with a 1–8 MHz convex transducer (i8CX1, Canon Medical System). ATI was obtained from the right anterior liver through an intercostal window with the subject in the supine position. For evaluation of the AC (dB/cm/MHz) within a breath-hold, a 2 × 4-cm fan-shaped ROI was placed in the sampling box (4 × 8 cm; Fig. 1). A detailed technical information on the ATI procedure is described elsewhere [19, 20]. AC measurements were repeated until five valid values ($R^2 \geq 80$, displayed value on ATI) were obtained, and the median of these five measurements was then used as the representative AC value. After completion of the ATI, the skin-capsular distance, defined as the distance from the skin to the liver capsule, was measured on B-mode imaging.

The CAP was measured on TE (FibroScan-502, Echosens) using an M probe (3.5 MHz) based on the recommendations of the World Federation for Ultrasound in Medicine and Biology (WFUMB) [24, 25]. The median of ten valid measurements was considered the representative value for each participant.

Liver biopsy and histopathologic analysis

After completion of a pair of US examinations, US-guided percutaneous liver biopsy was performed in the right anterior section of the liver by the same operators who conducted the ATI. Two liver specimens, each being approximately 1.5 cm in length, were obtained with 18-gauge needles (Stericut 18G Coaxial, TSK Laboratory). Histopathologic analysis of the liver specimens was performed by an experienced board-certified hepatic pathologist who was blinded to all clinical and radiologic information. Hepatic steatosis was visually quantified as the hepatic fat fraction (HFF) according to a percentage scale of the amount of liver parenchyma replaced by steatotic droplets on hematoxylin–eosin-stained specimens. The HFF was considered the reference standard for hepatic steatosis and was further categorized according to the histological scoring system for NAFLD as follows: S0 (< 5%, none), S1 (5–33%, mild), S2 (33–66%, moderate), and S3 (> 66%, severe) [26]. Fibrosis was categorized according to the METAVIR scoring system as follows: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with few septa), F3 (numerous septa without cirrhosis), and F4 (cirrhosis) [27].

Statistical analysis

The Mann–Whitney test was used to compare the median ACs based on the results of histopathology (S0 vs. S1–S3). Spearman correlation was employed to evaluate correlations between AC and HFF, and between AC and CAP. Coefficients of variation (CVs) were calculated to assess the reproducibility between the two operators for subgroups of 15 participants. CVs of ≤ 10%, 10–25%, and ≥ 25% were regarded as good, moderate, and poor reproducibility, respectively [28]. ROC curves of AC and CAP were calculated for diagnosis of hepatic steatosis (S1–S3), and the corresponding AUCs were compared using DeLong's test [29]. Sensitivity and specificity were estimated using the highest Youden index. All variables with a value of $p < 0.2$ on univariate analysis following logarithmic transformation

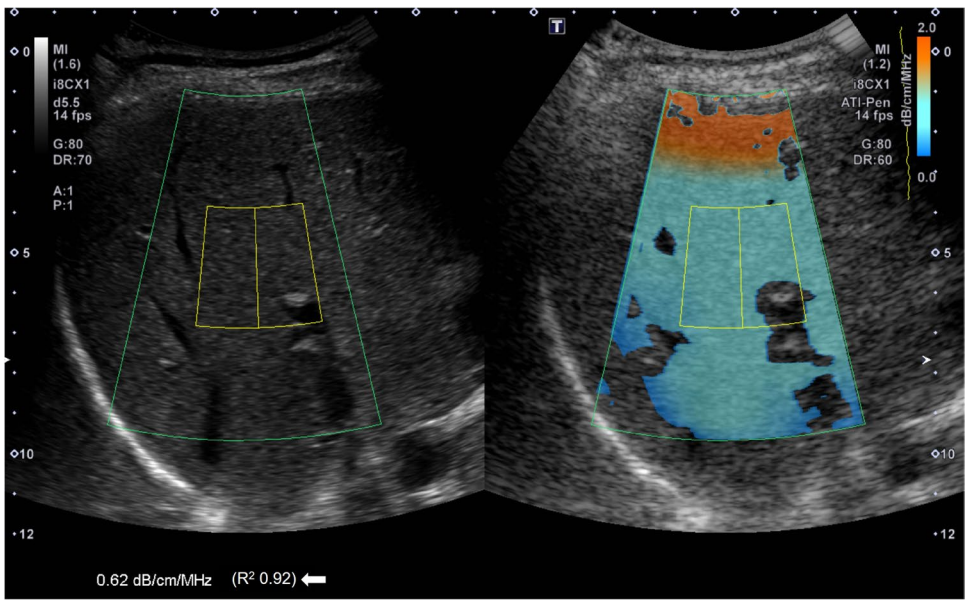

Fig. 1 Ultrasound attenuation imaging presenting the attenuation coefficient (AC, 0.62 dB/cm/MHz) in a 43-year-old female participant. A pair of B-mode images (left) and a color-coded attenuation image (right) with sampling box (green box) and region of interest (yellow box) are provided simultaneously. An R^2 value (arrow) indicating reliability of the AC measurement is displayed in the left lower corner next to the attenuation coefficient. The histopathologic hepatic fat fraction and steatosis grade are 5% and S1, respectively

of the measured AC were subjected to a multivariate linear regression analysis to identify factors significantly affecting the AC. p-values < 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed using the MedCalc statistical software package (version 16.8, MedCalc Software).

Results

Participant characteristics

A total of 60 participants who were potential liver donor candidates were initially included in this study. Among them, three participants were excluded from further analysis because of an inappropriate use of an M probe during CAP measurement (skin-capsular distance ≥ 25 mm) [30–32]. The technical feasibility of CAP measurement of TE was 95% (57/60). In all the participants, ATI successfully measured AC with R^2 values ≥ 80, and the technical feasibility of CAP was 100% (60/60). The characteristics of the 57 participants are shown in Table 1. Based on the histopathologic analysis, the median HFF of the 57 participants was 3%, ranging from 0 to 35%. Twenty-six (45.6%) participants were diagnosed with hepatic steatosis of grades S1–S2, with the majority of the cases being S1 (92.3%, 24/26). Only one (1.8%) participant was diagnosed as having portal fibrosis without septa (F1), with the others had no fibrosis. Among the 57 participants, 15 (26.3%) and 14 (24.6%) were classified as overweight, and 15 (26.3%) and one (1.8%) as obese according to the Asia–Pacific and World Health Organization guidelines, respectively [33, 34].

Table 1 Characteristics of the participants included in the study (n = 57)

Characteristic	Value
Age (years), mean ± SD	32.1 ± 9.7
Sex, (male)	28 (49.1%)
BMI (kg/m^2)*	23.1 (17.6–33.6)
Underweight/normal/overweight/obese†	1 (1.8%)/41 (71.9%)/14 (24.6%)/1 (1.8%)
Alcohol intake (g/day)*	0.0 (0.0–38.8)
AST (IU/L)*	17.0 (10.0–36.0)
ALT (IU/L)*	13.0 (5.0–40.0)
Skin to capsule distance (mm)*	15.0 (10.0–23.0)
Glucose (mg/dL)*	97.0 (68.0–125.0)
Total cholesterol (mg/dL)*	169.0 (102.0–259.0)
Triglyceride (mg/dL)*	98.0 (45.0–245.0)
HDL (mg/dL)*	52.0 (32.0–83.0)
LDL (mg/dL)*	93.8 (11.0–169.0)
Histopathologic steatosis grade	
S0 (< 5%)	31 (54.4%)
S1 (5–33%)	24 (42.1%)
S2 (34–66%)	2 (3.5%)
Histopathologic fibrosis stage	
F0	56 (98.2%)
F1	1 (1.8%)

Data are number of participants with percentage of the 57 participants in parentheses, unless indicated otherwise

*Values are expressed as the median (range)

†BMI was classified according to the World Health Organization guideline

ALT, alanine aminotransferase; *AST*, aspartate transaminase; *BMI*, body mass index; *HDL*, high-density lipoprotein cholesterol; *LDL*, low-density lipoprotein cholesterol

AC and CAP measurements

In all 57 participants, five repetitive AC measurements were made for each individual, resulting in a total of 285 valid AC values without any technical failure. In the acquisition of ten valid CAP measurements, no invalid measurement was noted in 46 participants (81%), whereas one invalid measurement was observed in six participants, and three in five participants.

The median AC was 0.59 (dB/cm/MHz), ranging from 0.46 to 0.93. The ACs in participants with histopathologically proven hepatic steatosis were significantly higher than in those without hepatic steatosis (0.665 [0.510 − 0.93] vs. 0.550 [0.460 − 0.680]; p < 0.001; Fig. 2). There was a significant positive correlation between AC and HFF (ρ = 0.619, 95% confidence interval [CI]: 0.428–0.758; p < 0.001). The median CAP value was 222.0 (dB/m), ranging from 139 to 346, and there was a significant positive correlation between AC and CAP (ρ = 0.509, 95% CI: 0.286–0.679; p < 0.001).

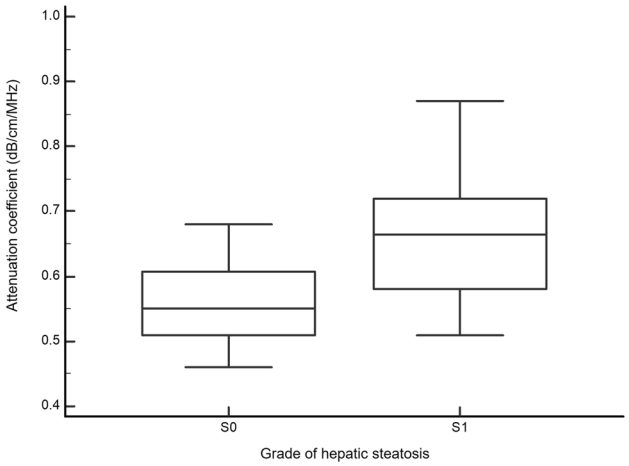

Fig. 2 Box plot graph showing the distribution of attenuation coefficient (AC) values in participants without (S0) vs. participants with any grade of steatosis (S1–S2). The median ACs were 0.550 for S0 and 0.665 for S1–S2 (p < 0.001)

The CV of the median AC values obtained from the two operators was 9.6% (95% CI, 7.2–11.6%), and thus, the reproducibility between them was considered as good.

Factors affecting AC

The factors affecting AC are summarized in Table 2. In the univariate linear regression analysis, HFF ($\rho = 0.013$, $p < 0.001$), skin-capsular distance ($\rho = 0.016$, $p = 0.020$), cholesterol/HDL ($\rho = 0.058$, $p = 0.020$), and triglyceride/HDL ($\rho = 0.052$, $p = 0.001$) were significantly associated with AC. However, in the multivariate linear regression, only HFF was positively associated with AC ($\rho = 0.011$, $p < 0.001$).

Diagnostic performance of AC for detection of hepatic

Figure 3 shows the ROCs of AC and CAP for detection of hepatic steatosis (S1) in all 57 participants. The AUCs of AC and CAP for the detection of hepatic steatosis (S1) were 0.808 (95% CI: 0.682–0.900) and 0.829 (95% CI: 0.706–0.916), respectively, which were not significantly different ($p = 0.762$; Table 3). The sensitivity (61.5% vs. 61.5%) and specificity (90.3% vs. 93.6%) of AC and CAP were similar at the estimated cut-off values with the highest Youden index.

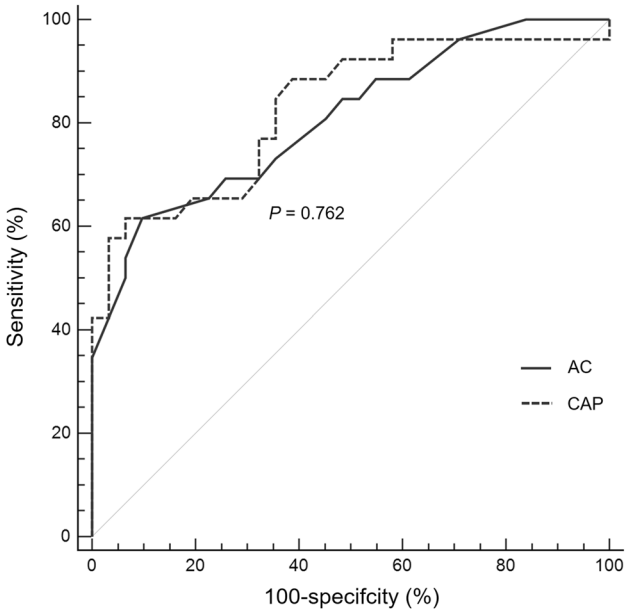

Fig. 3 ROCs of the attenuation coefficient (AC) and controlled attenuation parameter (CAP) for diagnosis of hepatic steatosis of any grade. The AUCs were 0.808 for AC and 0.829 for CAP ($p = 0.762$)

Discussion

In this study, ATI showed moderate sensitivity and high specificity for the diagnosis and quantification of hepatic steatosis in low-grade hepatic steatosis without fibrosis. ATI accurately identified hepatic steatosis (≥ S1) with a high AUC (0.808). In a head-to-head comparison using the same participants, the diagnostic performance of AC for diagnosing steatosis was not significantly different from that of CAP (AUC, 0.808 vs. 0.829, $p = 0.762$). In a multivariate analysis, AC was associated only with HFF ($\rho = 0.011$, $p < 0.001$), and was not significantly affected by anthropometric or laboratory findings. The ATI measurement procedure showed a high technical success rate along with good reproducibility.

Previous studies with biopsy-proven cohorts have shown that ATI can accurately detect hepatic steatosis (≥ S1; AUC values, 0.81–0.88) [22, 23, 35]. At the AC cut-off values of 0.64–0.69 determined in previous studies, the sensitivity and specificity were 75–76% and 77–100%, respectively. In our

Table 2 Factors affecting the attenuation coefficient

Factor	Univariate analysis			Multivariate analysis		
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Male sex	0.063	−0.019, 0.145	0.128	0.012	−0.056, 0.080	0.726
Age	< 0.001	−0.004, 0.005	0.888			
BMI	0.008	−0.005, 0.021	0.202			
Skin-capsular distance	0.016	−0.003, 0.029	0.020	0.009	−0.002, 0.019	0.099
Alcohol intake	−0.003	−0.008, 0.002	0.208			
Glucose	0.001	−0.003, 0.005	0.691			
Cholesterol/HDL	0.058	0.009, 0.107	0.020	−0.001	−0.050, 0.048	0.957
Triglyceride/HDL	0.052	0.023, 0.080	0.001	0.018	−0.014, 0.049	0.265
LDL	0.001	−0.001, 0.001	0.944			
Hepatic fat fraction	0.013	0.009, 0.016	< 0.001	0.011	0.007, 0.015	< 0.001

BMI, body mass index; *CI*, confidential interval; *HDL*, high-density lipoprotein cholesterol; *LDL*, low-density lipoprotein cholesterol

Table 3 Diagnostic accuracy of attenuation coefficient (AC) and controlled attenuation parameter (CAP) in detection of hepatic steatosis ($S \geq 1$)

	AUROC	Cut-off	Sensitivity (%)	Specificity (%)
AC	0.808 (0.682–0.900)	0.62 dB/cm/MHz	61.5 (40.6–79.8)	90.3 (74.2–98.0)
CAP	0.829 (0.706–0.916)	235 dB/m	61.5 (40.6–9.8)	93.6 (78.6–99.2)
	0.823* (0.809–0.837)	248* dB/m	68.8* (60.0–75.0)	82.2* (76.1–89.7)

Numbers in parentheses are 95% confidence intervals

*Values are from individual patient meta-analysis of CAP[18]

AUROC, area under the receiver operating characteristics

study, the AUC (0.81) and sensitivity (62% at an AC cut-off of 0.62) were slightly lower than those in the earlier studies. Given the differences in the distribution of the degree of hepatic steatosis, we conjecture that the differences between the studies can be attributed to spectrum bias [36]. Difference in patient characteristics across cohorts could result in different cut-off values and diagnostic accuracies. The prevalence of advanced steatosis (≥S2) in previous studies was much higher (20–50%) than in our study (3.5%); hence both the cut-off value and overall accuracy might have been overestimated in the earlier studies. The recent WFUMB guidelines suggest a large overlap between adjacent grades and no consensus for the CAP value cut-off [25]. Thus, the cut-off values and their diagnostic performance in our study also need further validation. Our study results also suggest a limitation in the detection of low-grade steatosis using US-based methods, as CAP values also indicated a similar sensitivity. A meta-analysis of CAP data reported 68.8% sensitivity for the detection of steatosis ≥S1 [18]. In addition, the proportion of participants with significant fibrosis (≥F2) was 33–50% in previous studies, as they included patients with various chronic liver diseases, while on the contrary, our study included healthy participants without significant fibrosis. Therefore, the results of this study are particularly relevant for living donor liver transplantation, where the participants under evaluation come from a healthy population with low-grade hepatic steatosis. Hepatic steatosis impairs hepatocyte function and regeneration after major hepatic resection, including liver donation. Some studies suggest that even the mildest form of steatosis can increase the incidence of primary nonfunction and decrease the chances of patient survival after liver transplantation [8]. In addition, in patients with NAFLD, early identification of hepatic steatosis may have a role in preventing disease progression [37, 38]. The performance of ATI for diagnosing a HFF ≥S1 in healthy participants was similar to that of CAP (AUC, 0.81 vs. 0.83, respectively; $p = 0.762$). This finding is in accord with previous studies reporting the AUCs of AC (0.90–0.91) and CAP (0.85) for HFF ≥S1 without significant difference ($p > 0.05$) [39, 40]. In addition, AC positively correlated with CAP ($\rho = 0.509$, $p < 0.001$) in our study, which is in line with a previous observation that showed a strong correlation ($\rho = 0.81$, $p < 0.001$) between the two measurements [41]. However, ATI offers the advantages of simultaneous B-mode US and indifference to the acoustic transmission characteristics of the probes, whereas CAP measurement on TE is performed without direct B-mode image guidance, and its accuracy varies according to the type of probe (M vs. XL probes) [32, 42]. ATI also allows the operator to visualize the tissue in which the measurement is performed and avoid artifacts, such as reverberation, and structures other than hepatic parenchyma, such as vessels.

Our study found that the only factor significantly affecting AC was HFF ($\rho = 0.011$, 95% CI: $0.007 - 0.015$; $p < 0.001$), with no other clinical or anthropometric factors having a substantial effect ($p > 0.099$). This result corresponds well with the findings reported in literature documenting that AC was only associated with steatosis grade [23, 35].

The results of this study also demonstrated the technical robustness of ATI, showing high interobserver agreement and low technical failure rates. The CV of ATI was 9.6% in the present study, indicating good reproducibility between the two operators. Yoo et al. had also demonstrated high intraobserver (ICC, 0.929) and interobserver agreement (ICC, 0.792) for ATI in healthy volunteers [43]. Invalid measurement, which is more common in obese patients, is another issue with the FibroScan system [16]. Because the reliability index (R^2) is displayed during the acquisition of the ATI, the operator can easily determine whether the measurement is valid or not. There was no invalid measurement in any of the total of 285 AC measurements made across 57 participants in our study, which is consistent with previous findings of very low rates of invalid measurements ($0 - 4\%$) [20, 23, 35].

This study has several limitations. First, because this is a sub-study of a prospective trial, a relatively small number of healthy adults recruited from a single center were included. Therefore, a further prospective multicenter trial with a larger population is required to verify our results. Second, the use of ROIs in ATI, and the use of liver biopsy as a reference standard, results in inherent limitations related to sampling errors. However, we used a large ROI (2×4-cm fan-shaped ROI) and tried to target the liver portion where the AC measurement was performed during the liver biopsy. Third, the diagnostic accuracy for advanced steatosis (≥S2) was not evaluated in this study. There were only two participants with S2, and none of the participants had S3. Fourth,

the proportion of participants who were overweight to obese was relatively small (26.3%). Thus, the findings of this study may not be extended to those with larger body habitus.

In conclusion, ATI showed moderate sensitivity and high specificity for the diagnosis and quantification of hepatic steatosis in healthy adults, with high reproducibility and success rates. Furthermore, the ATI-derived AC was only significantly affected by the HFF.

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Declarations

Guarantor The scientific guarantor of this publication is Dr. So Yeon Kim.

Conflict of interest Dr. Jang received grants from Canon Medical Systems Korea and personal fees and financial supports.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- prospective
- diagnostic study
- performed at one institution

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