



Quantification of hepatic steatosis with ultrasound: promising role of attenuation imaging coefficient in a biopsy-proven cohort

Marco Dioguardi Burgio^{1,2} · Maxime Ronot^{1,2,3} · Edouard Reizine¹ · Pierre-Emmanuel Rautou⁴ · Laurent Castera⁴ · Valérie Paradis⁵ · Philippe Garteiser² · Bernard Van Beers^{1,2,3} · Valérie Vilgrain^{1,2,3}

Received: 12 March 2019 / Revised: 30 August 2019 / Accepted: 27 September 2019 / Published online: 10 December 2019
© European Society of Radiology 2019

Abstract

Objectives To prospectively assess the role of the US attenuation imaging coefficient (AC) for the diagnosis and quantification of hepatic steatosis.

Methods One hundred and one patients underwent liver biopsy and US-AC measurement on the same day. Liver steatosis was graded according to biopsy as absent (S0 < 5%), mild (S1 5–33%), moderate (S2 33–66%), or severe (S3 > 66%); liver fibrosis was graded from F0 to F4. The correlation between AC and steatosis on pathology (%) was calculated using the Pearson correlation coefficient. The Student *t* or Mann–Whitney *U* test was used to compare continuous variables and ROC curve analysis was used to assess diagnostic performance of AC in diagnosing steatosis.

Results Overall, 43 (42%), 35 (35%), 12 (12%), and 11 (11%) patients were classified as S0, S1, S2, and S3, respectively. The AC was positively correlated with steatosis as a continuous variable (%) on pathology ($r = 0.58$, $p < 0.01$). Patients with steatosis of any grade had a higher AC than those without steatosis (mean 0.77 ± 0.13 vs. 0.63 ± 0.09 dB/cm/MHz, respectively; $p < 0.01$, AUROC = 0.805). Patients with S2–S3 had a higher AC than patients with S0–1 (0.85 ± 0.11 vs. 0.67 ± 0.11 dB/cm/MHz, respectively; $p < 0.01$, AUROC = 0.892). AC > 0.69 dB/cm/MHz had a sensitivity and specificity of 76% and 86%, respectively, for diagnosing any grade of steatosis (S1–S3), and AC > 0.72 dB/cm/MHz had a sensitivity and specificity of 96% and 74%, respectively, for diagnosing S2–S3. The presence of advanced fibrosis (F3–F4) did not affect the calculated AC.

Conclusions The attenuation imaging coefficient is a promising quantitative technique for the non-invasive diagnosis and quantification of hepatic steatosis.

Key Points

- Measurement of the attenuation coefficient is achieved with a very high rate of technical success.
- We found a significant positive correlation between the attenuation coefficient and the grade of steatosis on pathology.
- The attenuation imaging coefficient is a promising quantitative technique for the noninvasive diagnosis and quantification of hepatic steatosis.

Keywords Liver steatosis · Ultrasonography · NAFLD

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00330-019-06480-6>) contains supplementary material, which is available to authorized users.

✉ Marco Dioguardi Burgio
marco_dioguardi@hotmail.it

¹ Department of Radiology, University Hospitals Paris Nord Val de Seine, Beaujon, Clichy, Hauts-de-Seine, France

² INSERM U1149, centre de recherche biomédicale Bichat-Beaujon, CRB3, Paris, France

³ University Paris Diderot, Sorbonne Paris Cité, Paris, France

⁴ Department of Hepatology, University Hospitals Paris Nord Val de Seine, Beaujon, Clichy, Hauts-de-Seine, France

⁵ Department of Pathology, University Hospitals Paris Nord Val de Seine, Beaujon, Clichy, Hauts-de-Seine, France

Abbreviations

AC	Attenuation coefficient
ATI	Attenuation imaging
CAP	Controlled attenuation parameter
EASL	European Association for the Study of the Liver
NAFLD	Non-alcoholic fatty liver disease

Introduction

Hepatic steatosis is defined as the presence of at least 5% of fat containing hepatocytes on pathology [1]. It is the main manifestation of non-alcoholic fatty liver disease (NAFLD), whose incidence is increasing worldwide, especially in Western countries. An estimated 25% of adults have NAFLD worldwide [2, 3] with the highest prevalence in the Middle East and South America [4]. Hepatic steatosis is associated with several other conditions in particular alcohol abuse, chronic hepatitis C virus (HCV) infection, and receiving drugs such as chemotherapy [5].

Diagnosis of hepatic steatosis is crucial for patient outcome and management. Patients with NAFLD present with a high risk of associated comorbidities such as type 2 diabetes, cardiovascular disease, and obesity [6]. The pooled overall prevalence of diabetes and obesity among patients with NAFLD is estimated in more than 22% and 51% respectively [4], underlying the close association between these pathological conditions. Moreover, steatosis may lead to the development of chronic inflammation (non-alcoholic steatohepatitis) and liver fibrosis, which may progress to cirrhosis or favor the development of hepatocellular carcinoma. In patients with HCV infection, the presence of steatosis accelerates the progression of liver fibrosis [7]. Marked steatosis is also a risk factor for major complications following hepatectomy [8, 9] and may contraindicate the use of the liver for cadaveric allografts [10].

Visual US assessment of hepatic parenchyma is accurate for the diagnosis of high-grade steatosis [11]. Indeed, a “bright liver” is a common finding for patients who undergo US examination to explore liver test abnormality. A significant part of these patients ends up being diagnosed with NAFLD, underlying the clinical value of B-mode US. Nevertheless, the diagnostic performance and the interobserver agreement of this method can decrease when diagnostic threshold is based on low degrees of steatosis (5%) [12].

In the past few years, a transient elastography-derived technique, the controlled attenuation parameter (CAP), has been developed [13]. This approach assesses steatosis by quantifying the total ultrasonic attenuation (go-and-return path) produced by the transient elastography device in the liver (expressed in dB/m) [13]. Nevertheless, a high number (up to 7.7%) of non-valid measurements are a major clinical limitation to CAP [14]. Moreover, CAP measurements are not image-guided. Like CAP, attenuation imaging (ATI) is based

on the assumption that ultrasound attenuation can be used as proxy for the assessment of hepatic steatosis. ATI allows the calculation of the attenuation coefficient (AC—expressed in dB/cm/MHz), which expresses the variation of US intensity in the depth. We hypothesized that AC quantification may be valuable for the non-invasive diagnosis and quantification of hepatic steatosis. Yet, ATI differs from CAP because it is coupled with high-end real-time B-mode US that enables simultaneous visualization and clinical exploration of the hepatic parenchyma. AC measurements can be easily obtained by placing a ROI in a color box map. While the AC has been found to be promising for the quantification of steatosis [15, 16], its diagnostic value is largely unknown. The aim of this study is to prospectively assess the diagnostic performance of AC for the detection and quantification of hepatic steatosis using liver biopsy as the reference method

Material and methods

Patient selection

This study and the protocol review were approved by the local IRB, and patients provided informed consent. From April 2017 to February 2018, all patients scheduled for a liver biopsy in the Department of Radiology of Beaujon Hospital, Clichy, France, also underwent an ultrasound examination with measurement of the AC on the same day. AC quantification was performed immediately before the biopsy. When liver biopsy was indicated for tumor characterization, patients were only enrolled in the study if a biopsy of the adjacent liver was required so that the presence of steatosis and fibrosis could be evaluated. The flowchart is described in Fig. 1. Demographics, clinical, biological, and pathological data were extracted from the medical charts.

Attenuation imaging

For this study, US examinations were performed by using a clinical US scanner (Aplio i-800, Canon Medical System) with a i8CX1 1–8-MHz curved US transducer used for conventional B-mode examination. ATI technology is based on the attenuation of longitudinal sound waves while travelling through tissue. In this study, a setting for the ultrasound frequency in the range of 3.0 MHz has been selected. The ATI algorithm uses information of beam attenuation from the inside of the entire “ATI box” which is displayed over the normal B-mode image and color coded. ATI produces an average attenuation value including a quality measure that measures the correlation of the attenuation with the depth (goodness of fit— R^2). Therefore, it is important to minimize areas of inhomogeneity (such as vessels or focal lesions) in the “ATI box” as well as to avoid zones that contain strong reverberation

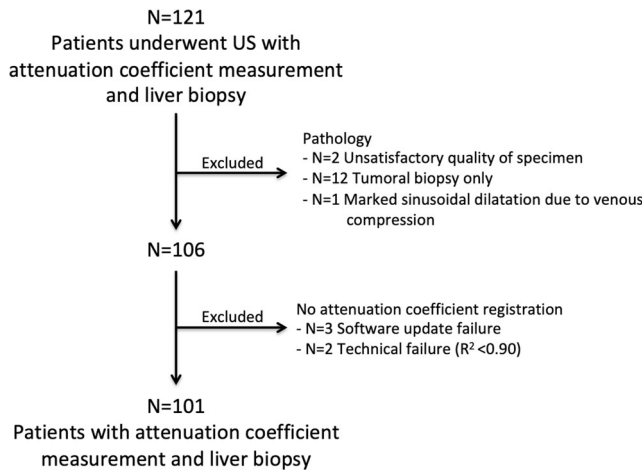


Fig. 1 Patient flow chart

signals. Regions with significant calculation errors (such as blood vessels) are automatically excluded from the map. When a ROI is placed in the ATI box, the software automatically measure the AC expressed in dB/cm/MHz (extracting the focus-dependent beam profile and internal gain control from the observed intensity on the ultrasound image to remove influence of the system on signal intensity). One operator performed the AC measurements for each patient (M.D.B. with 8 years of experience in the field of liver imaging) following recommendation for good practice provided by the manufacturer. ACs were computed during neutral apnea, by right intercostal approach. The operator was asked to manually place the ROI in the color-coded ATI box below the liver capsule to maximize the coefficient of determination (R^2) (Fig. 2). Care was taken during measurement to avoid any capsular artifacts (displayed in red in the superior part of the box—Fig.

2a) and the presence of large vessels. Two measurements with $R^2 > 0.90$ were obtained from each patient and averaged to obtain the AC values used for statistical analysis. The cutoff value of 0.90 was also provided by the manufacturer. If two measurements could not be obtained with $R^2 > 0.90$, this was considered a technical failure (Fig. 2). Raw data were stored in a secure external hard drive.

Pathological evaluation

Pathological analysis was performed by a pathologist expert in the field of liver diseases. The grade of steatosis (S) was assessed for each patient according to Brunt et al from S0 to S3 by quantification of lipid droplets in the hepatocytes as follows: absent (S0) < 5%, mild (S1) 5 to 33%, moderate (S2) 33 to 66%, and severe (S3) > 66% [17]. Liver fibrosis (F) was classified as absent (F0), mild (F1, perisinusoidal or periportal), moderate (F2, periportal and perisinusoidal), F3 (bridging fibrosis), and F4 (cirrhosis) according to METAVIR [18].

Statistical analysis

The primary endpoint of the study was the diagnostic performance of AC for the diagnosis and quantification of hepatic steatosis. In the absence of previously published study using the same ATI technology and the same reference method (i.e., liver biopsy), sample size calculation was not possible. Data were expressed as means ± standard deviations and ranges or *n* (%) as appropriate. The Pearson correlation coefficient between ACs and the percentage of

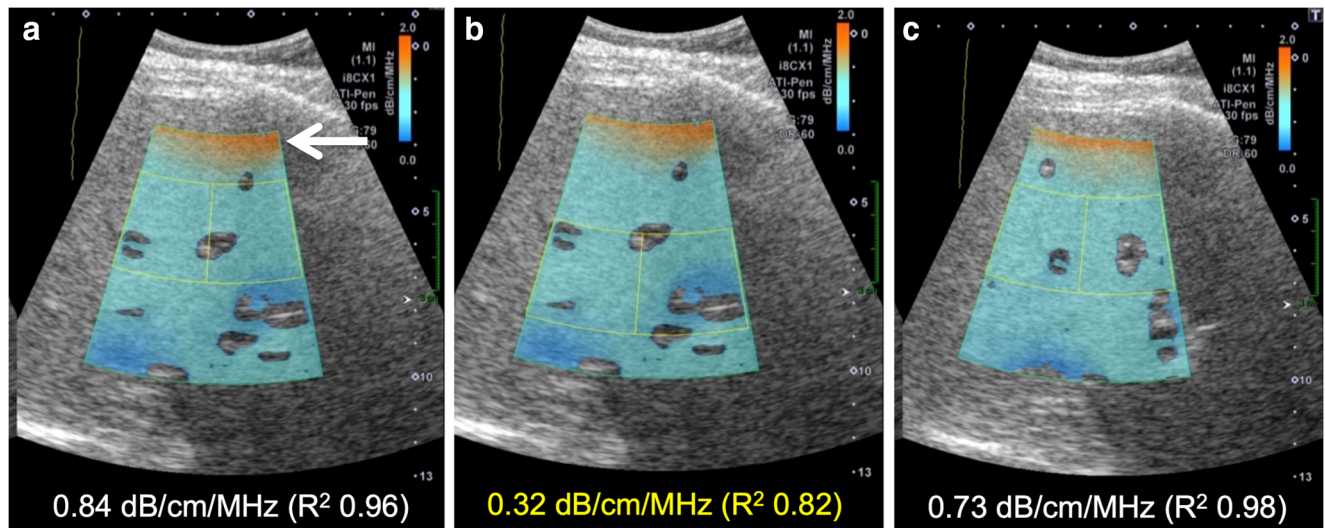


Fig. 2 Ultrasound attenuation imaging coefficient measurement in a 59-year-old female patient. A linear area of high attenuation due to a capsular artifact is visible in the superior part of the image (a, arrow). Three measurements were performed in this patient. The highest R^2 were obtained in the first (a) and third (c) measurements. Part (b) shows the

second measurement with $R^2 < 90$ (automatically highlighted in yellow) that was not retained for AC calculation. The mean attenuation coefficient obtained from averaging the first and third acquisitions was 0.78 dB/cm/MHz, indicating the presence of mild to moderate steatosis. Biopsy showed 20% steatosis (S1)

steatosis on pathology was calculated. Correlations were graded as follows: $r = 0–0.2$, very low; $r = 0.4–0.6$, reasonable; $r = 0.6–0.8$, high; and $r = 0.8–1.0$, very high. The Student t test or the Mann–Whitney U test was used to compare continuous variables, as appropriate (the d’Agostino–Pearson test was used to assess normality). Receiver operating curve (ROC) analysis was performed to evaluate the diagnostic performance of the AC for detecting the presence of any grade of steatosis (S0 vs. S1–S3) or the presence of moderate to severe steatosis (S0–S1 vs. S2–S3). Optimal AC cutoff values were identified by maximizing the Youden index, and corresponding sensitivities and specificities were derived. The DeLong test was used to compare the AUCs. One-way ANOVA was used to compare ACs according to the grades of steatosis, and a post hoc pair-wise comparison was performed using the Student–Newman–Keuls test. All tests were considered to be statistically significant in case of $p < 0.05$, except for pair-wise comparisons where $p < 0.0125$ was used. All tests were performed using dedicated software (MedCalc version 11.5.1.0).

Results

Patient characteristics

Patient characteristics are summarized in Table 1. The final population included 101 patients (63 men [62%] and 38

Table 1 Patient characteristics ($N = 101$)

Mean age (years) (range)	59 (25–89)
Gender (male/female)	63/38 (62%/38%)
NAFLD	40 (40%)
NASH	24 (24%)
Cirrhosis	27 (27%)
Liver fibrosis on pathology	
F0	36 (35%)
F1	12 (12%)
F2	8 (8%)
F3	18 (18%)
F4	27 (27%)
Liver steatosis on pathology	
S0	43 (42%)
S1	35 (35%)
S2	12 (12%)
S3	11 (11%)
Mean AC (dB/cm/MHz) \pm SD (range)	0.71 \pm 0.13 (0.44–1.04)
Mean BMI \pm SD (range)	27.17 \pm 5.37 (15.7–41.1)

AC, attenuation coefficient; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

women [38%]), mean age 59 years old (25–89). Liver biopsy was performed to characterize focal liver lesions in patients with ($n = 31$) or without ($n = 33$) chronic hepatitis, to explore patients with a suspected diagnosis of NAFLD ($n = 21$), or to explore liver test anomalies ($n = 16$).

Pathological analysis

According to pathological analysis, 43 (42%), 35 (35%), 12 (12%), and 11 (11%) patients were classified as S0, S1, S2, and S3, respectively. Thirty-six (35%), 12 (12%), 8 (8%), 18 (18%), and 27 (27%) were classified as F0, F1, F2, F3, and F4, respectively.

Attenuation coefficient and hepatic steatosis

AC measurement technical failures (i.e., $R^2 < 90$) occurred in 2/106 patients (1.9%) as shown in Fig. 1. The mean AC of the entire cohort was 0.71 dB/cm/MHz. There was a significant and positive correlation between the AC and steatosis on pathology (%) ($r = 0.58$, 95% confidence interval [CI] 0.44–0.70; $p < 0.01$)—supplemental Figure 1.

The mean AC was 0.63 ± 0.09 , 0.71 ± 0.11 , 0.87 ± 0.09 , and 0.84 ± 0.13 dB/cm/MHz in patients with S0, S1, S2, and S3, respectively. The AC was significantly different for the different grades of steatosis (ANOVA $p = < 0.01$, all pair-wise comparisons $p < 0.01$, except for S2 vs. S3, $p > 0.05$). Distribution of AC according to the different steatosis grades is detailed in supplemental Figure 2.

The AC in patients without steatosis on pathology (i.e., S0) was significantly lower than in those with any grade of steatosis (i.e., S1–S3) (0.63 ± 0.09 vs. 0.77 ± 0.13 dB/cm/MHz, $p < 0.01$ —Fig. 3a). The AC in patients with moderate/severe steatosis (i.e., S2–S3) was significantly higher than in those without or with mild steatosis on pathology (i.e., S0–S1) (0.85 ± 0.11 vs. 0.67 ± 0.11 dB/cm/MHz, $p < 0.01$ —Fig. 3b).

Performance of AC for the diagnosis of hepatic steatosis

The areas under the ROC curve (AUROC) of the ACs for the diagnosis of any grade of steatosis and moderate to severe steatosis were 0.805 (95%CI 0.71–0.88, $p < 0.01$) and 0.892 (95%CI 0.81–0.94, $p < 0.01$), respectively (Fig. 4).

The sensitivity and specificity of an AC > 0.69 dB/cm/MHz (Fig. 4a) for the diagnosis of any grade of steatosis (S1–S3) were 76% (95%CI 63–85) and 86% (95%CI 72–95), respectively. The sensitivity and specificity of an AC > 0.72 dB/cm/MHz (Fig. 4b) for the diagnosis of moderate or severe steatosis (S2–S3) were 96% (95%CI 78–100) and 74% (95%CI 63–84), respectively. Using the AC cutoff of the 0.69 dB/cm/MHz, 81/101 (80%) of patients were correctly

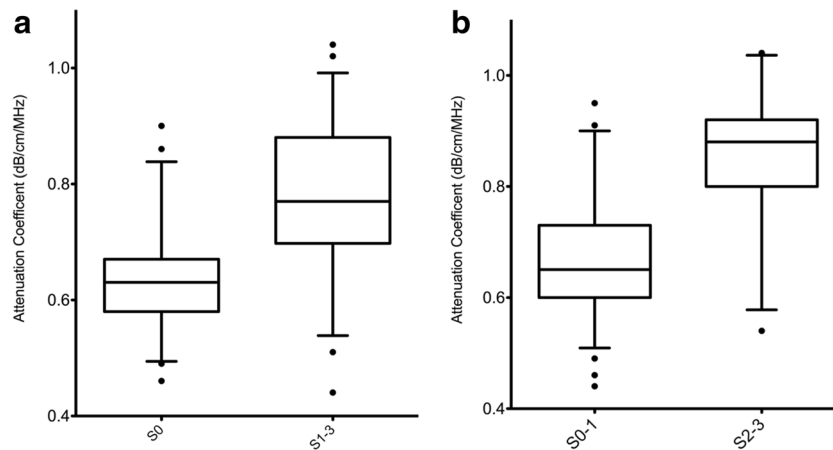


Fig. 3 Box plot graph shows the distribution of attenuation coefficient (AC) values in patients without (S0) vs. patients with any grade of steatosis (S1–S3) (a) and in patients with no or mild steatosis (S0–S1) vs. patients with moderate or severe steatosis (S2–S3) (b). Boxes

represent the 25th and 75th percentiles; whiskers represent the 5th and 95th. Dots are outliers. Mean AC was 0.63 ± 0.09 dB/cm/MHz for S0 vs. 0.77 ± 0.13 dB/cm/MHz for S1–S3 ($p < 0.01$) and 0.67 ± 0.11 dB/cm/MHz for S0–S1 vs. 0.85 ± 0.11 dB/cm/MHz for S2–S3 ($p < 0.01$)

classified as S0 or S1–S3. Using the AC cutoff of 0.72 dB/cm/MHz, 78/101 (77%) of patients were correctly classified as S0–S1 or S2–S3.

The AC rule-in threshold (100% specificity and 19% sensitivity) was > 0.90 dB/cm/MHz for the presence of any grade of steatosis (S1–S3), while the rule-out threshold (100% sensitivity and 0% specificity) was < 0.44 dB/cm/MHz.

Examples of AC measurements in two different patients are reported in Fig. 5.

Influence of fibrosis and BMI on attenuation imaging coefficient measurement

A total of 45/101 (44%) patients presented with advanced fibrosis on pathology (F3–F4). The AC of patients with advanced fibrosis (F3–F4) was not significantly different from

that of patients with F0–F2 (0.72 ± 0.13 vs. 0.70 ± 0.13 dB/cm/MHz, $p = 0.38$).

For each separate class of steatosis, the mean AC was not found to be significantly different according to the presence of advanced liver fibrosis (F3–F4) or not (F0–F2). Detailed results are provided in Table 2.

Overall, 27 patients were obese (i.e., BMI ≥ 30), and 74 were not. Steatosis was more frequent in obese patients (24/27 [89%] vs. 34/74 [46%] in non-obese ones, $p < 0.01$). When present, steatosis was not more severe in obese patients (12/24 patients with S2–S3 [50%] vs. 11/34 [32%] in non-obese ones, $p = 0.18$).

The AUROC of AC for the diagnosis of any grade of steatosis was 0.79 ± 0.06 and 0.79 ± 0.10 in non-obese and obese patients, respectively (DeLong test, $p = 0.95$). The AUROC of AC for the diagnosis of moderate or severe steatosis was 0.85 ± 0.08 and 0.95 ± 0.04 in non-obese and obese patients, respectively (DeLong, $p = 0.047$).

Fig. 4 Receiver operating curve for the diagnostic performance of the attenuation coefficient (AC) in the diagnosis of the presence of any grade of hepatic steatosis (S1 to S3) (a) and the presence of moderate to severe steatosis (S2 to S3) (b). The areas under the ROC curve were 0.805 (95%CI 0.71–0.88, $p < 0.01$) and 0.892 (95%CI 0.81–0.94, $p < 0.01$) for the diagnosis of any grade of steatosis (S1–S3) and of moderate to severe steatosis (S2–S3), respectively

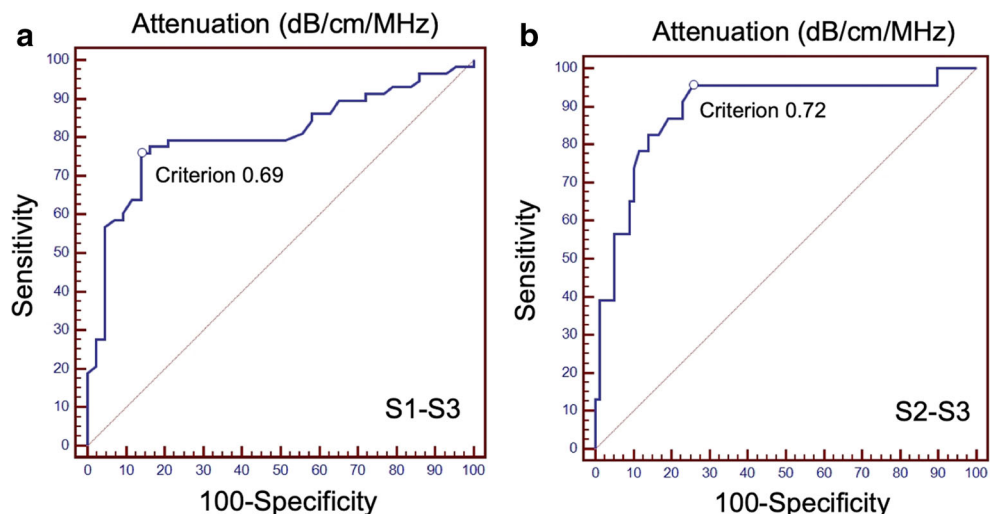
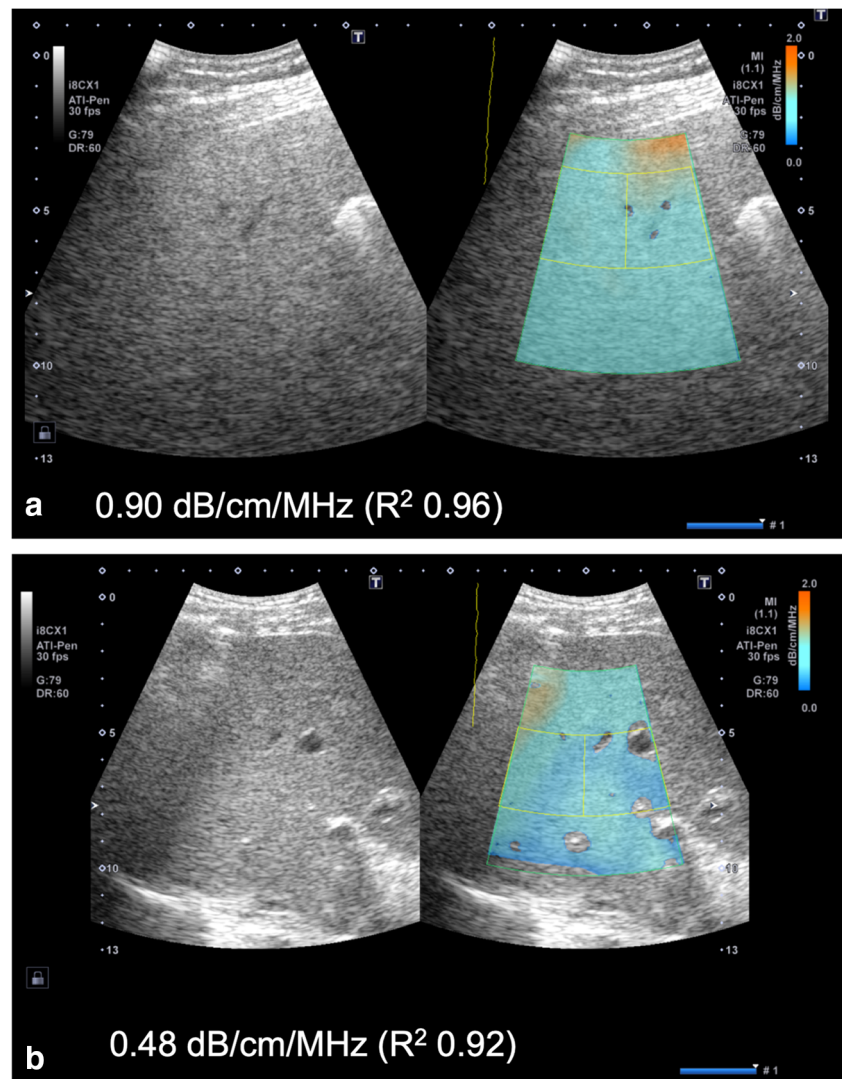


Fig. 5 Attenuation coefficient (AC) quantification measurement in a 71-year-old male patient (**a**) with non-alcoholic steatohepatitis and in a 50-year-old HIV-positive male patient (**b**) presenting with a focal liver lesion. For patient 1, AC was 0.90 dB/cm/MHz with high R^2 (0.96) indicating the presence of severe steatosis that was confirmed on pathology (grade 3–70%). For patient 2, AC was 0.48 dB/cm/MHz with high R^2 (0.92) indicating the absence of steatosis, which was confirmed by pathology (grade 0–0%)



Discussion

This study shows that ultrasound attenuation imaging is a promising tool for the diagnosis of steatosis, with a high sensitivity and specificity. The EASL guidelines recommend ultrasound as the first-line imaging technique to detect steatosis [1]. The qualitative evaluation of hepatic steatosis by US is usually obtained by comparing the echogenicity of the liver and kidney or evaluating several US features including

attenuation of the ultrasound beam, vessel blurring, reduced visualization of the gallbladder wall and the diaphragm, and the presence of fatty sparing areas [19, 20]. However, the sensitivity of US for detecting mild steatosis [21, 22] is limited with a sensitivity and specificity of 73% and 84%, respectively, in a meta-analysis [12]. Moreover, and probably more importantly, the intra- and interobserver agreement of qualitative approaches is low [23]. Results are usually categorized on a 4-point scale (i.e., absent, mild, moderate, or severe steatosis).

Table 2 Influence of advanced (F3–F4) fibrosis on attenuation coefficient (dB/cm/MHz) values for each class of steatosis taken separately

Steatosis		Non-advanced fibrosis (F0–F2)		Advanced fibrosis (F3–F4)	p^*
S = 0	$N = 28$	0.63 ± 0.09	$N = 15$	0.64 ± 0.08	0.95
S = 1	$N = 16$	0.71 ± 0.11	$N = 19$	0.71 ± 0.12	0.93
S = 2	$N = 8$	0.88 ± 0.11	$N = 4$	0.86 ± 0.07	0.98
S = 3	$N = 4$	0.81 ± 0.05	$N = 7$	0.86 ± 0.16	0.76
S = 1–3	$N = 28$	0.77 ± 0.13	$N = 30$	0.77 ± 0.14	0.96

*Mann–Whitney U test

Thus, changes in the amount of steatosis over time cannot be confidently monitored by visual assessment of steatosis on US. This calls for accurate quantitative approaches that can be implemented into US scanners to be routinely used.

One quantitative approach is based on the use of elastography techniques that quantify liver stiffness via the speed of shear waves propagating in the liver. Transient elastography is routinely performed and is now part of clinical algorithms for the managements of patient with various liver diseases [24]. Yet, liver stiffness quantification is used for the assessment of liver fibrosis and portal hypertension, but not for the quantification of steatosis because it has been reported that stiffness values are not correlated with liver steatosis [25]. Nevertheless, this technique is coupled with the quantification of the US attenuation (the so-called CAP) that has been shown to accurately quantify steatosis [13, 26]. How performant CAP may be, it is limited by a rate of technical failure of up to 7.7% [14]. Moreover, it is not an imaging technique. ATI is based on the same assumption that ultrasound attenuation can be used as a proxy for the assessment of hepatic steatosis. Differently from CAP, ATI is coupled to a real-time B-mode visualization. On top of allowing conventional clinical exploration of the liver with high-quality images, it allows probe repositioning to obtain a good-quality images before attenuation measurements are performed. Indeed, real-time B-mode US helps the operator know exactly where the measurements are performed. This approach helps avoid the major artifacts in images (such as those induced by rib reverberation), large hepatic vessels, or focal liver lesions and finally to detect the presence of heterogeneous depositions of steatosis. This is confirmed by our results, since the rate of technical failures was very low (2% of patients in our study). Moreover, the performance of the AC for the diagnosis of any grade of steatosis (S1–S3) was good, similar to the results from recently published studies [15, 16]. The results of AC are also comparable to those of the CAP, which was found to have a pooled sensitivity of 78% and specificity of 79% for the diagnosis of steatosis in a recent meta-analysis [27]. In our study, sensitivity was found to be almost the same (76%) with greater specificity (86%). Finally, results were not altered by the presence of obesity.

Tada et al [15] investigated the diagnostic performance of AC for the diagnosis of steatosis using MRI-PDFF as the reference standard. They found that a cutoff value of 0.60 dB/cm/MHz had a sensitivity of 85.5% and specificity of 88.5% for the diagnosis of any grade of steatosis while a cutoff of 0.69 dB/cm/MHz had a sensitivity of 82.7% and a specificity of 81.1% for the diagnosis of moderate or severe steatosis. Our results show slightly higher cutoff values (0.69 and 0.72 dB/cm/MHz, respectively). These discrepancies may be due to the difference in reference technique in the two studies. Indeed, we used liver biopsy while Tada et al used MR-PDFF. Although PDFF is extremely accurate in

diagnosing steatosis, there is no strict consensus on which PDFF cutoffs should be used to grade steatosis. Second, the manufacturer of the AC measurement was not the same in the two studies [15]. Finally, our patient population differed because we also included patients with chronic liver disease, which is a better reflection of clinical practice because many patients have both fibrosis and steatosis. Although our group was more heterogeneous due to the inclusion of patients with chronic liver disease, this allowed us to investigate the influence of fibrosis and cirrhosis on the measured AC value, which was one of the limitations of the study by Tada et al [15].

A recent publication from Bae et al [16] explored the potential role of ATI using liver biopsy as a reference standard. Reported results were close to ours, with similar diagnostic performance (AUC of AC of 0.80 vs. 0.84 for any grade of steatosis, and of 0.89 vs. 0.89 for S2–S3 steatosis) and similar optimal AC cutoff values (0.69 vs. 0.635 dB/cm/MHz for any grade of steatosis and 0.72 vs. 0.70 dB/cm/MHz for S2–S3 steatosis). This confirms the potential clinical role of the AC measurement with ATI for the diagnosis of hepatic steatosis. Noticeably, we used a more stringent R^2 threshold to define technical failure (0.90 vs. 0.80 in the study from Bae et al [16]) explaining the slightly higher rate of technical failure in our study (2% vs. 0%). Finally, due to a higher rate of patients with significant fibrosis in our cohort, we could accurately show that significant fibrosis has no influence on AC value. In this setting, we believe that AC measurement could be added to US elastography to classify both steatosis and fibrosis, allowing this technique to be a comprehensive non-invasive tool for liver diseases.

This study has several limitations. First, the included population was heterogeneous, including patients with chronic liver disease from different etiologies and some with cirrhosis. It has been shown that CAP cutoff values are influenced by the etiologies of liver disease [26]. This must be assessed with ATI. For this reason, more studies including homogeneous cohorts are necessary. We did not compare AC measurements with other quantitative or semi-quantitative US methods such as semi-quantitative visual comparison of hepatic and renal echogenicity or hepatorenal index. Nevertheless, the aim of this study was to assess the ability of this new technique to detect steatosis. We observed an overlap between AC values, especially in patients with S2 or S3 steatosis. This may be due to the limited number of patients with high degrees (S2–S3) of steatosis. Nevertheless, from a clinical point of view, this seems to be of limited consequence as ultrasound visual approach alone is performant to diagnose such high grades of steatosis. Moreover, patients with S2 do not differ from those with S3 in terms of management and possible treatment. The added value of ATI is to enable detecting small amounts of fatty deposition in the liver. Finally, our reference method for steatosis was liver biopsy, which can suffer from sample bias

[28]. To the best of our knowledge, ATI is not available on other US scanners. This may limit its use but we are confident that, as for elastography, similar technology will be progressively implemented by other vendors.

In conclusion, this study shows that measurement of ultrasound AC is a promising quantitative method for the detection and quantification of hepatic steatosis.

Funding information The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Marco Dioguardi Burgio.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

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.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Methodology

- prospective
- diagnostic study
- performed at one institution

References

1. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO) (2016) EASLEASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 64:1388–1402
2. Browning JD, Szczepaniak LS, Dobbins R et al (2004) Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 40:1387–1395
3. Vernon G, Baranova A, Younossi ZM (2011) Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 34:274–285
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M (2016) Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 64:73–84
5. Bellentani S, Bedogni G, Miglioli L, Tiribelli C (2004) The epidemiology of fatty liver. *Eur J Gastroenterol Hepatol* 16:1087–1093
6. Ballestri S, Zona S, Targher G et al (2016) Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *J Gastroenterol Hepatol* 31:936–944
7. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G (2001) Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 33:1358–1364
8. McCormack L, Petrowsky H, Jochum W, Furrer K, Clavien PA (2007) Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case-control study. *Ann Surg* 245:923–930
9. d'Assignies G, Fayard C, Leitao H et al (2016) Liver steatosis assessed by preoperative MRI: an independent risk factor for severe complications after major hepatic resection. *Surgery* 159:1050–1057
10. Koneru B, Dikdan G (2002) Hepatic steatosis and liver transplantation current clinical and experimental perspectives. *Transplantation* 73:325–330
11. Palmentieri B, de Sio I, La Mura V et al (2006) The role of bright liver echo pattern on ultrasound B-mode examination in the diagnosis of liver steatosis. *Dig Liver Dis* 38:485–489
12. Bohte AE, van Werven JR, Bipat S, Stoker J (2011) The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis. *Eur Radiol* 21:87–97
13. Sasso M, Beaugrand M, de Ledinghen V et al (2010) 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* 36:1825–1835
14. de Ledinghen V, Vergniol J, Capdepon M et al (2014) Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. *J Hepatol* 60:1026–1031
15. Tada T, Kumada T, Toyoda H et al (2019) Utility of attenuation coefficient measurement using an ultrasound-guided attenuation parameter for evaluation of hepatic steatosis: comparison with MRI-determined proton density fat fraction. *AJR Am J Roentgenol* 212:332–341
16. Bae JS, Lee DH, Lee JY et al (2019) Assessment of hepatic steatosis by using attenuation imaging: a quantitative, easy-to-perform ultrasound technique. *Eur Radiol*. <https://doi.org/10.1007/s00330-019-06272-y>
17. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR (1999) Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 94:2467–2474
18. Bedossa P, Dargere D, Paradis V (2003) Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 38:1449–1457
19. Hamaguchi M, Kojima T, Itoh Y et al (2007) The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. *Am J Gastroenterol* 102:2708–2715
20. Ballestri S, Lonardo A, Romagnoli D et al (2012) Ultrasonographic fatty liver indicator, a novel score which rules out NASH and is correlated with metabolic parameters in NAFLD. *Liver Int* 32:1242–1252
21. Fishbein M, Castro F, Cheruku S et al (2005) Hepatic MRI for fat quantitation: its relationship to fat morphology, diagnosis, and ultrasound. *J Clin Gastroenterol* 39:619–625
22. Stern C, Castera L (2017) Non-invasive diagnosis of hepatic steatosis. *Hepatol Int* 11:70–78
23. Strauss S, Gavish E, Gottlieb P, Katsnelson L (2007) Interobserver and intraobserver variability in the sonographic assessment of fatty liver. *AJR Am J Roentgenol* 189:W320–W323

24. Friedrich-Rust M, Ong MF, Martens S et al (2008) Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology* 134:960–974
25. Suh CH, Kim SY, Kim KW et al (2014) Determination of normal hepatic elasticity by using real-time shear-wave elastography. *Radiology* 271:895–900
26. Karlas T, Petroff D, Sasso M et al (2017) Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *J Hepatol* 66:1022–1030
27. Shi KQ, Tang JZ, Zhu XL et al (2014) Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Gastroenterol Hepatol* 29:1149–1158
28. Ratziu V, Charlotte F, Heurtier A et al (2005) Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 128:1898–1906

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.