

Ultrasound-Guided Attenuation Parameter Is Useful for Quantifying Hepatic Steatosis in Nonalcoholic Steatohepatitis

Yu Ogino

Toho University

Noritaka Wakui (✉ wakui@med.toho-u.ac.jp)

Toho University

Hidenari Nagai

Toho University

Yoshinori Igarashi

Toho University

Research Article

Keywords: nonalcoholic steatohepatitis, ultrasonography, attenuation imaging, hepatic steatosis

Posted Date: December 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-113530/v1>

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Abstract

Background: The number of patients with nonalcoholic fatty liver disease has been steadily increasing, and around 10%-20% of these patients are classified as having nonalcoholic steatohepatitis (NASH). The first step to identifying patients with NASH is assessing for hepatic steatosis, which is commonly done noninvasively by ultrasound examination. However, conventional methods are not always effective at lower levels of steatosis. Thus, we sought to determine the utility of a new method using the ultrasound-guided attenuation parameter (UGAP) for quantifying hepatic steatosis in NASH.

Methods: Subjects were 36 patients with NASH (20 men, 16 women; mean age 56 [37 to 73] years) who underwent liver biopsy and ultrasonography using a GE LOGIQ E9 system and C1-6 probe at our hospital between 2017 and 2020. B-Mode imaging of segment V in the liver was acquired and echo attenuation was assessed using UGAP. Steatosis score (S0: <5%; S1: 5%-33%; S2: 34%-66%; S3: \geq 67%) from liver specimens was compared with the attenuation coefficient (AC; dB/cm/MHz) using UGAP.

Results: Steatosis score was S0 in 4 patients, S1 in 16, S2 in 10, and S3 in 6. AC by steatosis score was 0.54 ± 0.06 , 0.63 ± 0.05 , 0.74 ± 0.05 , and 0.79 ± 0.05 dB/cm/MHz for S0, S1, S2, and S3, respectively. AC by UGAP differed significantly between S0 and S2 ($p < 0.05$), S0 and S3 ($p < 0.05$), S1 and S2 ($p < 0.01$), and S1 and S3 ($p < 0.01$), demonstrating a significant increase with steatosis score. Receiver operating characteristic analysis showed good diagnostic performance of UGAP for patients with steatosis score ≥ 1 , ≥ 2 , and ≥ 3 (AUROC = 0.95, 0.96, and 0.93, respectively). Liver fat content (%) from liver specimens and AC ($r = 0.83$, $p < 0.01$) showed a significant positive correlation.

Conclusions: UGAP is useful for quantifying hepatic steatosis in patients with NASH.

Background

The number of patients with nonalcoholic fatty liver disease (NAFLD) has been steadily growing in recent years [1]. NAFLD affects 25.24% of the world's population and 23.71% of people in Europe, 24.13% in North America, 30.45% in South Africa, 31.79% in the Middle East, and 27.37% in Asia [2]. It is predicted that more than 20 million people in Japan will have NAFLD by the year 2030, of which more than 1 million will have high-risk NAFLD with stage 3 or 4 fibrosis [3]. About 10%-20% of NAFLD cases are classified as nonalcoholic steatohepatitis (NASH), which must be diagnosed and treated proactively because it can lead to cirrhosis and liver cancer [4]. Liver biopsy is currently the only method for definitive diagnosis of NASH [5–7], but it is unreasonable to routinely perform invasive liver biopsy in all patients with such a globally prevalent condition as NAFLD. The first step to identifying patients with NASH is to assess for hepatic steatosis. This is commonly done noninvasively by ultrasound examination. However, studies have shown that although B-mode images alone are useful for assessing steatosis at levels of $\geq 30\%$ [8], they have low sensitivity at lower levels of steatosis [9, 10]. In addition, the histopathological diagnostic criteria for NASH require detection of $> 5\%$ steatosis in the liver [11]. Consequently, an accurate quantitative method for assessing hepatic steatosis is needed.

We conducted this retrospective study to determine whether a new method of attenuation imaging using the ultrasound-guided attenuation parameter (UGAP) would be useful for quantifying hepatic steatosis in patients for NASH.

Materials And Methods

Enrolment of patients

Subjects were patients with NAFLD scheduled to undergo liver biopsy at Toho University Omori Medical Center between 2017 and 2020. Inclusion criteria were (1) age \geq 16 years, and (2) meeting the diagnostic criteria for NAFLD. NAFLD was diagnosed based on the latest guidelines established by the American Association for the Study of Liver Diseases [1] as follows: (i) fatty change of the liver observed on imaging; (ii) no heavy alcohol consumption (ethanol intake $<$ 210 g per week for men and $<$ 140 g per week for women); (iii) no other factors that induce fatty change of the liver; and (iv) no chronic liver disease with clear aetiology, such as viral infection (hepatitis C or hepatitis B virus), primary biliary cholangitis, or autoimmune hepatitis. Information about the study was published on the Toho University website, and patients who opted out were excluded from the study. The protocol for this study was in accordance with the Declaration of Helsinki and was approved by the ethics committee at our institution (No. M19244).

Ultrasonography

Ultrasonography was performed from the right intercostal space using a LOGIQ E9 XDclear 2.0 ultrasound scanner (GE Healthcare) with a C1-6-D convex array probe. According to the method reported by Fujiwara et al. [13], a single calibration of the ultrasound system was performed using a specific acquisition setup (fundamental B-mode at 4.0 MHz). Images showing liver parenchyma of the right hepatic lobe (segment V) were used in the analysis. Participants were examined in the supine position with the right arm elevated above the head while breath-holding. Patients fasted overnight before the examination. All ultrasound examinations were performed by an independent examiner who was blinded to patient characteristics and had 25 years of experience as an ultrasonographer.

Ultrasound-guided attenuation parameter

We measured the attenuation coefficient (AC) of the liver using UGAP [12, 13]. This method is based on comparison with a reference signal previously measured for a known attenuating material. UGAP analyses the difference between the measured liver signals and the referential signal, and estimates the liver attenuation based on the difference. We set a region of interest (ROI) to avoid obvious large vessels, but the algorithm will automatically exclude small structures in the liver such as cross-sections of the small vessels.

AC values and serological markers

AC values obtained for each patient by ultrasound examination were compared with the following parameters to assess correlations: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), triglycerides (TG), platelet count, prothrombin time (PT%), fasting plasma glucose (FPG), and glycated haemoglobin (HbA1c). Blood samples were collected from all patients within 3 days prior to ultrasound examination.

AC values and other parameters

Correlations of AC values with body mass index (BMI) and skin-liver capsule distance were also assessed.

Liver biopsy specimens

Needle biopsies were performed after sonography with a 16-gauge liver biopsy needle (Core^{ll} semiautomatic biopsy instrument; InterV Clinical Products). Specimens were obtained from the anterior segment of the right lobe (segment 5) under ultrasound guidance and fixed in 10% formalin, embedded in paraffin, sectioned, and stained with haematoxylin-eosin and Azan for histological evaluation.

Histological characteristics, NAFLD activity score, and fibrosis were evaluated using standard histological criteria by a single experienced pathologist blinded to the identity of the participants and their clinical information. The NAFLD activity score [11] was determined based on histopathological features of steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2). Steatosis was scored as follows: <5% = 0, 5%–33% = 1, >33%–66% = 2, and >66% = 3. Liver fat content (LFC; %) within the field of view was also determined. For lobular inflammation, the scoring was as follows: no foci = 0, < 2 foci = 1, 2–4 foci = 2, and > 4 foci = 3. Hepatocellular ballooning was scored as follows: none = 0, few = 1, and many = 2. Fibrosis stage was scored as follows: none = 0, mild at zone 3 = 1A moderate at zone 3 = 1B, portal/periportal = 1C, zone 3 and periportal = 2, bridging = 3, and cirrhosis = 4.

NASH was diagnosed based on the classification described by Matteoni et al. [14]. Briefly, type 1 is defined as fatty liver alone; type 2 is defined as fat accumulation and lobular inflammation; type 3 is defined as fat accumulation and ballooning degeneration; and type 4 is defined as fat accumulation, ballooning degeneration, and either Mallory-Denk bodies or fibrosis. Type 3 or 4 is defined as NASH. Steatosis scores (S0–3) and LFC (%) obtained by liver biopsy were compared against AC values (dB/cm/MHz) obtained by ultrasound to assess the diagnostic performance of AC values for hepatic steatosis.

Statistical analysis

Parameter analysis according to range of AC values by steatosis score: Box plots were used to study the distribution of the range of AC values by steatosis score. Trends were evaluated using the Jonckheere-Terpstra trend test. Data were compared between the groups using the Steel-Dwass test. The diagnostic performance of AC values was assessed using receiver operating characteristic (ROC) curves. The ROC curve is a plot of the sensitivity versus 1 – specificity for all possible cutoff values. The most commonly

used index of accuracy is the area under the receiving operating characteristic (AUROC), with values close to 1.0 indicating high diagnostic accuracy.

Spearman's rank correlation coefficients were used to examine the correlation of AC values with steatosis score and LFC (%) obtained by biopsy, as well as AST, ALT, total bilirubin, albumin, HDL-C, LDL-C, TG, platelet count, PT%, FPG, HbA1c, BMI, and skin-liver capsule distance.

All analyses were performed using Excel Statistics 2015 software (SSRI Co., Tokyo, Japan). Differences were considered significant at $p < 0.05$.

Results

Patients

This study enrolled 91 patients who consented to participate. After excluding 7 patients (5 histopathologically diagnosed with a disease other than NAFLD and 2 with poor biopsy quality), the remaining 84 patients were screened for NAFLD. Finally, 36 patients were diagnosed as having NASH (20 men and 16 women aged 56 ± 11 [range 37–73] years) and included in the analysis.

The steatosis score was S0 in 4 patients, S1 in 16 patients, S2 in 10 patients, and S3 in 6 patients. By steatosis score, AC values were 0.54 ± 0.06 , 0.63 ± 0.05 , 0.74 ± 0.05 , and 0.79 ± 0.05 dB/cm/MHz for S0, S1, S2, and S3, respectively.

The clinical and biochemical characteristics of the 36 patients with chronic liver disease enrolled in this study are summarised in Tables 1 and 2.

Table 1
Clinical and biochemical characteristics

Variable	Value ^a
	NASH
Number	36
Sex (M/F)	20/16
Age (years)	56 ± 11
Comorbidities (HT/DM/dyslipidaemia)	22/24/33
Body mass index (kg/m ²)	28.6 ± 4.4
Skin thickness overlying the liver (mm)	20.3 ± 3.7
Aspartate aminotransferase (IU/L)	53.1 ± 24.5
Alanine aminotransferase (IU/L)	66.7 ± 38.1
Albumin (g/dL)	4.2 ± 0.4
Total bilirubin (mg/dL)	0.9 ± 0.6
Fasting plasma glucose (mg/dL)	131.9 ± 35.4
Haemoglobin A1c (%)	6.8 ± 1.1
HDL-C (mg/dL)	50.2 ± 12.3
LDL-C (mg/dL)	108.6 ± 27.6
Triglyceride (mg/dL)	172.2 ± 65.5
Platelet count (× 10 ⁴ /μL)	19.7 ± 7.1
Prothrombin time (% of normal)	97.8 ± 17.1
^a Values are expressed as the mean ± standard deviation or numbers of patients.	
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; HT, hypertension; DM, diabetes mellitus.	

Table 2
Histological characteristics

Variable	Value ^a
	NASH
Fibrosis stage	
F0	3
F1	8
F2	4
F3	10
F4	11
Lobular inflammation (activity grade)	
A0	0
A1	22
A2	14
A3	0
Steatosis score	
S0 (< 5%)	4
S1 (5%-33%)	16
S2 (34%-66%)	10
S3 (> 67%)	6
Hepatocellular ballooning	
B0	-
B1	32
B2	4
Liver fat content (%)	34.6 ± 23.1
^a Values are expressed as the mean ± standard deviation or numbers of patients.	

NASH, nonalcoholic steatohepatitis.

Correlation between AC values and serological markers

AC values showed a significant positive correlation with ALT ($r = 0.50, p < 0.01$), platelet count ($r = 0.44, p < 0.01$), and PT% ($r = 0.56, p < 0.01$), demonstrating that AC increased with increases in ALT, platelet count, and PT%. There was no significant correlation of AC values with AST ($r = 0.16, p = 0.36$), T-Bil ($r = -0.13, p = 0.45$), albumin ($r = 0.20, p = 0.24$), HDL-C ($r = -0.19, p = 0.34$), LDL-C ($r = 0.30, p = 0.08$), TG ($r = 0.06, p = 0.72$), FGP ($r = 0.30, p = 0.07$), or HbA1c ($r = 0.24, p = 0.15$).

Correlation between AC values and other parameters

AC values were not significantly correlated with BMI ($r = -0.24, p = 0.16$) or skin thickness overlying the liver ($r = -0.06, p = 0.71$).

Correlation between AC values and liver pathological factors

Steatosis score

The AC value by steatosis score was 0.54 ± 0.06 for S0, 0.63 ± 0.05 for S1, 0.74 ± 0.05 for S2, and 0.79 ± 0.05 for S3. The Jonckheere-Terpstra trend test for strain index variation in S0–S3 patients showed a significant decreasing trend in the AC value with increasing steatosis score.

Multiple comparison tests showed significant differences between S0 and S2 ($p < 0.05$), S0 and S3 ($p < 0.05$), S1 and S2 ($p < 0.01$), and S1 and S3 ($p < 0.01$), demonstrating that AC increased significantly with the progression of steatosis (Fig. 1a).

The cutoff value and AUROC by steatosis score were respectively 0.63 and 0.94 for S0 and \geq S1, 0.71 and 0.96 for stages S0–1 and \geq S2, and 0.76 and 0.93 for S0–S2 and \geq S3. The sensitivity and specificity of AC values were respectively 78.1% and 100% for \geq S1 cases, 87.5% and 90.0% for \geq S2 cases, and 100% and 90.0% for \geq S3 cases (Fig. 2a-c; Table 3).

Table 3

Assessment of histological steatosis score based on attenuation coefficient values in 36 patients with NASH

	\geq S1	\geq S2	\geq S3
Cut-off value (mm)	0.63	0.71	0.76
Sensitivity (%)	78.1	87.5	100.0
Specificity (%)	100.0	90.0	90.0
AUROC curve	0.95	0.96	0.93

AUROC, area under receiver operating characteristic curve; NASH, nonalcoholic steatohepatitis

Fibrosis stage

The AC value for each fibrosis stage was 0.8 ± 0.03 for F0, 0.75 ± 0.07 for F1, 0.68 ± 0.05 for F2, 0.68 ± 0.07 for F3, and 0.61 ± 0.09 for F4. Multiple comparison tests showed significant differences between F1 and F4 ($p < 0.05$), demonstrating that AC decreased significantly with the progression of fibrosis (Fig. 1b).

Inflammation score and ballooning score

AC values were not significantly correlated with inflammation score or ballooning score.

Correlation between AC values and LFC (%)

There was a significant positive correlation between LFC (%) obtained by liver biopsy and AC values ($r = 0.83$, $p < 0.01$; Fig. 3).

Discussion

The prevalence of hepatic steatosis has been increasing rapidly, and it is currently detected in over 25% of people undergoing routine health check-ups in Japan [15]. There is a long history of using ultrasound to diagnose hepatic steatosis, starting when Joseph et al. proposed the concept of a “bright liver” in 1979 [16], and it is still often routinely used for this purpose in clinical practice. New findings such as hepatorenal echo contrast [17], deep attenuation, and vascular blurring were subsequently added to form a set of 4 characteristic features to aid in the diagnosis of this condition. However, improved beam penetration resulting from advances in ultrasound systems has altered how the characteristic features of hepatic steatosis appear on ultrasound. Specifically, deep attenuation has become difficult to capture with modern ultrasound systems because attenuation correction methods cause deep attenuation to be displayed as if there were no attenuation at all. Thus, it is actually becoming more difficult to accurately assess hepatic steatosis using conventional methods alone. Also, there is now a critical need to assess whether hepatic steatosis occurs in $> 5\%$ of the liver because this is the definition of steatosis used in the diagnosis of NASH, which can progress to cirrhosis [1]. Studies have also shown that the level of hepatic steatosis correlates with cardiovascular events [18], and that steatosis $\geq 25\%$ clearly worsens the prognosis for liver transplantation [19]. Accurate quantification of hepatic steatosis is therefore necessary, but liver biopsy has been the only quantitative method available to date. However, liver biopsy is a poorly suited diagnostic test for such a prevalent condition because of the costs, possible risks, and invasiveness of the procedure [20].

One method currently available for quantifying steatosis is the attenuation imaging (ATI) modality offered by Canon Medical Systems. Tada et al. [21] compared ATI results against liver biopsy results in 38 patients with NAFLD using ROC curve analysis and found good diagnostic performance for steatosis scores of 1, 2, and ≥ 3 (AUROC = 0.77, 0.88, and 0.86, respectively). Bae et al. [22] compared ATI results with liver biopsy results in 108 patients with diffuse liver disease using ROC curve analysis and also found good diagnostic performance for steatosis scores of 1, 2, and ≥ 3 (AUROC = 0.843, 0.886, and 0.926, respectively). Other methods have also been evaluated. Hyodo et al. [23] evaluated the utility of computed tomography (CT) for quantifying steatosis. They compared dual-energy CT results with liver biopsy results in 33 NAFLD patients by ROC curve analysis and found good diagnostic performance for

steatosis scores of ≥ 1 based on AUROC. Two studies have evaluated the utility of magnetic resonance imaging (MRI). Igarashi et al. [24] compared multi-slice and multi-point MRI findings with liver biopsy findings in 52 patients with NAFLD by ROC curve analysis and found good diagnostic performance for steatosis scores of 1, 2, and ≥ 3 (AUROC = 0.975, 0.929, and 0.969, respectively). Imajo et al. [25] compared MRI-based proton density fat fraction results with liver biopsy results in 142 NAFLD patients by ROC curve analysis and found good diagnostic performance for steatosis scores of 1, 2, and ≥ 3 (AUROC = 0.98, 0.90, and 0.79, respectively).

In this study, we tested the performance of the UGAP developed as an attenuation imaging method for quantifying relative attenuation in the liver caused by the properties of living tissues for the quantification of steatosis in patients with NASH. We found a significant positive correlation between LFC (%) obtained by liver biopsy and AC values ($r = 0.83$, $p < 0.01$), as well as good diagnostic performance of AC values for steatosis scores of 1, 2, and ≥ 3 in ROC curve analysis (AUROC = 0.95, 0.96, and 0.93, respectively). Our results indicate that ultrasound diagnosis of steatosis using UGAP has comparable performance to that previously reported for diagnosis of steatosis by ultrasound with ATI, CT, and MRI. The assessment results obtained using UGAP were favourable probably because this technology automatically detected 2 different positions within the ROI that were in the most suitable condition for measuring liver signals to determine attenuation.

In 36 patients with NASH, AC values showed a positive correlation with ALT ($r = 0.50$, $p < 0.01$), PLT ($r = 0.44$, $p < 0.01$), and PT% ($r = 0.56$, $p < 0.01$). Also, in patients with NASH, comparison of the AC value with fibrosis, which is one of the liver pathological factors, showed that the AC value decreased significantly with the progression of fibrosis. When NASH progresses to cirrhosis, the degree of steatosis decreases (so-called burnout NASH), and this may be one of the possible reasons for the positive correlations of AC with PLT and PT%, and for the decreases in AC with the progression of fibrosis.

The positive correlation between AC values and ALT suggests the degree of liver inflammation influences the AC value, but this needs to be investigated further in the future.

Our study has some limitations. This was a single-centre study with a small sample size, and the results will need to be validated in a multicentre study with a larger sample size. Research in different racial groups will also need to be conducted because we evaluated only Japanese patients in this study.

Conclusions

Taken together, our findings indicate that AC values obtained using UGAP could be a useful new method for quantifying steatosis in NASH.

List Of Abbreviations

AC, attenuation coefficient; ALT, alanine aminotransferase; AST, serum aspartate aminotransferase; ATI, attenuation imaging; AUROC, area under the receiving operating characteristic; BMI, body mass index; CT,

computed tomography; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; LFC, liver fat content; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PT%, prothrombin time; ROC, receiver operating characteristic; ROI, region of interest; TG, triglycerides; UGAP, ultrasound-guided attenuation parameter.

Declarations

Ethics approval and consent to participate

The protocol for this study was in accordance with the Declaration of Helsinki and was approved by the ethics committee at our institution (No. M19244), and informed consent was obtained from all patients in this study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

Study concepts: Yu Ogino

Study design: Noritaka Wakui

Data acquisition: Yu Ogino, Noritaka Wakui,

Data analysis and interpretation: Hidenari Nagai

Statistical analysis: Hidenari Nagai

Manuscript preparation: Yu Ogino

Manuscript editing: Noritaka Wakui

Acknowledgements

Not applicable.

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Figures

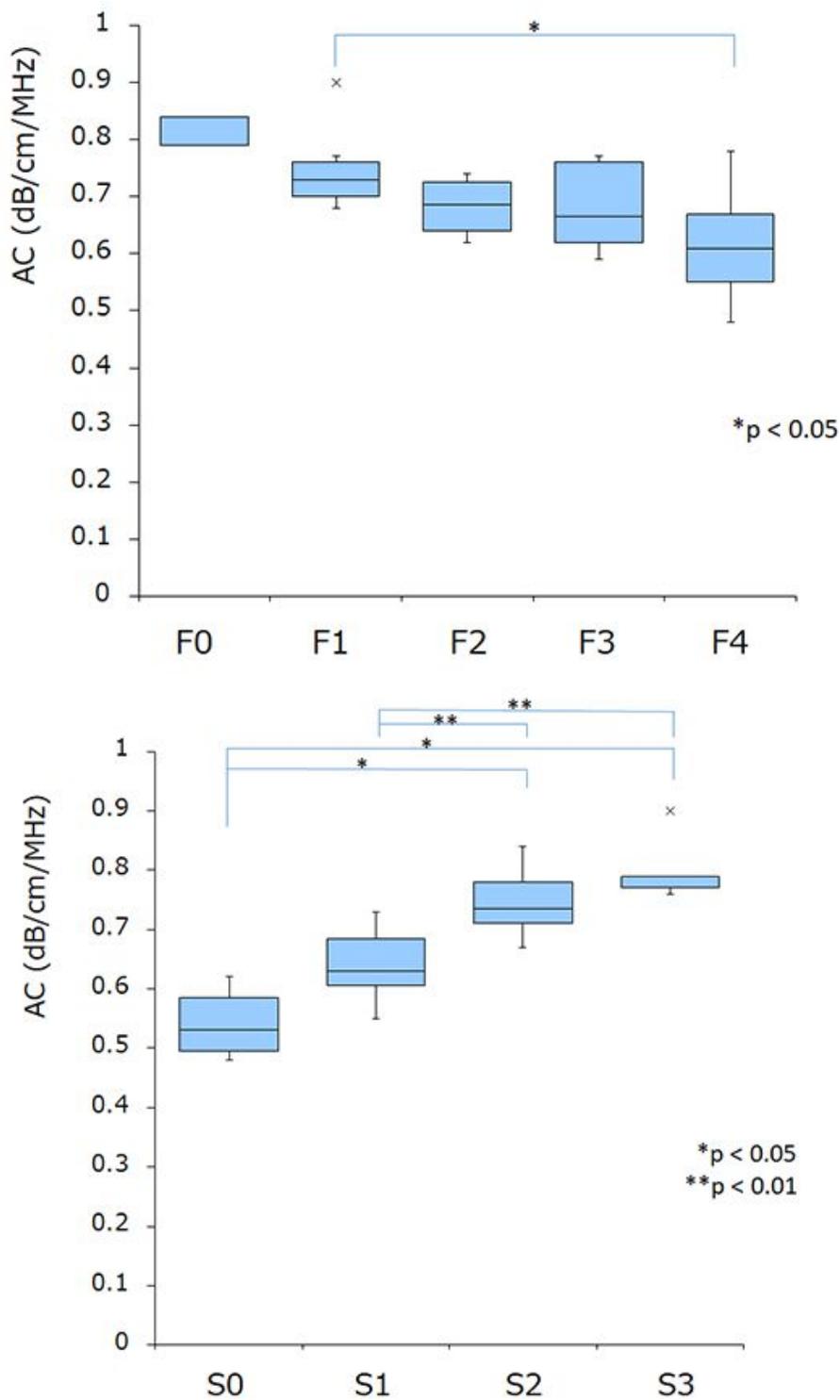


Figure 1

Correlation of AC values with steatosis score and fibrosis stage in NASH By steatosis score, the AC value was 0.54 ± 0.06 for S0, 0.63 ± 0.05 for S1, 0.74 ± 0.05 for S2, and 0.79 ± 0.05 for S3. (a) Multiple comparison tests showed significant differences between S0 and S2 ($p < 0.05$), S0 and S3 ($p < 0.05$), S1 and S2 ($p < 0.01$), and S1 and S3 ($p < 0.01$), demonstrating that AC increased significantly with the progression of

steatosis. (b) Multiple comparison tests showed a significant difference between F1 and F4 ($p < 0.05$), demonstrating that AC decreased significantly with the progression of fibrosis.

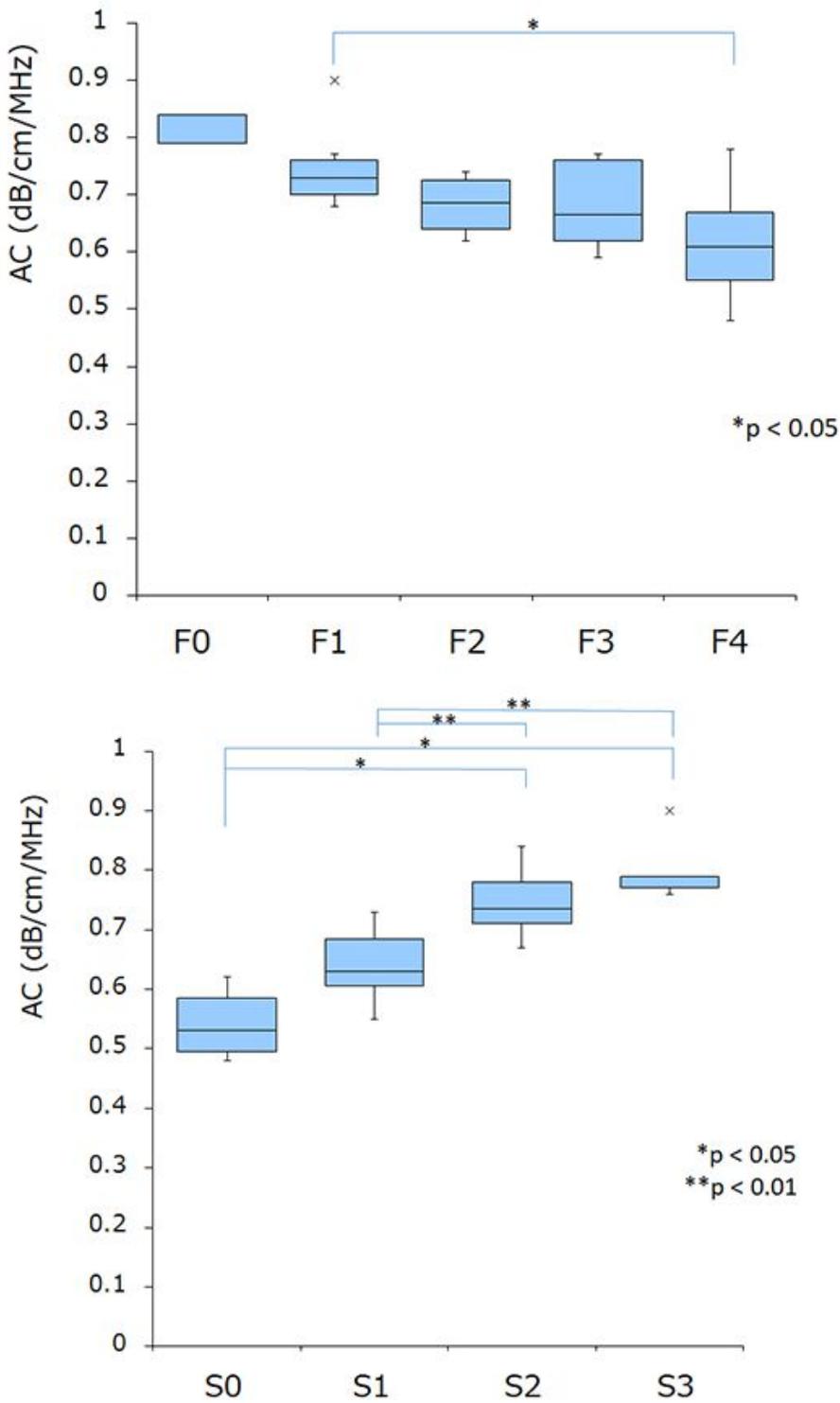


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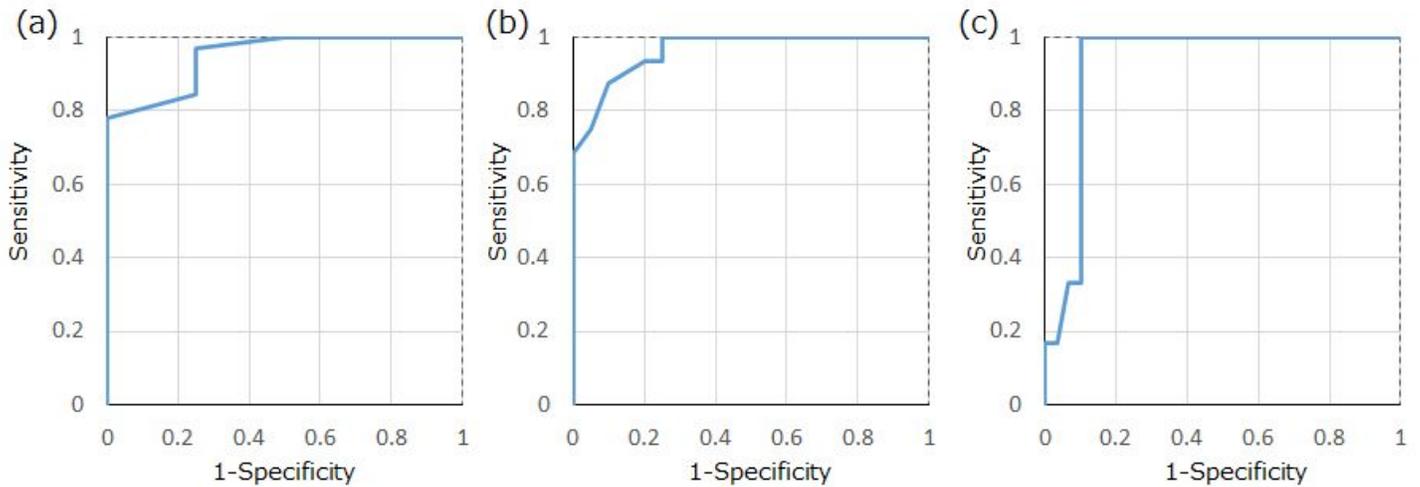


Figure 2

Diagnostic performance of AC values for liver steatosis score in NASH By steatosis score, the cutoff value and AUROC were respectively (a) 0.60 and 0.94 for S0 and \geq S1, (b) 0.71 and 0.96 for S0–1 and \geq S2, and (c) 0.76 and 0.93 for S0–S2 and \geq S3. The sensitivity and specificity of AC values were respectively 78.1% and 100% for \geq S1 cases, 87.5% and 90.0% for \geq S2 cases, and 100% and 90.0% for \geq S3 cases.

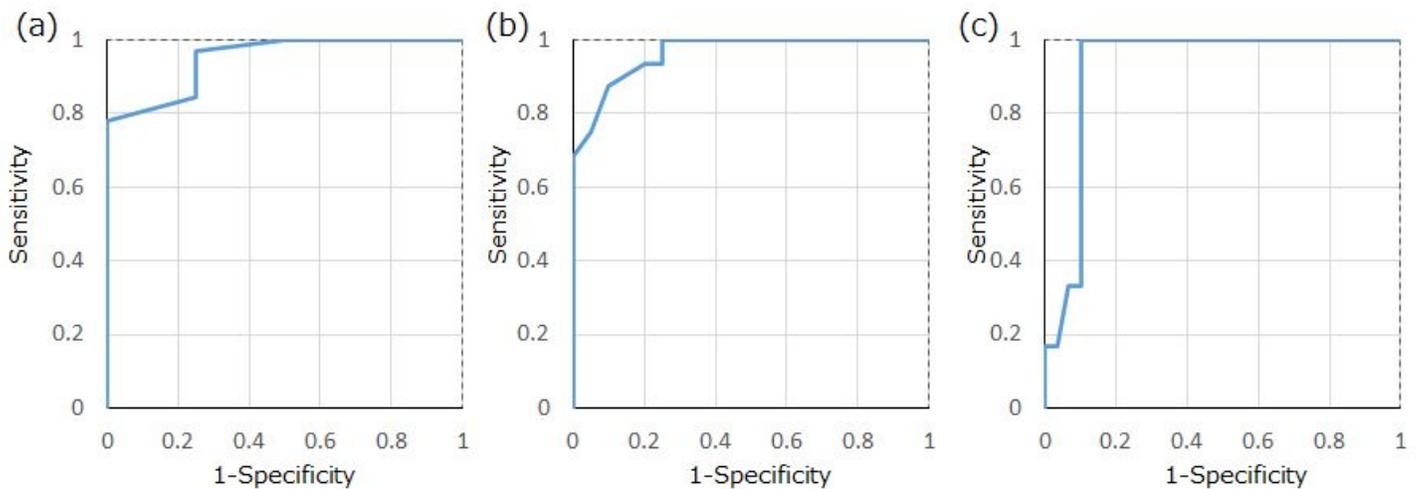


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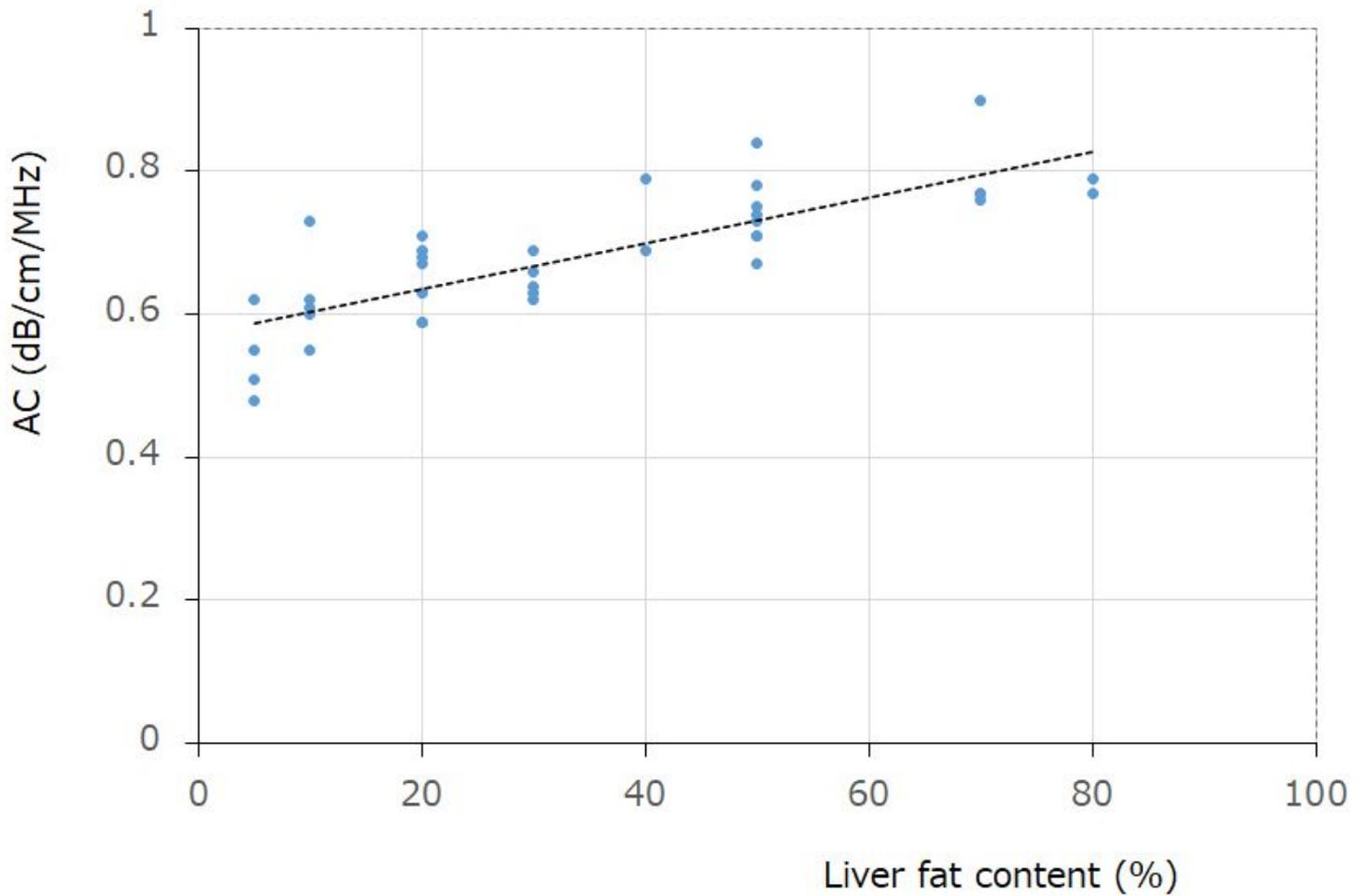


Figure 3

Correlation between AC values and LFC (%) in NASH There was a significant positive correlation between LFC (%) obtained by liver biopsy and AC values ($r = 0.83$, $p < 0.01$)

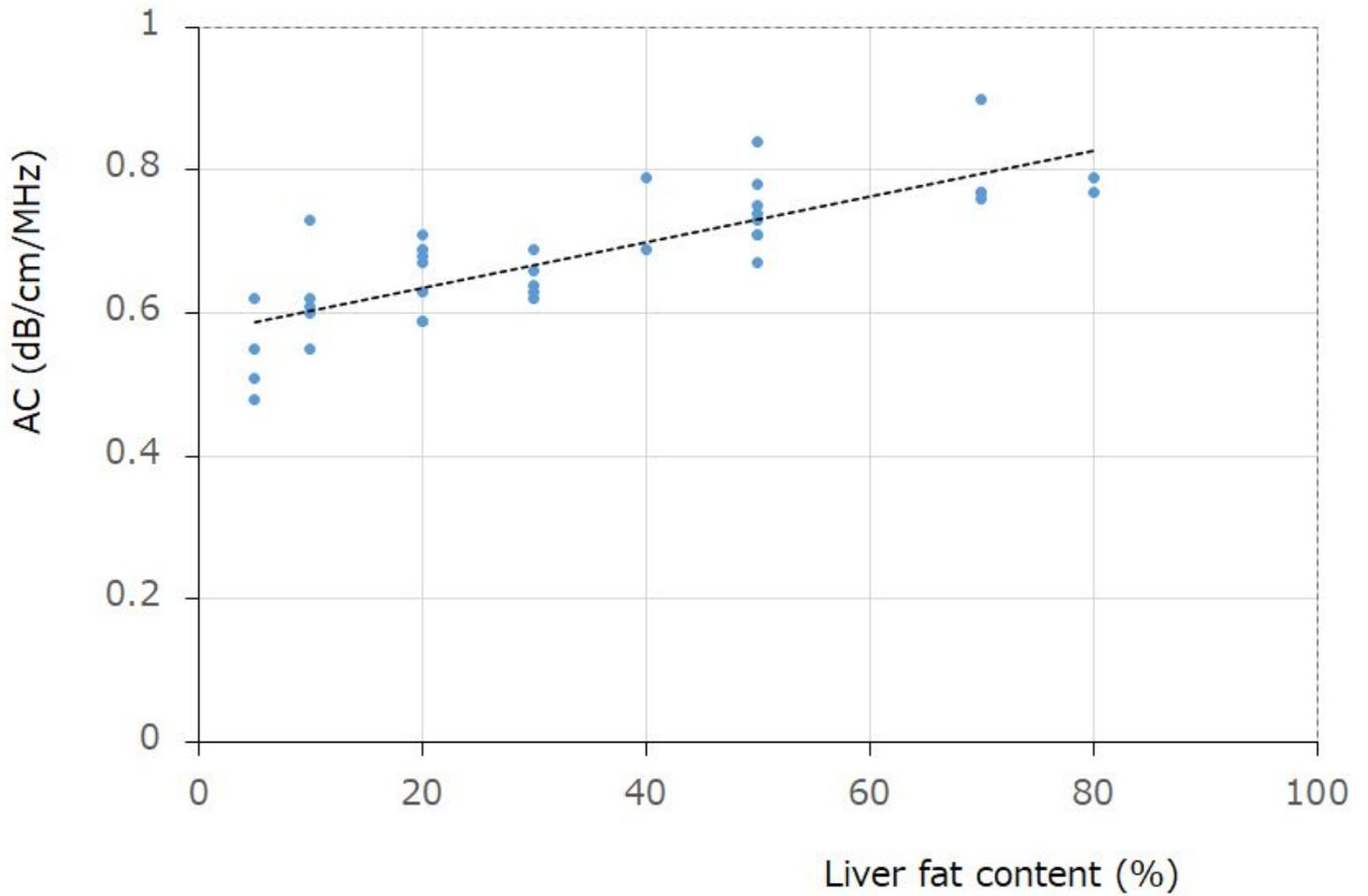


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