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Diagnostic performance of a novel ultrasound-based quantitative method to assess liver steatosis in histologically identified nonalcoholic fatty liver disease

Kyung A Kang*[1], Sung Ryol Lee*[2], Dae Won Jun[3], In-Gu Do[4], Mi Sung Kim[5]
** the authors share the first authorship*

[1]Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, [2]Department of Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [3]Department of Internal Medicine, Hanyang University College of Medicine, [4]Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, [5]Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Abstract

Aims: To investigate the diagnostic performance of ultrasound-guided attenuation parameter (UGAP) for the detection of hepatic steatosis in nonalcoholic fatty liver disease (NAFLD) cohorts using histopathology as the reference standard and comparing it with that of various imaging modalities. **Materials and methods:** A total of 87 subjects who underwent UGAP, controlled attenuation parameter (CAP), and magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) between December, 2020 and January, 2022 were enrolled. Of these patients, 38 patients had NAFLD. The association between UGAP and clinical and imaging parameters was assessed using Pearson's or Spearman's correlations. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the diagnostic performance. **Results:** The UGAP and MRI-logPDFF demonstrated strong positive correlations (correlation coefficient= 0.704, P <0.0001). UGAP showed excellent diagnostic performance for distinguishing steatosis grade ≥1 with an AUROC of 0.821 (95% confidence interval [CI], 0.729–0.913), which was comparable to that of MRI-PDFF (0.829, 95%CI, 0.723–0.936). The AUROCs of BUSG (B-mode ultrasonography) (0.766, 95% CI, 0.767–0.856) and CAP (0.788, 95% CI, 0.684–0.891) were slightly lower than those of UGAP. The AUROCs of UGAP, MRI-PDFF, CAP, and BUSG for detecting steatosis grade ≥2 were 0.796 (95% CI, 0.616–0.975), 0.971 (95% CI, 0.936–1.000), 0.726 (95% CI, 0.561–0.891) and 0.774 (95% CI, 0.612–0.936), respectively. **Conclusion:** UGAP may be a valuable potential screening tool as a first-line assessment of liver steatosis in patients with NAFLD.

Keywords: ultrasound-guided attenuation parameter; pathology; magnetic resonance imaging; non-alcoholic fatty liver disease; prospective studies

Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has been increasing along with increasing rates of obesity, diabetes, and metabolic syndrome worldwide [1]. Although liver fibrosis is a key driver of morbidity and mortality in chronic liver disease, early detection and monitoring of simple steatosis are also important because identifying fatty liver is the first step in the screening of hepatic fibrosis in the general population. Furthermore, it has been reported that coexistence of steatosis accelerates the disease progression to hepatic fibrosis [2,3].

Various imaging techniques have been developed for NAFLD diagnosis. In routine clinical practice, ultrasound (US) is the most commonly used tool for the evaluation of fatty liver, owing to its easy accessibility and cost-effectiveness. However, there are several obstacles to conventional B-mode US; for example, the results

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Corresponding author: Mi Sung Kim, MD
Department of Radiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea
Phone/fax: +82-2-2001-1031
+82-2-2001-1030
E-mail: misung70@gmail.com

are highly operator dependent and subjective. Moreover, it performs poorly in cases of mild steatosis [4].

Several US-based methods have been proposed for quantitative assessment of steatosis. The controlled attenuation parameter (CAP) using transient elastography is one of the techniques that enables the quantification of liver fat. However, it can only be performed in the A-mode using a dedicated probe without visual guidance.

Recently, a new method for attenuation coefficient measurements using an US-guided attenuation parameter (UGAP) was introduced to quantify hepatic steatosis. For this technique to be widely used as a screening tool for fatty liver, validation studies using gold standard methods must precede it. Thus far, there have been limited validation studies on UGAP, including the heterogeneous etiology of chronic liver disease [5-9]. The usefulness of the UGAP in specific population groups, particularly in patients with NAFLD, has not yet been fully established. Validation studies in patients with NAFLD using liver biopsy as the reference standard are difficult to establish, because liver biopsies in asymptomatic patients with NAFLD are rarely available.

This study aimed to investigate the diagnostic performance of UGAP in the diagnosis of hepatic steatosis in a cohort of adults with biopsy-confirmed NAFLD. In addition, magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) has emerged as a leading quantitative imaging method for the assessment of steatosis. Hence, the diagnostic performance of UGAP was compared with that of MRI-PDFF, using histopathology as the reference standard.

Materials and methods

Study population and design

The study population was obtained from a cohort of patients prospectively collected from two different hospitals in Korea. This cohort study was conducted among adults aged ≥20 years, who underwent cholecystectomy for benign gall bladder disease. Most of these cases involved patients with cholecystitis. This prospective study aimed to investigate the association between NAFLD and bile acid alterations in the general population. The diagnosis of NAFLD was based on the detection of hepatic steatosis by histology together with the absence of the secondary causes of hepatic steatosis. To exclude other identifiable cases of secondary hepatic steatosis and minimize the effect of cholecystitis on hepatotoxicity, we excluded participants with the following criteria: 1) moderate-to-severe acute cholecystitis according to the Tokyo guidelines 2018 (grade II or III) [10]; 2) significant biomarker abnormalities, defined as aspartate transaminase and alanine aminotransferase five times the upper limit of normal (ULN), total bilirubin three times the ULN, or platelet counts $<50\times10^3/mm^3$; 3) alcohol intake of 210 g/week for men and 140 g/week for women [11]; 4) positive serologic markers for hepatitis B or C; and 5) past or current use of medications associated with NAFLD, such as valproate, amiodarone, methotrexate, tamoxifen or corticosterodis. After applying the exclusion criteria, liver biopsy was performed during cholecystectomy in all the patients enrolled in the study. The study protocol was approved by the institutional review board of each hospital.

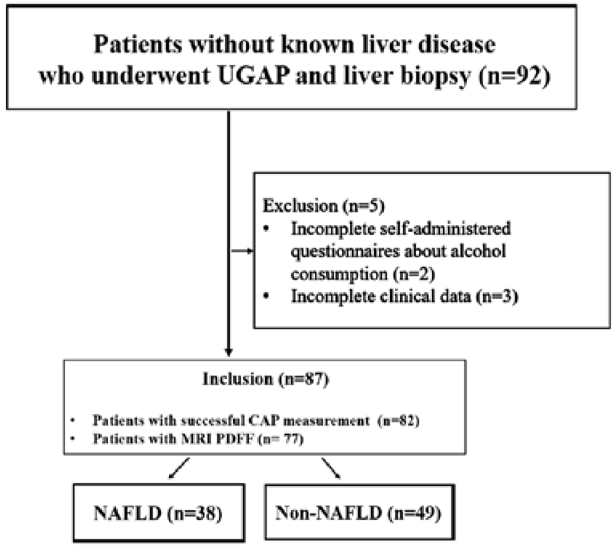

Fig 1. Study participant flow.

The study population comprised 92 consecutive patients who underwent UGAP, CAP, and MRI-PDFF at Kangbuk Samsung Hospital from December 2020 to January 2022. This study was approved by the institutional review board, and all participants signed an informed consent form. Of these patients, five were excluded because of incomplete self-administered questionnaires about alcohol consumption (n=2) or incomplete clinical data (n=3). Ultimately, 87 patients were enrolled in this study (fig 1).

US examination

All US examinations were performed 1 or 2 days before surgery using the LOGIQ E10 US machine (GE Healthcare, Wauwatosa, WI, USA), which was equipped with UGAP. Two experienced abdominal radiologists with 20 and 7 years of post-fellowship experience performed the examinations using a C1-6 convex array probe. All measurements were performed after at least 4 hours of fasting.

Before the UGAP measurements, qualitative scoring of fatty liver was performed using B-mode ultrasonography (BUSG) based on known standard criteria [12]. Fatty liver degree was scored as follows: 1) mild steatosis, diffuse increase of liver parenchymal echoes compared with the kidney; 2) moderate steatosis, impaired visualization of wall echogenicity of the main portal vein; and 3) severe steatosis, blurring of the diaphragm.

For the UGAP measurements, a single fixed-size region of interest (ROI) was placed on the right liver, avoiding large vascular structures, with a fixed depth of 4–8 cm using an intercostal scan. A quality map was used to obtain high-quality signals. The UGAP measurements were considered reliable when at least 10 valid measurements had an interquartile range (IQR)/median lower than 30%. The success rate of obtaining reliable measurements using UGAP was 100%, irrespective of body mass index (BMI).

CAP measurements

Immediately after the UGAP measurements, CAP measurements were performed using intercostal scan of the right liver using FibroScan502 (Echosens, Paris, France) and M probe (3.5 MHz). Because the reliability criteria for CAP measurements are not yet well-defined, CAP measurements with 10 successful acquisitions were considered reliable [13,14]. Of the 87 patients, 5 were excluded from the evaluation of diagnostic performance because of failed measurements with the M probe.

MRI-PDFF

Preoperative magnetic resonance cholangiopancreatography (MRCP) was performed to detect unexpected common bile duct stones in 77 patients using 3 T MRI (Ingenia CX, Philips Healthcare, Best, Netherlands). The mean interval between operation and MRCP was 7.6±27.3 days. The MRCP examination included in- and opposed phases and T2* maps (mDIXON Quant) to obtain the PDFF maps with the following parameters: TR/TE = 5.7/0.9–4.8 ms; FOV = 40 cm; flip angle = 3°; phase FOV = 0.8; matrix = 160×133; slice thickness = 5 mm; acquisition time = 15 s; bandwidth = 252.02 kHz. Images were processed using an interactive post-processing platform (Intelli-space Portal, ISP) provided by the manufacturer. Semi-automatic segmentation of the whole liver was performed, and the hepatic fat fraction was automatically calculated. A hepatic fat fraction of less than 5% was considered normal. The cut-off values for the diagnosis of mild, moderate, and severe steatosis were 5.2%, 11.3%, and 17.1%, respectively [15].

Liver biopsy and histopathologic examination

Liver biopsies of segment IV of the gallbladder fossa were performed using laparoscopic scissors. The incised liver surface was then coagulated using a monopolar device. A single expert pathologist reviewed the tissue slides. The severity of steatosis was assessed using a 4-point scale based on the percentage of hepatocytes with macrovesicular steatosis: 0 (<5%), 1 (5–33%), 2 (33–66%), and 3 (>66%) [16].

Statistical analysis

All statistical analyses were conducted using R software (v.4.0.4). Continuous variables were expressed as a mean ± standard deviation or median (IQR) according to the data distribution. Categorical variables were expressed as frequencies (percentages). The significance between the two groups (NAFLD vs. non-NAFLD) was assessed using the two-sample t-test or Wilcoxon rank-sum test for continuous variables, and chi-squared test or Fisher's exact test for categorical variables. The association between UGAP and clinical and imaging parameters was assessed using Pearson's or Spearman's correlation according to normal distribution. A correlation coefficient () below 0.2 was considered to be minimal (<0.2), 0.2–0.4, weak; 0.4–0.7, moderate; and >0.7, strong [17]. We also used one-way ANOVA to compare the UGAP values for the different steatosis grades. For pair-wise comparisons, post-hoc analysis with Bonferroni correction was used after ANOVA. We set optimal cut-off values where the sum of the sensitivity and specificity was maximized for the diagnosis of NAFLD. We compared the sensitivity, specificity, positive predictive value, and negative predictive value between the imaging modalities using cut-offs obtained from the receiver operating curves. Statistical significance was set at $p<0.05$.

Results

Baseline characteristics

The characteristics of the 87 participants according to the presence of NAFLD are summarized in Table I. Of the 38 patients with NAFLD, 28, 8, and 2 had histological steatosis grades 1, 2, and 3, respectively. Patients with NAFLD had a higher BMI, waist circumference, and liver enzyme levels. The mean and median values of CAP, UGAP, and MRI-PDFF were significantly higher in the NAFLD group than in the non-NAFLD group (all $p<0.0001$). The mean UGAP values for the non-NAFLD and NAFLD group were 0.57 ± 0.08 dB/cm/MHz and 0.68 ± 0.09 dB/cm/MHz, respectively. The median MRI-PDFF values for the non-NAFLD and NAFLD groups were 4.1% (IQR, 2.9–4.8%) and 8.8% (IQR, 5.0–11.1%), respectively. Of the 38 patients with NAFLD, 8, 28, 1, 1 had histological fibrosis grades 0, 1, 2, and 3, respectively. The mean values of UGAP were 0.64±0.54 dB/cm/MHz and 0.69±0.98 dB/cm/MHz for fibrosis grade 0 and 1. UGAP values were 0.72 dB/cm/MHz and 0.79 dB/cm/MHz for grade 2 and 3.

Table I. Baseline characteristics

Characteristics	Non-NAFLD N= 49	NAFLD N= 38	*P*-value
Age (years)	44.73 ± 9.98	49.11 ± 12.01	0.0745
Males, n (%)	21 (42.86)	19 (50)	0.6555
Body mass index (kg/m^2)	22.21 (20.08, 24.69)	25.33 (23.59, 27.32)	<0.0001
Waist circumference (cm)	79 (73.5, 86)	88 (84, 92.75)	<0.0001
Diabetes, n (%)	3 (6.12)	4 (10.53)	0.6941
Hypertension, n (%)	2 (4.08)	7 (18.42)	0.0379
Metabolic syndrome, n (%)	3 (6.12)	12 (31.58)	0.0046
Platelet (10^9/L)	237 (210, 279)	242.5 (223, 274.75)	0.7192
AST (U/L)	17 (14, 21)	19.5 (17, 26.75)	0.003
ALT (U/L)	14 (11, 17)	22 (18, 26.75)	<0.0001
GGT (U/L)	22 (13, 30)	27 (20, 51.75)	0.0028
TG (mg/dL)	89 (70, 127)	137.5 (106, 200)	<0.0001
HDL-C (mg/dL)	59 (48, 68)	52.5 (49.25, 62)	0.3397
LDL-C (mg/dL)	115.47 ± 31.19	119.55 ± 30.47	0.5412
Fasting glucose (mg/dL)	93 (88, 103)	93 (86.25, 103.75)	0.9181
HbA1c (mmol/L)	5.5 (5.2, 5.7)	5.5 (5.3, 5.8)	0.1314
Insulin (IU/mL)	5.72 (4.01, 9.41)	8.67 (7.06, 14.54)	<0.0001
Total bilirubin (mg/dL)	0.59 (0.47, 0.73)	0.54 (0.46, 0.66)	0.5264
CAP (dB/m)*	211 (193, 241)	264 (244, 289)	<0.0001
UGAP (dB/cm/MHz)	0.57 ± 0.08	0.68 ± 0.09	<0.0001
UGAP (dB/m)	200.55±27.28	238.76±32.12	<0.0001
MRI-PDFF (%)†	4.05 (2.88, 4.77)	8.80 (5, 11.05)	<0.0001

NAFLD = nonalcoholic fatty liver disease; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl-transferase; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = hemoglobin A1c; CAP = controlled attenuation parameter; UGAP = ultrasound-guided attenuation parameter; MRI = magnetic resonance imaging; PDFF= proton density fat fraction. * Data on 82 patients; † Data on 77 patients

Correlation between UGAP and clinical and imaging parameters

Table II shows the correlation between UGAP and clinical and imaging parameters. The MRI-PDFF values were log-transformed because the data showed a skewed distribution. There was a strong positive relationship between UGAP and MRI-logPDFF (r=0.704, p<0.0001) (fig 2). CAP values were positively associated with UGAP values (r=0.623, p<0.0001). There was no significant association between liver stiffness measurements by transient elastography and UGAP values (r=0.013, p=0.91).

Correlation between UGAP and steatosis grade

Figure 3 shows the step-wise increase in UGAP values corresponding with the severity of steatosis (p<0.0001). The mean UGAP values were 0.57, 0.67, 0.69, and 0.84 dB/cm/MHz for steatosis grades 0, 1, 2, and 3, respectively. In pair-wise comparisons, there were significant differences between subjects with S0 versus S1 (p<0.0001), S0 versus S2 (p=0.002), S0 versus S3 (p<0.0001), and S1 versus S3 (p=0.033).

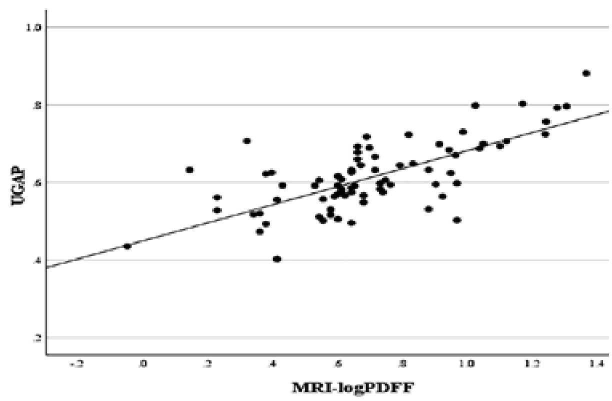

Fig 2. Scatterplot for linearity between UGAP and MRI-log-PDFF.

Diagnostic performance of UGAP

Table III summarizes the results of the comparison of diagnostic performance between the imaging modalities. The areas under the receiver operating curves (AUROCs) for the diagnosis of fatty liver were 0.821 (95% confidence interval [CI], 0.729–0.913), 0.829 (95% CI,

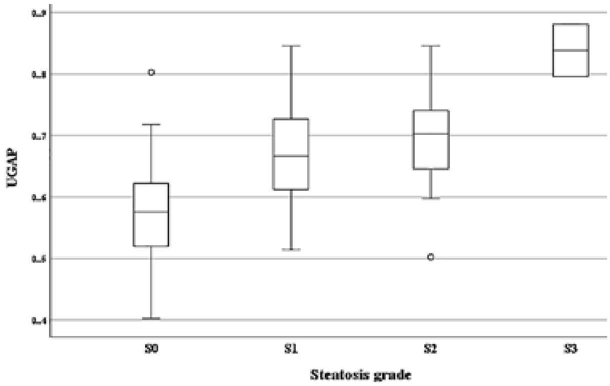

Fig 3. UGAP values according to the steatosis grade.

0.723–0.936), 0.788 (95% CI, 0.684–0.891), and 0.766 (95% CI, 0.767–0.856) for UGAP, MRI-PDFF, CAP, and BUSG respectively. The best cut-off value of UGAP for diagnosing fatty liver was 0.59 (dB/cm/MHz) according to Youden index. The accuracy of UGAP was comparable to that of MRI-PDFF (75.9% vs. 76.8%); however, the sensitivity of UGAP was superior to that of MRI-PDFF (86.8% vs. 71.0%). For the diagnosis of grade ≥2, the AUROCs were 0.796 (95% CI, 0.616–0.975), 0.971 (95% CI, 0.936–1.000), 0.726 (95% CI, 0.561–0.891), and 0.774 (95% CI, 0.612–0.936) for UGAP, MRI-PDFF, CAP, and BUSG, respectively. The numbers of correctly diagnosed patients with histologic steatosis grade ≥2 were 8 of 10, 9 of 10, 6 of 10, and 6 of 10 when using UGAP, MRI-PDFF, and CAP, respectively.

Table II. Association between UGAP and clinical and imaging parameters

Characteristics	Correlation coefficient (r)	p-value
Age	0.223	0.0375
Body mass index	0.501	<0.0001
AST	0.256	0.0168
ALT	0.310	0.0035
GGT	0.149	0.1686
Fasting glucose	-0.095	0.3828
HbA1c	0.184	0.0882
Insulin	0.373	0.0004
Total bilirubin (mg/dL)	-0.064	0.5548
CAP (dB/m)*	0.623	<0.0001
Transient elastography	0.013	0.9051
MRI-PDFF (%)†	0.660	<0.0001
MRI-PDFF (%) in log scale†	0.704	<0.0001

AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; HbA1c, hemoglobin A1c; CAP, controlled attenuation parameter; MRI, magnetic resonance imaging; PDFF, proton density fat fraction. * Data on 82 patients; † Data on 77 patients

Discussion

Our study demonstrated a high diagnostic yield of UGAP for detecting fatty liver in patients with NAFLD using histopathology as the gold standard. The AUROC for hepatic steatosis grade ≥1 was higher for UGAP for BUSG, which is the most widely used in routine clinical practice for the detection of fatty liver (0.821 vs. 0.766). Additionally, the AUROC of UGAP was similar to that of MRI-PDFF (0.821 vs. 0.829), and UGAP showed superior sensitivity and similar accuracy than it did in MRI-PDFF (sensitivity, 86.8% vs. 71.0%; accuracy, 75.9% versus 76.8%). UGAP not only had a high diagnostic performance, similar to that of MRI-PDFF for the diagnosis of steatosis, but also had the advantages of conventional US in terms of easy accessibility and cost-saving. Ultimately, UGAP is expected to be a valuable screening tool for first-line assessment of steatosis in patients with NAFLD.

Overall, these findings are in accordance with findings reported by previous studies with AUROCs of 0.83–0.92 [5-8]. However, even when using the same method to define an optimal cut-off for the diagnosis of fatty liver (Youden index), substantial discrepancies were found with a cut-off of 0.53–0.69. Several covariates, such as etiology, BMI, and age, may have contributed to these differences. In a previous study of 163 patients with two different etiologies (hepatitis C virus infection and NAFLD), patient characteristics were significantly different between the two groups [6]. This finding supports the notion that UGAP values are influenced by etiology. Therefore, the study of specific populations is essential to establish optimal cut-off values that appear to be specific for individual etiologies. Previous studies have investigated the accuracy of UGAP including the heterogeneous etiology of chronic liver disease. The strength of this study was that the data were gathered from patients in the pure NAFLD group. In this study, the optimal cut-off value of UGAP for the detection of fatty liver in patients with NAFLD was 0.59 (dB/cm/MHz). Imajo K et al [7] have proposed an optimal cut-off of UGAP for the diagnosis of NAFLD grade 1 of 0.69 dB/cm/MHz in the subgroup analysis. The difference between the cut-off values can be attributed to demographic differences in the enrolled populations. Here, we recruited participants with average-to-low risk of NAFLD; however, they enrolled patients with chronic liver disease. Also, the difference between the cut-off values may be the result of the small number of NAFLD patients with unbalanced steatosis distribution in this study. The majority of NAFLD patients were steatosis grade 1 (74%, 28/38) and only 10

Table III. Diagnostic performance of imaging modalities for the diagnosis and grading of NAFLD

	Modalities	Cut-off	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥S1	UGAP	0.59 (206.5)*	0.821 (0.729-0.913)	75.9	86.8	67.4	67.4	86.8
	MRI-PDFF†	5.70	0.829 (0.723-0.936)	83.1	71.0	91.3	84.6	82.4
	CAP‡	243.0	0.788 (0.684-0.891)	76.8	75.7	77.8	73.7	79.6
	BUSG	NA	0.766 (0.767-0.856)	81.6	81.3	83.6	78.9	83.7
≥S2	UGAP	0.69 (241.5)*	0.796 (0.616-0.975)	83.9	80.0	84.4	40.0	97.0
	MRI-PDFF†	9.25	0.971 (0.936-1.000)	93.5	100.0	92.7	64.3	100.0
	CAP‡	285.5	0.726 (0.561-0.891)	81.7	60.0	84.7	35.3	93.9
	BUSG	NA	0.774 (0.612-0.936)	90.8	60.0	94.8	60.0	94.8

NAFLD = nonalcoholic fatty liver disease; UGAP = ultrasound-guided attenuation parameter; MRI = magnetic resonance imaging; PDFF= proton density fat fraction; CAP = controlled attenuation parameter; BUSG = B-mode ultrasonography; NA = Not applicable. *The numbers in parentheses indicate values of UGAP measurements in dB/m. †Data on 77 patients; ‡Data on 82 patients.

patients were steatosis grade 2 or higher (26%, 10/38). Finding robust estimates for cutoff values require considerable sample size. However, our sample size was too low to optimize cutoff values.

Previous studies have shown a very high accuracy of UGAP in differentiating all steatosis grades. The overall AUROCs of UGAP for differentiating grade 2 or higher were 0.87–0.95 [6-8]. The result from this study was slightly lower (AUROC 0.80, 95% CI 0.616–0.975) than those reported in previous studies. This may be because the sample size of grade ≥2 was too small here (n=10). In addition, the etiology may have contributed to this difference. Imajo K et al [7] reported that in subgroup analysis with 525 patients with NAFLD, the AUROCs were 0.90, 0.87, and 0.83 for grading steatosis S1, S2, and S3, respectively, which were slightly lower than those in the whole group (0.90, 0.91, and 0.89 for grading S1, S2, and S3, respectively).

The major limitation of this study was the small sample size and uneven steatosis grade. Cutoff values for differentiating steatosis grade were limitedly assessed in this study as we had only 10 NAFLD patients with grade 2 or higher. Our data were gathered from subjects with benign gallbladder disease with or without fatty liver. Therefore, the number of subjects with moderate-to-severe fatty liver disease was expected to be small. Further studies with larger cohorts of NAFLD patients with even steatosis grades should be performed. Second, NAFLD and gallstone disease often coexist; therefore, gallstone disease may have affected the results. However, the sequential relationship between these two diseases remains controversial, and we applied strict exclusion criteria to minimize the effects of gallstone disease on hepatotoxicity. Finally, our reference standard was the histological examination. Although liver biopsy remains the gold standard for the evaluation of steatosis, the spatial variability in steatosis may result in sampling errors.

In **conclusion**, UGAP may be considered a promising screening tool for first-line assessment of liver steatosis in patients with NAFLD.

Conflict of interest: none

References

1. Estes C, Chan HL, Chien RN, et al. Modelling NAFLD disease burden in four Asian regions—2019-2030. Aliment Pharmacol Ther 2020;51:801-811.
2. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33:1358-1364.
3. Rubbia-Brandt L, Fabris P, Paganin S, et al. Steatosis affects chronic hepatitis C progression in a genotype specific way. Gut 2004;53:406-412.
4. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123:745-750.
5. 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.
6. Fujiwara Y, Kuroda H, Abe T, et al. The B-mode image-guided ultrasound attenuation parameter accurately detects hepatic steatosis in chronic liver disease. Ultrasound Med Biol 2018;44:2223-2232.
7. Imajo K, Toyoda H, Yasuda S, et al. Utility of Ultrasound-Guided Attenuation Parameter for Grading Steatosis With Reference to MRI-PDFF in a Large Cohort. Clin Gastroenterol Hepatol 2022;20:2533-2541.e7.
8. Tada T, Kumada T, Toyoda H, et al. 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 2019;212:332-341.
9. Paige JS, Bernstein GS, Heba E, et al. A pilot comparative study of quantitative ultrasound, conventional ultrasound,

and MRI for predicting histology-determined steatosis grade in adult nonalcoholic fatty liver disease. AJR Am J Roentgeno 2017;208:W168-W177.
10. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:41-54.
11. 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;67:328-357.
12. Ballestri S, Lonardo A, Romagnoli D, et al. Ultrasonographic fatty liver indicator, a novel score which rules out NASH and is correlated with metabolic parameters in NAFLD. Liver Int 2012;32:1242-1252.
13. Boursier J, Zarski JP, de Ledinghen V, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013;57:1182-1191.
14. Kwok R, Choi KC, Wong GLH, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016;65:1359-1368.
15. Imajo K, Kessoku T, Honda Y, et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 2016;150:626-637.e7.
16. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321.
17. Guilford JP. Fundamental statistics in psychology and education. McGraw Hill 1956.