Original Article

Correlation of ultrasound attenuation imaging versus MRI proton density fat fraction in non-alcoholic fatty liver

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Abstract

Background: Attenuation Imaging (ATI) is a novel method for assessment of hepatic steatosis, based on ultrasound attenuation by calculating attenuation coefficient which increases in the fatty liver condition. The previous published data comparing ATI and Magnetic Resonance Proton Density Fat Fraction (MR-PDFF) has moderate to high correlation coefficient (r=0.66-0.81). However, fatty liver is commonly associated with obesity which may be an influencing factor of the ATI measurement.

Objective: The purpose of this study was to evaluate diagnostic accuracy of ATI in non-alcoholic fatty liver disease (NAFLD) compared to MRI-PDFF.

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Materials and Methods: The 62 non-alcoholic fatty liver disease (NAFLD) patients with available ATI, MRI-PDFF, and MRE examination, excluding cirrhosis, history of significant alcohol drinking, and chronic liver condition were retrospectively evaluated.

Results: The correlation coefficient (r) of ATI vs MRI-PDFF were in moderate correlation ($r = 0.63$-0.69, $p<0.001$). The inter-observer reliability of two observers was 100% with the Cohen kappa coefficient of 1.00 ($p < 0.001$). Area under the receiver operating characteristics of ATI for diagnosis of steatosis grade > 0 was 0.96 and for diagnosis of steatosis grade > 1 was 0.83.

Conclusions: ATI is a novel ultrasound method to quantify the degree of fat deposition with a moderate correlation to MRI-PDFF with high interobserver' reliability. Obesity commonly associated with fatty liver may be an interfering factor of ATI measurement.

Keywords: Attenuation imaging, Fatty liver, Steatosis, MRI-PDFF, MRE, NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease worldwide, is increasing rapidly in terms of prevalence, estimated to be 25.24%, 20-30%, and 9.26% in the world, Western countries, and Asia, respectively [1,2]. NAFLD is associated with metabolic risk factors including obesity, insulin resistance and hyperlipidemia. The estimated prevalence of NAFLD in obese people, defined as those who have the body mass index (BMI) >25 kg/m^2, hyperlipidemia, and diabetic patients have been reported to be 67%- 94%, 50%, and 70%, respectively [3-7].

The excessive accumulation of triglyceride in the hepatocyte in NAFLD patients, could induce inflammation, leading to non-alcoholic steatohepatitis (NASH)

and clinically significant fibrosis which eventually progresses to hepatic cirrhosis and potentially develops into hepatocellular carcinoma (HCC) [1]. Although the degree of fibrosis is reported to be related to mortality, significant steatosis is found to associate with fibrosis progression in NAFLD [8]. Unlike the cirrhotic stage, NAFLD and early-stage NASH are considered reversible with proper treatment and lifestyle modification [9]. Hence, the ability to early detect and begin treatment monitoring are crucial steps to prevent disease progression to irreversible liver cirrhosis.

Liver biopsy is the gold standard for diagnosing and grading hepatic steatosis, inflammation and fibrosis. However, this procedure is invasive and still has some disadvantages and complications, including sampling error, bleeding, and infection [10]. To overcome these limitations, non-invasive imaging methods have been developed as surrogate methods such as magnetic resonance imaging proton density fat fraction (MRI-PDFF), computed tomography (CT), controlled attenuation parameter (CAP), and conventional ultrasound [11].

MRI-PDFF is an accepted non-invasive standard method to quantify fat using chemical-shift imaging (CSI), which has been reported by earlier studies to have excellent correlation with liver biopsy in detection and grading hepatic steatosis [12]. Some studies also demonstrate that MRI-PDFF can be used to evaluate treatment response for NAFLD in the clinical trials [13-15]. Since this method is expensive and not wildly available, it is not practical to perform MRI-PDFF as a screening tool in large population.

Non-contrast enhanced CT scan is a method to assess hepatic steatosis, using attenuation values to interpret fat component in hepatocytes [16]. This method has high sensitivity and specificity in detection of significant fatty liver > 30% steatosis, limiting the detection of mild steatosis. Radiation exposure is also a main limitation for monitoring purpose [17].

CAP is a non-invasive method based on ultrasound properties, which is implemented in the FibroScan®(Echosens, Paris, France). This method is reported

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to have high diagnostic accuracy to detect histologically diagnosed hepatic steatosis [11, 18, 19]. Still, some factors such as skin to liver capsule distance, technical error related to operator, invalid value, intolerable pain, and undetectable liver could lower the accuracy rate [20]. Furthermore, the CAP technique is a dedicated measurement method that does not provide hepatic imaging information; therefore, surveillance of other liver conditions cannot be accessed using this method alone.

Conventional ultrasound is widely used for the screening hepatic steatosis, owing to the inexpensiveness and availability. Bright liver score, a semi-quantitative scale, is used to grade hepatic steatosis by comparing liver parenchymal echogenicity to the kidney and wall of hepatic vessels [21]. Many studies reported a good correlation between bright liver score and liver biopsy in the detection of hepatic steatosis [22, 23]. However, in patients with mild steatosis, the accuracy of this method is dramatically decreased [24], impeding the detection of early NAFLD [25].

To overcome the conventional ultrasound limitations, the novel technique implemented in the ultrasound system for assessment of hepatic steatosis based on ultrasound attenuation properties has been developed. Attenuation imaging (ATI; Canon Medical Systems Corporation, Otawara, Tochigi, Japan) is a potential tool for quantifying fat in the liver by calculating the attenuation coefficient of ultrasound in liver tissue, presuming that higher fat composition will increase ultrasound attenuation. ATI can be performed by defining the region of interest (ROI) for attenuation measurement with ultrasound imaging. This method eliminates the interfering factors including time gain compensation and beam focusing in order to receive simple signal intensity profile of the sound to calculate attenuation coefficient of the liver [26, 27].

Several published data, regarding ATI, have shown positive results. A few recent studies claimed a moderate to high correlation between ATI and MRI-PDFF with correlation coefficient = 0.66-0.81, $p<0.001$). Tada et al, reported a good performance of ATI, as compared to liver biopsy, with the diagnostic accuracy

between 76.4-85.1% and area under the receiver operating characteristic curve (AUROC) between 0.85-0.91. However, in the subgroup of the obese patients, the diagnostic accuracy drops from 76-85% to 58-68% in significant fatty liver (grade ≥ 2) [26]. According to recent information, ATI could potentially be another non-invasive method to quantitatively evaluate hepatic steatosis with the need of more data validation, especially in obese population.

The purpose of this study was to investigate the diagnostic capability and correlations of ATI, comparing with MRI-PDFF for detection and staging of hepatic steatosis in NAFLD patients, focusing on obese patients.

Materials and methods

Study design and population

This retrospective study was approved by the Ethics Committee for Human Research of the Chulabhorn Research Institute (Certificate number 071/2562). This was undertaken to follow the international ethical guideline and Declaration of Helsinki patients. Informed consent was waived.

All consecutive non-alcoholic fatty liver disease patients who underwent MR elastography, MRI-PDFF with available ATI information at Chulahborn hospital from August to October 2019 were included.

Information of clinical evaluation for fatty liver, basic anthropometric examination, fasting biochemical tests including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), Triglyceride (TG), Cholesterol and Platelet values were collected. Inclusion criteria were (i) patients at the age of 18 or above (ii) patients who were clinically diagnosed as having the non-alcoholic fatty liver disease (NAFLD) defined by elevated ALT (≥ 40 U/L) with liver sonography findings suggestive of fatty liver. Exclusion criteria included (i) known cirrhosis (ii)

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daily alcohol drinking > 30 g in men, 20 g in women (iii) chronic viral hepatitis B, C, and other known chronic liver diseases such as autoimmune hepatitis, primary biliary cholangitis, etc.

ATI Evaluation technique

All patients who underwent conventional gray-scale US and ATI examinations were performed by two operators (S.S. and P.H.) with 12 and 3 years of experience in abdominal US imaging, respectively. Both operators were blinded to the patients' clinical details as well as MRI-PDFF and laboratory results. Liver sonography and ATI examinations were performed using an ultrasound scanner (Aplio i800, Canon Medical Systems, Otawara, Japan) with a 1-8 MHz multi-frequency convex probe. All patients who underwent ATI had fasted for at least 6 hours before examination. All images were obtained in the supine position and the intercostal approach.

For attenuation coefficient measurement of ATI, a 2x4 cm fixed measurement region of interest (ROI) was placed in the middle of the attenuation coefficient map (26). The included ROI was placed on the liver parenchyma, avoiding internal vessels, with the upper margin at least 2 cm below the liver capsule (Figure 1).

The degree of attenuation was color-coded and displayed in the sampling box of ATI. The resulting attenuation coefficient was displayed in the units of dB/cm/MHz. Automated linear regression comparing the observed and the expected values by the machine was represented as R^2 values, which are classified as poor ($R^2 < 0.80$), good ($R^2 = 0.80$-0.89), or excellent ($R^2 \geq 0.90$) [28].

For the evaluation of inter-observer reliability, the assessment was conducted in a series of 18 subjects. Two operators (S.S. and P.H) performed two sets of 5 ATI measurements on the same subject by an alternating set of measurements between two operators. Measured attenuation coefficient will be categorized into steatosis grade S1, S2, and S3 using cut off level at 0.63, 0.72, 0.75 cm/dB/MHz, respectively according to prior published studies [26-29].

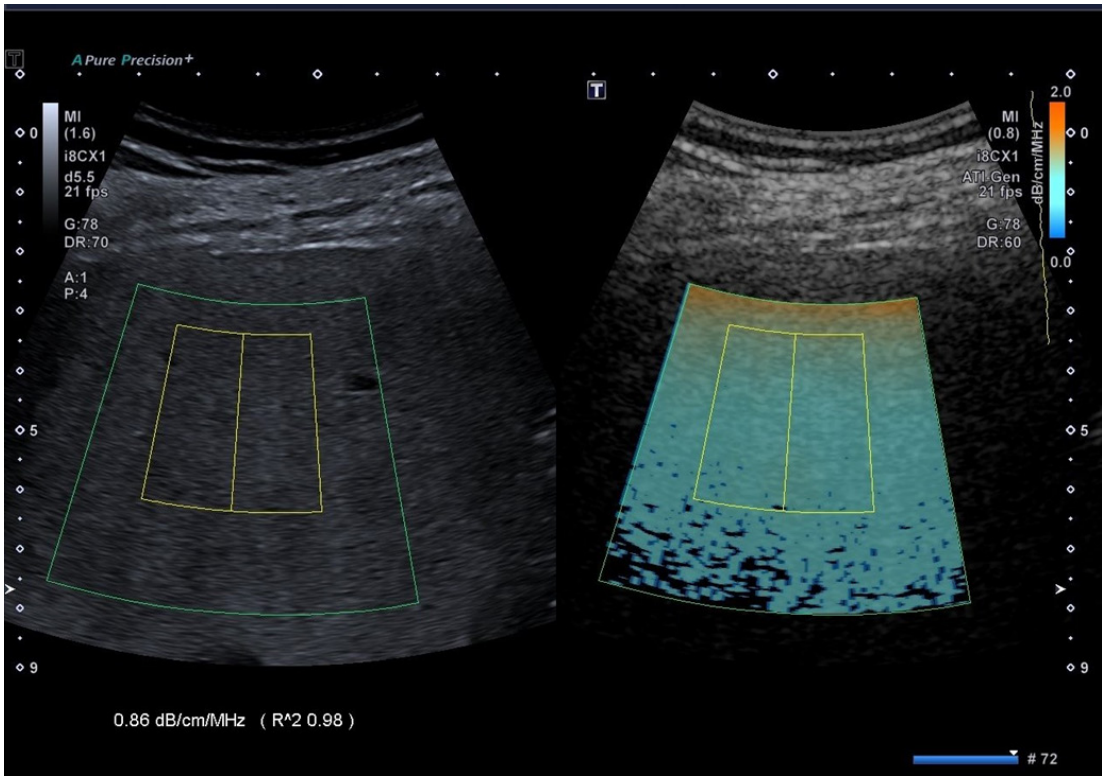

Figure 1. *The green box in the right image shows the attenuation color map of ROI (region of interest). The upper margin of the ROI should be about 2 cm below the liver capsule. The measurement area, a yellow box of a fixed 4X2cm as shown in the right image, should be placed at the center of ROI, avoiding major vasculatures.*

MRI-PDFF and MR elastography

MRI-PDFF and MRE are incorporated into the routine MRI protocol to assess hepatic steatosis and fibrosis in NAFLD patients. MRI was performed with 3.0 Tesla (Ingenia; Philips Healthcare, Best, Netherlands) Protocol of MR-PDFF and MRE are shown in Table 1.

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Table 1. *MRI technique for MRI proton density fat fraction and MR elastography.*

Parameter	MRI-PDFF	MRE
Pulse sequence	FSPGR	GRE
Matrix	300x300	300x85
No. of signal acquired	1	1
Echo time (msec)	5.9	20
Repetition time (msec)	1.05	50
Delta echo time (msec)	0.7	-
Flip angle (deg)	5	30
Bandwidth (kHz)	-	287
No. of sections	64	4
Section thickness (mm)	5	10
Section gab (mm)	10	1
No. of phases	-	4
MEG frequency (Hz)	-	60
Axis of MEG	-	Z
Driver frequency (Hz)	-	60
Driver cycles per trigger	-	3
No. of breath holds	1	4
Breath hold mode	Expiration	Expiration
Acceleration factor	-	2
Imaging time	7 sec	1.10 min
mDIXON images	Water, fat, fat fraction, T2*	-

Percentage fat fraction measurement on the MRI-PDFF was performed using a 3x3 cm ROI at the parenchyma of the left lateral hepatic lobe, right anterior, and posterior of the right hepatic lobe, respectively (Figure 2).

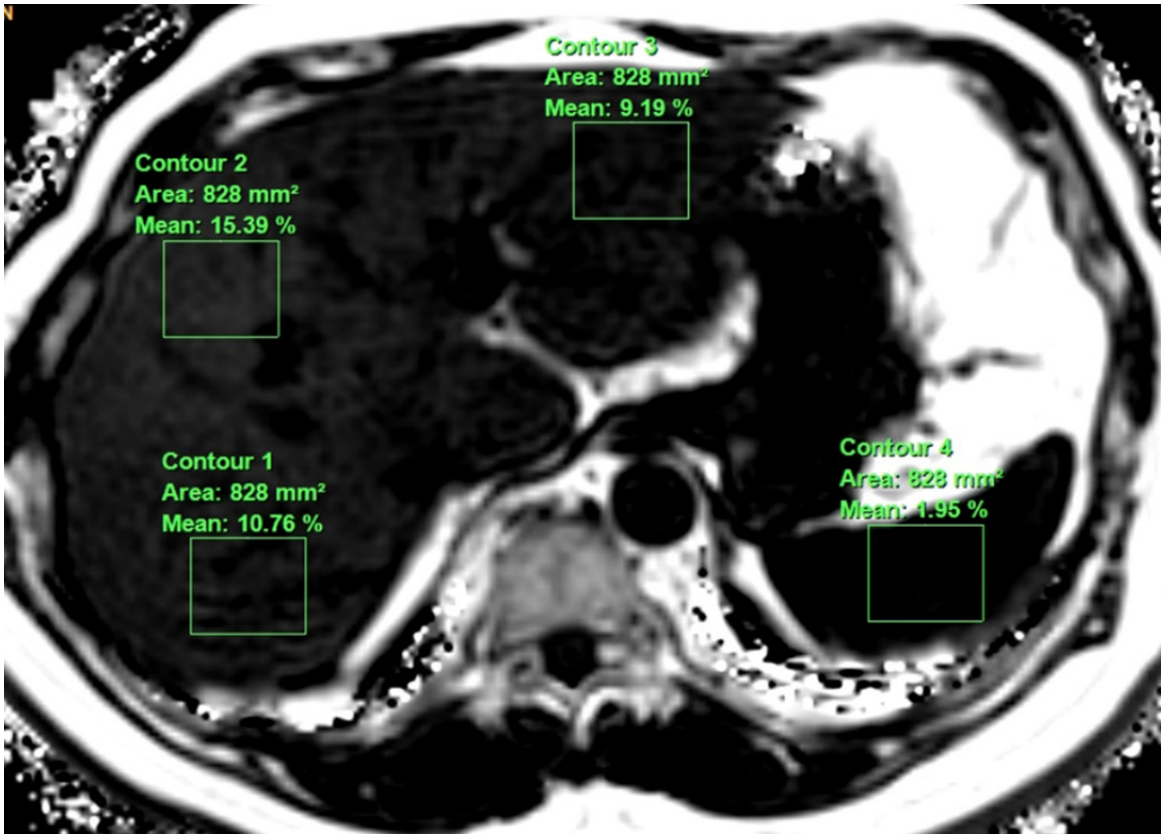

Figure 2. *Fast-spoiled gradient echo MR image of fat mapping image, showing measurement area including the posterior segment of the right hepatic lobe (contour 1), the anterior segment of the right hepatic lobe (contour 2), the left hepatic lobe (contour 3), and the spleen (contour 4).*

Quantification of liver fat was categorized by MRI-PDFF as follows; ≥5% (S ≥1: steatosis), ≥16.3% (S≥2: significant steatosis), and ≥21.6% (S≥3: severe steatosis) [30], and MRE was categorized into fibrosis stage f1-f2, f2-f3, f3-f4 and f4 at the cut off value 2.9–3.5 kPa, 3.5–4.0 kPa, 4.0–5.0 kPa, >5.0 kPa respectively [31].

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Statistical analysis

Demographic and anthropometric data of the patients, including age, gender, Body mass index (BMI), and liver function test were evaluated using independent t-test and Mann-Whitney U test to compare demographic data.

The univariate r coefficient was tested to compare ATI and MRI-PDFF using the Spearman rank correlation method and categorized as follows: 0.00-0.25 none or slight; 0.26 to 0.50 fair to moderate; 0.51-0.75 moderate to good; 0.76-1.00; almost perfect [32].

The diagnostic performance of ATI was evaluated by using receiver operation characteristic (ROC) curves and the area under the ROC (AUROC) curves analysis along with Youden index to optimal cut-off value, sensitivity and specificity [33].

The concordance between inter-observer was assessed by Cohen's kappa coefficient, whose results could be interpreted as follows; 0 as an agreement equivalent to chance; 0.01-0.20 as slight agreement; 0.21-0.40 as fair agreement; 0.41-0.60 as moderate agreement; 0.61-0.80 as substantial agreement; 0.81-0.90 as near perfect agreement; 1.00 as a perfect agreement [34]. Analyses were conducted using STATA version 12; Stata Corporation, College Station, Tx) at 2 sided p-value < 0.05 as the level of significance.

Results

There were 62 patients; two patients were excluded due to incomplete data of ATI. Of all patients, average BMI and percentage of patient BMI ≥ 25 kg/m^2 were 27.4 kg/m^2, and 72%, respectively. None of the patients had significant liver fibrosis with the stiffness mean of 2.1±0.4 kPa.

The characteristics of all 62 patients (31 women and 31 men), including gender, weight, height, BMI, liver stiffness, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose (FBG), triglycerides (TG), cholesterol (CHOL), and platelet count (PLT) are summarized in Table 2.

Table 2. *Demographic data of patients.*

	Female (n=31)	Male (n=31)	All patients (n=62)	p-value*
Age (mean ± SD)	54.8±10.6	46.9±11.1	50.9±11.5	0.0054*
Weight (kg)	70.4±8.5	78.2±10.6	74.3±10.4	0.0022*
Height (cm)	159.5±6.6	170.0±4.1	164.8±7.6	<0.001*
Waist circumference (cm)	92.8±6.1	97.8±7.0	95.8±7.0	0.0255*
BMI (kg/m2)	27.7±3.5	27.1±3.4	27.4±3.4	0.4418
< 25	8 (25.8%)	8 (25.8%)	16 (25.8%)	-
≥ 25	23 (74.2%)	23 (74.2%)	46 (74.2%)	-
Stiffness* (kPa)	2.0±0.4	2.2±0.3	2.1±0.4	0.107
Baseline Laboratory values (mean ± SD)				
AST (IU/L)	34.9±20.5	28.2±6.2	30.9±14.0	0.750
ALT (IU/L)	49.7±27.5	48.5±19.4	49.0±22.7	0.499
FBG (mg/dL)	114.4±42.2	98.2±21.9	104.7±32.1	0.0323*
TG (mg/dL)	123.3±45.4	146.0±83.4	136.9±70.9	0.525
CHOL (mg/dL)	190.0±43.0	194.5±31.2	192.7±35.9	0.294
Plt(x10^3/ul)	298.1±58.2	266.6±51.3	279.2±55.7	0.122

Stiffness (kPa) by MR scanner 3.0 Tesla (Ingenia; Philips Healthcare, Best, Netherlands) with MRE protocol*

The correlation of ATI vs MRI-PDFF values at the lateral segment of the left lobe, the anterior and posterior of right hepatic lobe, and average value correlation of ATI vs MRI-PDFF showed a moderate correlation with the highest correlation of the right posterior segment. ($r = 0.63$, $p < 0.001$, $r = 0.66$, $p < 0.001$; $r = 0.69$, $p < 0.001$, $r = 0.67$, $p < 0.001$; respectively) (Figure 3A-D).

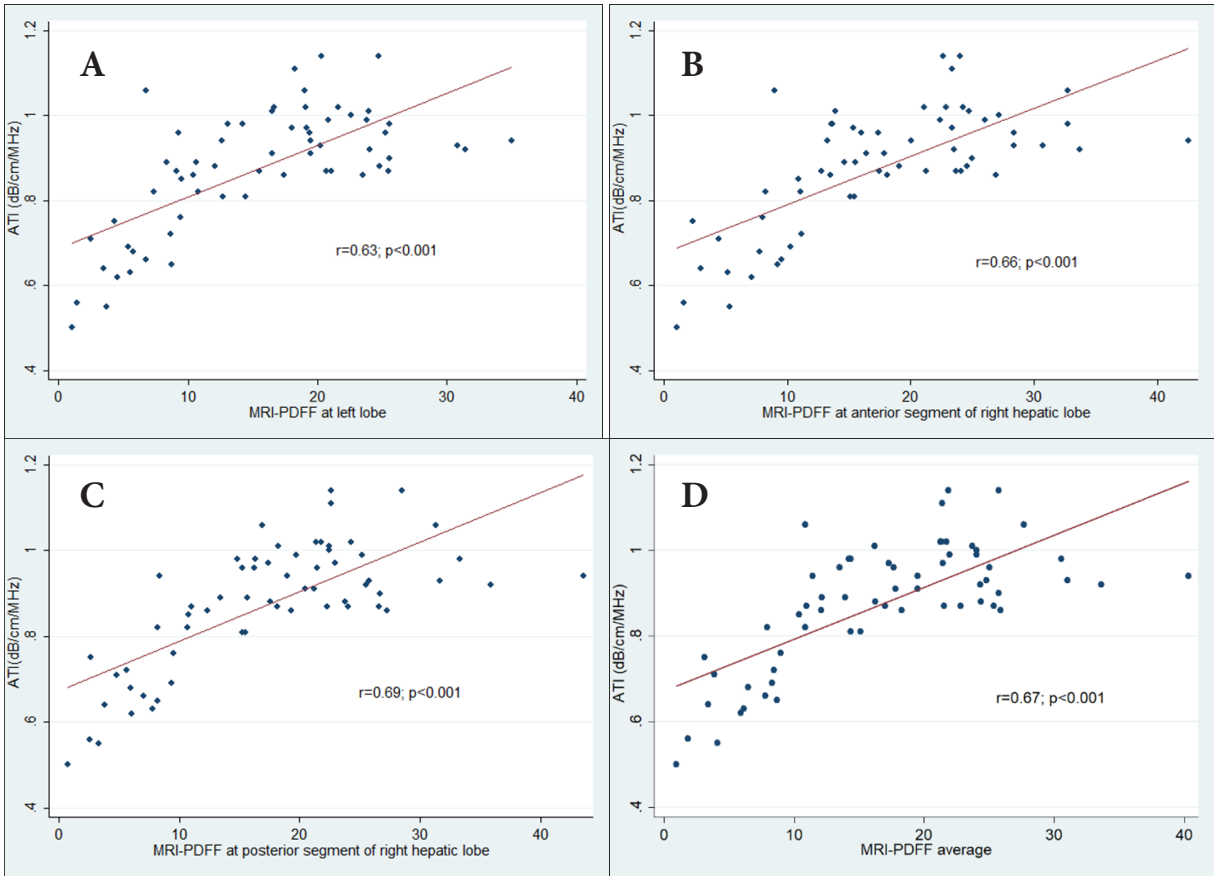

Figure 3. *The Spearman's correlation analysis between ATI of liver and MRI-PDFF of different hepatic areas and the average MRI-PDFF value (a) left lobe liver (r = 0.63). (b) anterior segments of right hepatic lobe (r = 0.66). (c) posterior segments of right hepatic lobe (r = 0.69). (d) average value of different hepatic areas (r = 0.67).*

The AUROC value for diagnosis of steatosis grade > 0 was 0.96 using a cutoff point of 0.72 dB/cm/MHz with 89.3% of sensitivity and 83.3% of specificity. The AUROC value for diagnosis of steatosis grade > 1 was 0.83 using a cutoff point of 0.88 dB/cm/MHz with 81.8% of sensitivity and 72.4% of specificity (Figure 4A-B).

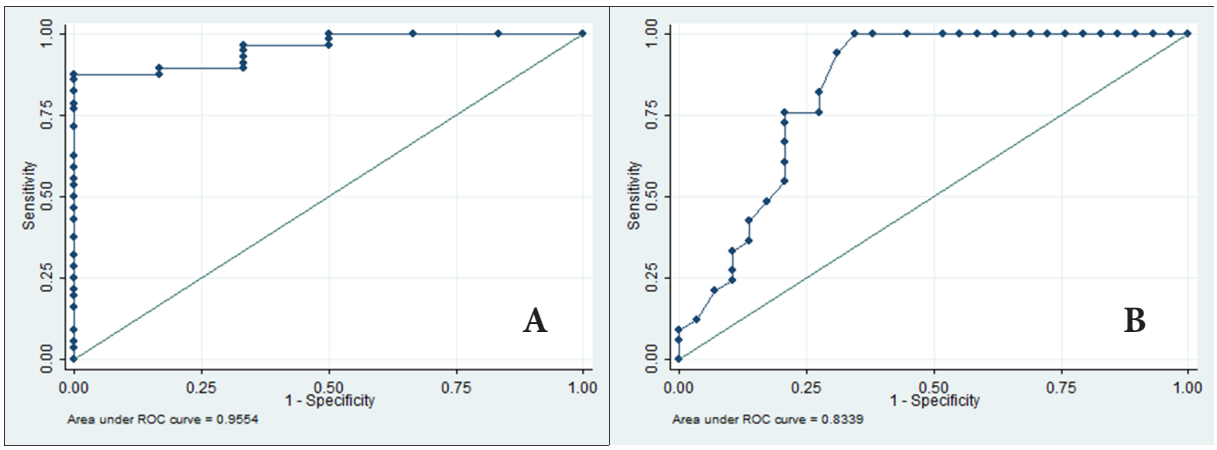

Figure 4. *The receiver operation characteristic (ROC) curve for (a) diagnosis of steatosis grade > 0 and (b) grade > 1.*

The agreement of the inter-observer reliability of two observers was 100% with the Cohen kappa coefficient of 1.00 ($p < 0.001$) (Figure 5).

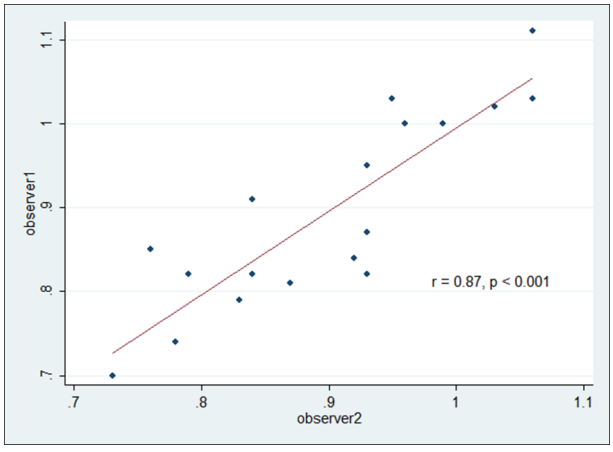

Figure 5. *Correlation of ATI measurements between two operators.*

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Discussion

MRI-PDFF, a complex based gradient echo sequence with a low flip angle, is a non-invasive biomarker method for the estimated fat concentration of the entire liver [13, 35]. MRI-PDFF is suited for baseline assessment and monitoring of hepatic steatosis after treatment, because of the high correlation between MRI-PDFF and the grading of hepatic steatosis on liver biopsy [13, 35, 36]. However, MRI-PDFF is costly, with limited availability, and requires extra visit in addition to the routine US liver surveillance.

The liver bright score has been commonly used for fatty liver grading using the renal cortex and internal hepatic vascular wall echogenicity as internal references. However, liver bright score is a semi-qualitative evaluation and has certain limitations for follow up indications since the liver bright score grading has a wide range of percentage of fat composition; for example, liver bright score of 1 corresponds to the percentage of about 5-33% of fat. Therefore, subtle changes in the degree of hepatic steatosis will not change in grading on the liver bright score [37]. Besides, the bright liver score may have operator-dependent factors which results in variation in performance [22, 23, 38-41].

ATI is a novel method that has the basic concept of sound attenuation measurement based on fatty tissue that should have higher sound attenuation compared to normal liver tissue [42]. Measurement of attenuation coefficient allows quantitative measurement in addition to the conventional US imaging and potential for follow up indication.

In our study, the correlation coefficient value of ATI with MRI-PDFF was concordant with previously published studies with a slightly lower correlation coefficient of r = 0.63–0.69 compared to r = 0.66–0.81 [27, 29]. This may be explained by the fact that ATI provides real-time grayscale image correlation during the measurement. Furthermore, ATI provides color mapping for the degree of attenuation and coefficient of determination (R^2) for optimal ROI placement [43, 44]. However, there are potential interfering factors of the ATI

measurement which may cause less reliability. Jeon et al. have found that the patients with the skin-to-liver distance greater than 20 mm had significantly less correlation between ATI and MRI-PDFF [27].

The majority of studies comparing ATI and MRI-PDFF have limited data on S3 patients [26, 29]. Tada et al. found less specificity and AUROC of ATI in categorizing the steatosis stage of the NAFLD patients as compared with other groups of patients. Tada et al. reported the subgroup of higher grading of fatty liver tends to have less diagnostic performance [26]. Our study may substantiate these interfering factors since 75% of our population have BMI of over 25 and all patients are diagnosed with fatty liver. ATI is less reliable in an obese patient, which is possibly due to the deeper the sound passing through, the greater attenuation, resulting in higher attenuation coefficient [45]. Obese patients presumably have the thicker abdominal wall and preperitoneal fat which increases the distance between the transducer and the measurement area. This factor may interfere with ATI measurement, causing decreased correlation.

Overall, the ATI value shows a better correlation to MRI-PDFF at the right posterior hepatic lobe as compared with other locations. This could be explained by the technique of ATI measurement at the right intercostal approach, mainly representing the posterior right hepatic lobe. Therefore, the correlation of ATI is more concordant with the measurement of fat at the right posterior hepatic lobe than other places.

ATI may have limitations in the sampling area which is mainly measured in right hepatic lobe; however, fatty liver is a diffuse process which involves the entire liver parenchyma. Thus, MRI-PDFF is still more suitable for evaluation of the whole liver.

Perfect interobserver reliability (k=1.0) in grading liver steatosis is observed in our study, which is maybe because ATI is relatively non-complicated to use with fix measurement ROI box, and measurable area. Jeon et al. also reported high reliability in both interobserver and intraobserver (k 0.8-1.0) [27]. With this

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high reproducibility, ATI may be a good alternative method for monitoring the treatment of NAFLD.

There were a few limitations in this study. First of all, this study was a retrospective study resulting in uncontrolled protocols and operators at the beginning. Second, the number of S2 and S3 patients were too small to analyze.

Conclusion

In this regard, ATI equipped in the US system allows additional quantitative measurement of liver steatosis in the same setting of liver US study. ATI may potentially be a surrogate method to evaluate and assess the degree of fatty liver in the routine clinical setting.

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