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Quantitative US (QUS) for assessing hepatic steatosis in NAFLD

RS85 Prestige

Prof. Sun Kyung Jeon, MD, PhD
Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine

Introduction

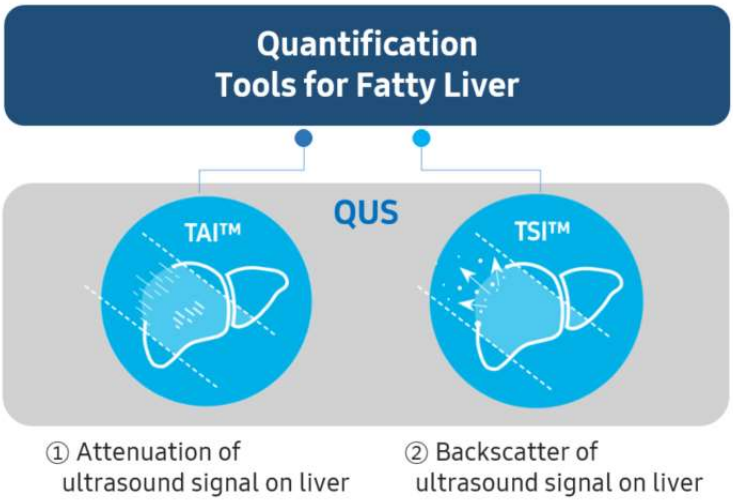
Background

Nonalcoholic fatty liver disease (NAFLD) affects approximately 25% of the global population, with the key histologic feature of hepatic steatosis [1]. NAFLD may progress to a more advanced nonalcoholic steatohepatitis (NASH), which can contribute to the development of fibrosis, cirrhosis, and hepatocellular carcinoma [2]. As timely management of hepatic steatosis can arrest or reverse disease progression, early detection and accurate staging of hepatic steatosis are important in patients with NAFLD.

Liver biopsy is the current reference standard for diagnosing NAFLD, but it is invasive and may introduce sampling errors [3]. Magnetic resonance imaging (MRI)-based proton density fat fraction (PDFF) is an accurate and reproducible method for liver fat quantification and has been used as a reference standard in several clinical trials [4-5]. However, it is not widely applied in routine clinical practice due to its high cost and low accessibility. In this context, ultrasound (US) could be promising as it is noninvasive, widely available, and cost-effective [6]. However, conventional B-mode US has disadvantages such as its qualitative and subjective nature and modest accuracy, especially for mild steatosis.

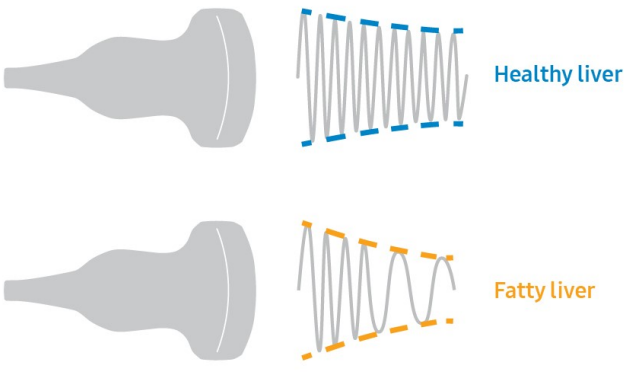
Quantitative US (QUS) examination

Recently, quantitative US (QUS) techniques have been introduced as objective tools for the detection and grading of hepatic steatosis. Among various QUS techniques, Samsung Medison's two QUS techniques, Tissue Attenuation Imaging (TAI™) and Tissue Scatter distribution Imaging (TSI™), measured the attenuation or backscatter of ultrasound signals in order to assess the degree of hepatic steatosis. Previous studies using the prototype of these QUS techniques of Samsung Medison demonstrated good diagnostic performance for detecting hepatic steatosis in patients with NAFLD or chronic liver disease [7-9]. However, these studies evaluated the performance of prototypes of QUS techniques that measured values used an offline software, and the performance of QUS tools built into the clinical US machine was not fully investigated.

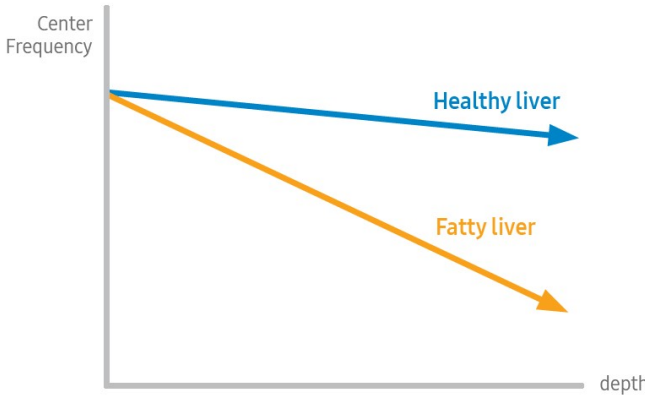


- **Basic principles of TAI (Tissue Attenuation Imaging)**

TAI is a tool that quantitatively measures the attenuation of ultrasound signals received from the liver. Attenuation of ultrasound signal refers to the energy loss when an ultrasound signals pass through tissues, and it is dependent on the tissue properties and the ultrasound frequency. Hepatic tissue attenuation increases with hepatic fatty infiltration, which may appear as impaired visualization of the diaphragm or hypoechoic appearance in the far field on conventional ultrasound images. TAI measures attenuation at each depth by comparing the receive center frequency to the transmit center frequency along the depth. As attenuation is greater in higher frequency components, the center frequency of the US signal gets lower with further depth. The figure below shows that attenuation causes changes in the center frequency at deeper depths, while the worse fatty liver is associated with a greater attenuation (Fig. 1).



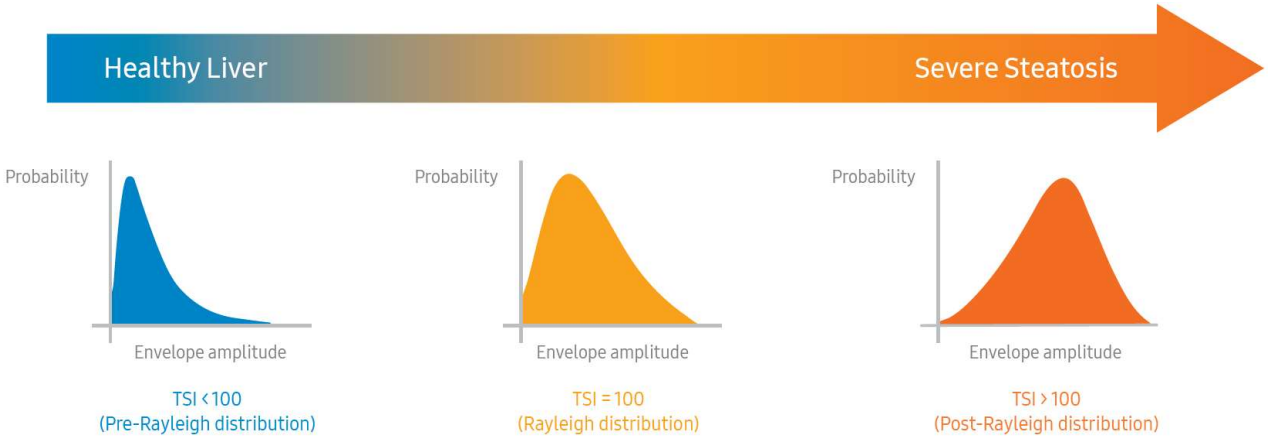
[Fig. 1a] Ultrasound attenuation between healthy liver and fatty liver



[Fig. 1b] Center frequency shift along the depth

- **Basic principles of TSI (Tissue scatter distribution imaging)**

TSI is a tool that quantifies the scattered signal distribution based on backscattered signals. Scattering, the reflection of ultrasonic waves in multiple directions that is not affected by their entry angle, produces speckled patterns in ultrasound images. The number and distribution of scattering particles per resolution cell affect the statistical distribution of the envelope signal of the ultrasonic radiofrequency signal, so the distribution characteristics of scattering particles can be quantified using the parameters of the statistical distribution model. TSI indicates whether a large number of scattered particles are randomly distributed based on the Nakagami distribution model. The Nakagami distribution encompasses most scattering conditions from a small number of randomly distributed scatterers to a larger number and even additional periodic scatterers. Based on this model, TSI represents scattering by quantifying the correlation between the backscattered signals and the Nakagami distribution (Fig. 2).



[Fig. 2] Backscattered distribution depending on the severity of fatty liver

Objective

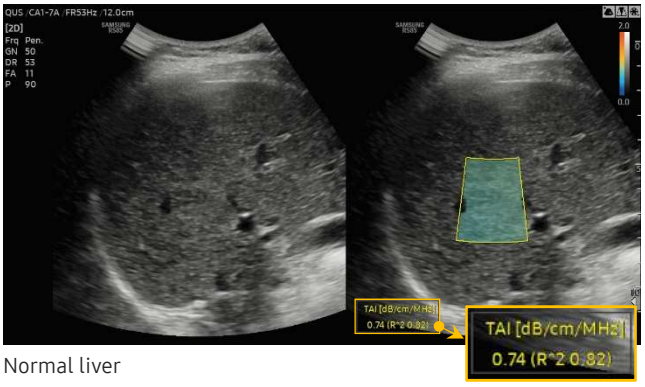
The purpose of this study was to prospectively evaluate the performance of QUS for assessing hepatic steatosis in patients with NAFLD using MRI-PDFF as the reference standard.

Materials and Methods

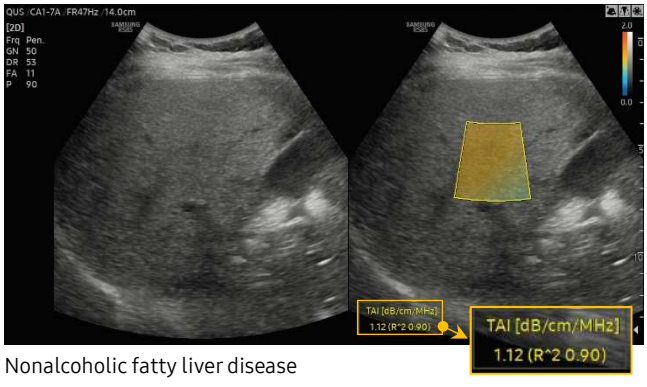
Study population

The institutional review board of Seoul National University Hospital approved this prospective study, and written informed consent was obtained from all participants. Between July 2020 and June 2021, a total of 173 participants with clinically suspected NAFLD or who were scheduled to undergo hepatectomy for liver donation were enrolled. Data from all participants were previously reported in a previous study [10], which evaluated the performance of two-dimensional convolutional neural network algorithm using QUS parametric maps and B-mode images for assess hepatic steatosis. For each participant, QUS examinations (TAI and TSI) using an RS85 Prestige US system (Samsung Medison Co., Ltd.) with a convex probe (CA1-7S) and MRI-PDFF were performed. MRI-PDFF thresholds of 5%, 15% and 25% were used to define different stages of hepatic steatosis (steatosis grades 1 [S1], 2 [S2], and 3 [S3]) [11].

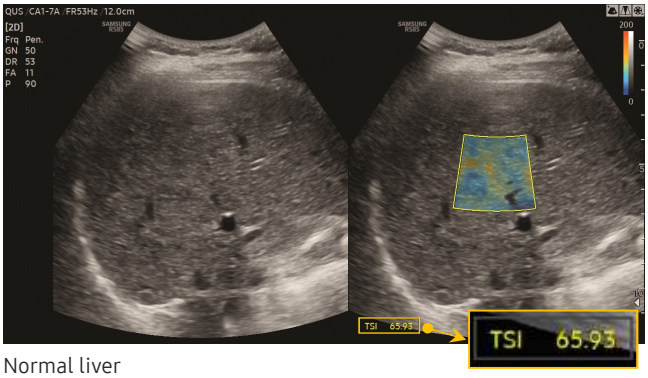
Measurement of QUS parameters



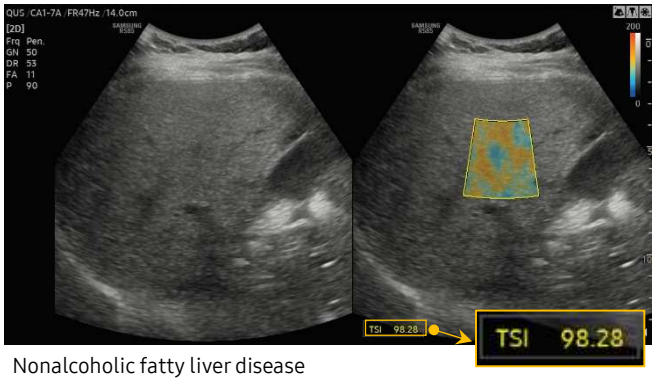
Normal liver



Nonalcoholic fatty liver disease



Normal liver



Nonalcoholic fatty liver disease

[Fig. 3] Measurement of Tissue attenuation imaging (TAI; a, b) in patients without (a) and with hepatic steatosis (b) and Tissue scatter-distribution imaging (TSI; c, d) in patients without (c) and with hepatic steatosis (d).

For measurement of two QUS parameters (TAI and TSI), a 2 x 3 cm fan-shaped region-of-interest (ROI) was placed on the liver right lobe at least 2cm below the liver capsule to avoid reverberation artifacts, while avoiding areas with large vessels or focal lesions. Areas with significant errors in the calculation of parameters, such as vascular structures, were automatically excluded from the calculation, and present as a vacancy on the TAI and TSI maps (Fig. 3). In addition, the reliability of measurement was presented as an R^2 value, and the operator tried to obtain values with an R^2 value $\geq$0.6. Each participant underwent two same-day examination sessions to assess the reliability of the measurements of QUS parameters. During each session, the five measurements were performed and averaged to obtain the representative value of each QUS parameter.

Statistical analysis

Pearson correlation coefficients were used to assess the correlation of QUS parameters and MRI-PDFF. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of QUS parameters for assessing various degrees of hepatic steatosis (MRI-PDFF thresholds of 5%, 15% and 25% for S1, S2, and S3, respectively). For each ROC analysis, the area under the ROC curve (AUC), optimal cutoff values, and the following performance parameters were calculated: sensitivity, specificity, positive predictive value, and negative predictive value. The optimal cutoff value of each QUS parameter was determined using the Youden index [12]. Additionally, cutoff values of TAI and TSI at sensitivity and specificity for exceeding 90% were also derived. Inter-examination reliability was evaluated using intra-class correlation coefficients (ICCs) and interpreted as follows: ≥ 0.90, excellent; 0.75-0.90, good; 0.50-0.75, moderate; <0.50, poor reliability [13]. The coefficient of variation (CV), that is the ratio of the standard deviation to the mean, was calculated to provide an additional estimate of reliability, and a smaller value was considered a more reliable measurement [14]. All statistical analyses were performed using MedCalc version 20.115 (MedCalc Software). A *P*value of <0.05 was considered statistically significant.

Exam Protocol

1. After checking the probe and the application, start a scan
2. Tab the [QUS] on the touch screen and then, activate the [TAI] or [TSI] function
3. Scan the right liver through intercostal space
4. Once you obtain the desired image, press the [Freeze] button
5. Use the trackball to move ROI box to a desired ROI measurement position
    - Place the ROI Box on the liver parenchyma, while avoiding large vessels
    - The ROI must be positioned at least 1.5 cm below the liver capsule
6. Press the [Set] button on the control panel to confirm the results

Scan recommendations

- Liver ultrasound image acquisition
    - Instructing the patient to fast for at least 4 hours before the procedure
    - Imaging the patient in a supine or slight left lateral decubitus position (not more than 30°) with their right hand above their head
    - Obtain measurements through the intercostal space
    - Placing the transducer perpendicular to the liver capsule
- ROI position
    - More than 1.5cm below the surface of the liver capsule (over 2cm is recommended)
    - To avoid the area with large vessels
    - In an as homogeneous area as possible
    - To avoid too deep portion (>8cm)
    - To be near the center line as the results may be unreliable if the ROI is positioned further from the center line
- Avoid motion during measurements
- Perform a measurement in a region with an R^2 value of 0.6 or above

Results

Participant characteristics

A total of 173 participants (96 men and 77 women, mean age, 51.1 ± 14.1 years) were included in the analysis. The mean MRI-PDFF was 11.2% ± 7.8% (range, 1.5%-46.4%). Based on MRI-PDFF values, 47, 79, 37, and 10 patients were categorized as having S0, S1, S1, and S3. The number of patients with ≥S1, ≥S2, and S3 was 126 (72.8%), 47 (21.2%) and 10 (5.8%). The participant characteristics are summarized in Table 1.

[Table 1] Characteristics of study population

Characteristics	Value
Age (years)	51 .1± 14.1 (19-74)
Sex	
Male	96 (55.5)
Female	77 (44.5)
Body mass index (kg/m^2)	26.5 ± 3.5 (19.2-39.8)
Skin-to-liver capsular distance (mm)	20.7 ± 4.3
MRI-PDFF (%)	11.2 ± 7.8 (1.5-46.4)
< 5% (S0)	47 (27.2)
≥5% to < 15% (S1)	79 (45.7)
≥15% to < 25% (S2)	37 (21.4)
≥25% (S3)	10 (5.8)

Note. Values are presented as mean ± standard deviation (range) or number (%), as appropriate.

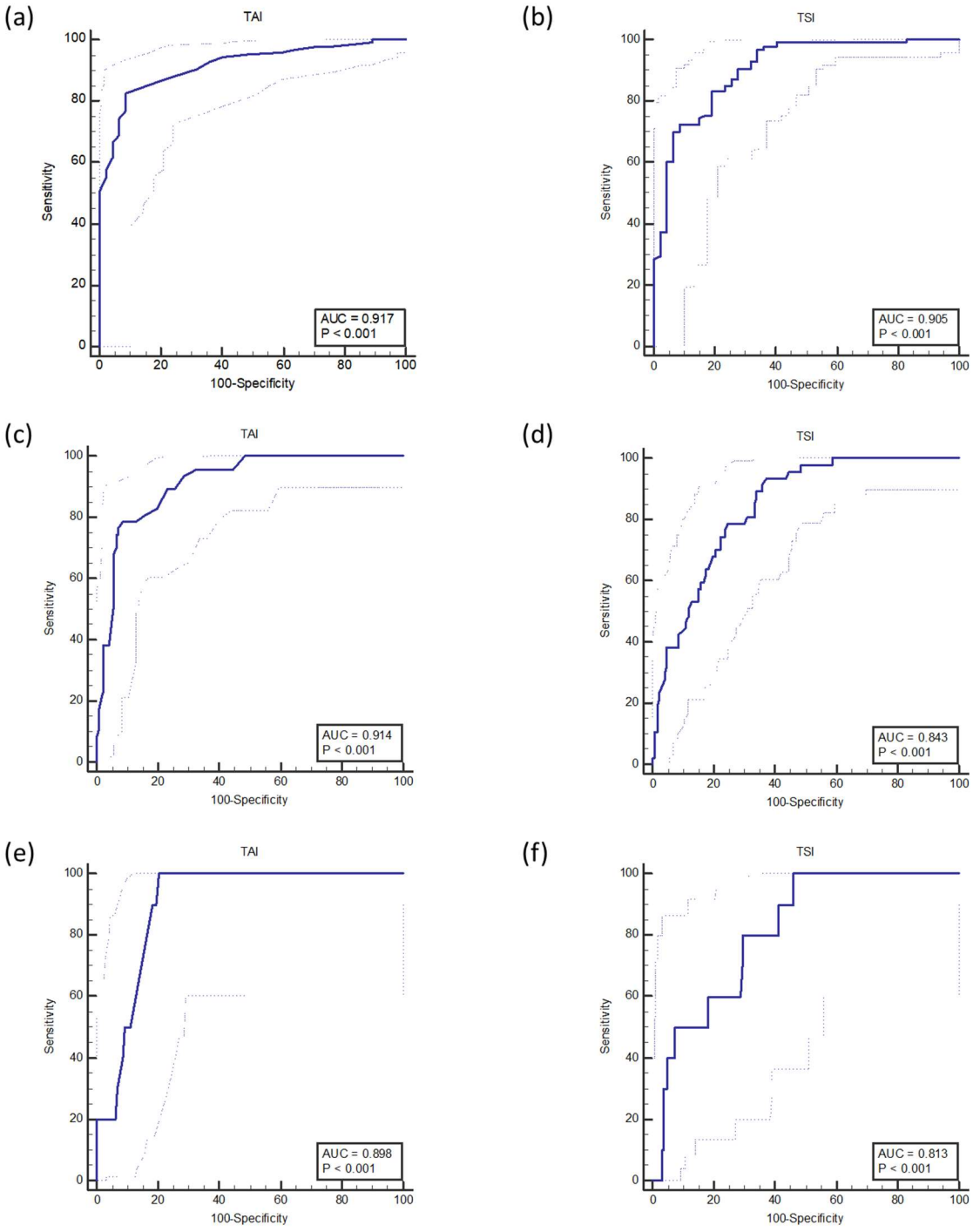
Diagnostic performance of QUS parameters for hepatic steatosis

The diagnostic performance of QUS parameters for evaluating hepatic steatosis based on MRI PDFF are summarized in Table 2 and Figure 4. The AUCs of TAI and TSI for the detection of hepatic steatosis (≥S1) were 0.917 and 0.905 (95% CI, 0.865-0.953 and 0.851-0.944, P<0.001), respectively. In the detection of hepatic steatosis, TAI > 0.72 dB/cm/MHz had a sensitivity of 82.5% and a specificity of 91.5%, whereas TSI >95.6 had a sensitivity of 83.3% and a specificity of 80.9%.

The AUCs of TAI and TSI for the detection of moderate to severe hepatic steatosis (≥S2) were 0.914 and 0.843 (95% CI, 0.862-0.951 and 0.780-0.894, P<0.001), respectively. When detecting moderate to severe hepatic steatosis, TAI > 0.83 dB/cm/MHz had a sensitivity of 78.7% and a specificity of 91.3%, whereas TSI > 98.4 had a sensitivity of 93.6% and a specificity of 64.3%. The AUCs of TAI and TSI for the detection of severe hepatic steatosis (S3) were 0.898 and 0.813 (95% CI, 0.843-0.939 and 0.747-0.868, P<0.001), respectively). For detecting severe hepatic steatosis, TAI > 0.86 dB/cm/MHz had a sensitivity of 100% and a specificity of 79.8%, whereas TSI >98.9 had a sensitivity of 100% and a specificity of 54.0% (Table 2 and Fig. 4).

[Table 2] Diagnostic performance of TAI and TSI

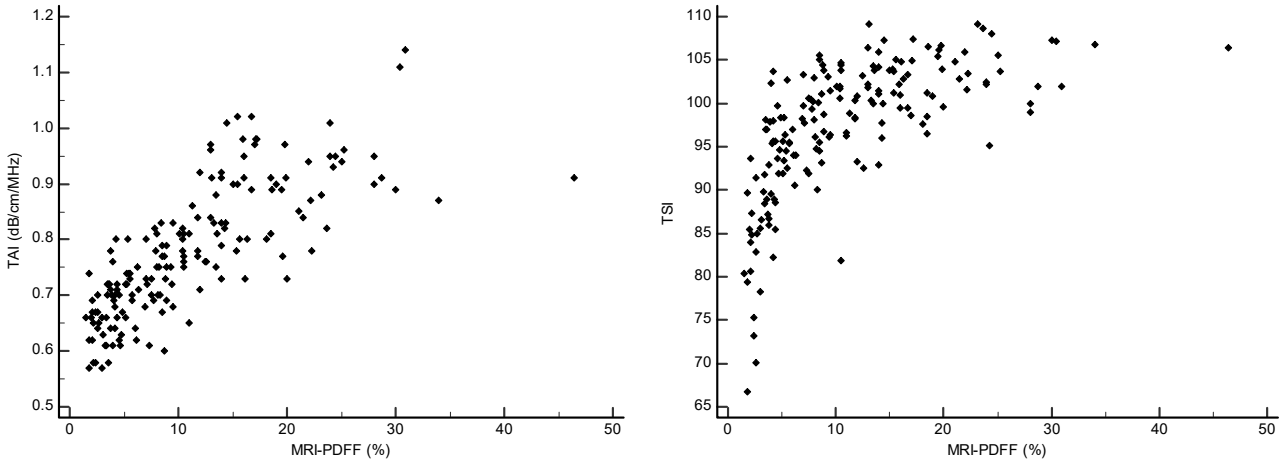
	TAI				TSI			
	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Cutoff	Sensitivity (%)	Specificity (%)
MRI-PDFF ≥5% (≥S1)	0.917 (0.865-0.953)				0.905 (0.851-0.944)			
Optimal cutoff		**>0.72**	82.5	91.5		**>95.6**	83.3	80.9
90% Sensitivity		>0.69	90.5	68.1		>93.4	90.5	72.3
90% Specificity		>0.72	82.5	91.5		>98.1	71.4	91.5
MRI-PDFF ≥15% (≥S2)	0.914 (0.862-0.951)				0.843 (0.780-0.894)			
Optimal cutoff		**>0.83**	78.7	91.3		**>98.4**	93.6	64.3
90% Sensitivity		>0.77	93.6	71.4		>98.4	93.6	64.3
90% Specificity		>0.83	78.7	91.3		>103.8	42.6	91.3
MRI-PDFF ≥25% (≥S3)	0.898 (0.843-0.939)				0.813 (0.747-0.868)			
Optimal cutoff		**>0.86**	100	79.8		**>98.9**	100	54.0
90% Sensitivity		>0.88	90.0	81.6		>100.0	90.0	58.9
90% Specificity		>0.93	50.0	90.8		>105.5	50.0	92.6



[Fig. 4] The diagnostic performance of TAI (a, c, e) and TSI (b, d, f) for the detection of hepatic steatosis (≥S1 (a,b), ≥S2 (c,d), and S3 (e,f)).

Correlation between QUS parameters and MRI-PDFF

Both TAI and TSI values showed significant positive correlations with MRI-PDFF (r = 0.776 and 0.635; 95% confidence interval [CI] = 0.708-0.829 and 0.537-0.716, *P* <0.001). The distribution of TAI and TSI values according to MRI-PDFF are present in Figure 5.



[Fig. 5] Distribution of TAI (a) and TSI (b) according to MRI-proton density fat fraction (MRI-PDFF)

Reproducibility of TAI and TSI

The inter-examination reproducibility of TAI and TSI was excellent with ICCs of 0.975 (95% CI, 0.966-0.982) and 0.924 (0.898-0.944), respectively. CVs of TAI and TSI were 3.3% (95% CI, 2.9-3.7) and 3.2% (95% CI, 2.8-3.6), respectively.

Conclusion

In conclusion, QUS (TAI and TSI) provided good performance in detecting and assessing the degree of hepatic steatosis, and thus it can be used as a valuable tool in assessing hepatic steatosis in patients with NAFLD.

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