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Original Article

Comparison of Ultrasound-Based Techniques and Magnetic Resonance Imaging Proton Density Fat Fraction in Measuring the Amount of Hepatic Fat in Children with Hepatosteatosis

Hepatosteatozlu Çocuklarda Hepatik Yağ Miktarının Ölçülmesinde Ultrason Tabanlı Teknikler ile Manyetik Rezonans Görüntüleme Proton Yoğunluğu Yağ Fraksiyonunun Karşılaştırılması

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ABSTRACT

Objective: The aim of this study is to demonstrate the reliability of Quantitative Ultrasound (QUS) in assessing liver fat content in children, using magnetic resonance imaging proton density fat fraction (MRI-PDFF) values as a reference, and to determine threshold values for QUS in grading hepatosteatosis.

Methods: The study group consisted of pediatric patients under 18 years of age without known liver disease who volunteered to participate. All patients underwent MRI-PDFF scanning, and QUS imaging was performed using the tissue attenuation imaging (TAI) ve tissue scatter distribution imaging (TSI) tools. The cut-off values for MRI-PDFF were set at ≥5%, ≥16.3%, and ≥21.7%, corresponding to mild, moderate, and severe steatosis, respectively. The diagnostic performance of TAI and TSI in detecting various degrees of hepatic steatosis was evaluated using the area under the ROC (AUROC) curves.

Results: The frequencies of hepatosteatosis grading were as follows: S1: 19 (37%), S2: 5 (10%), S3: 22 (43%). The AUROCs for TAI and TSI tools in detecting QUS measurements (MRI PDFF ≥5%) were 0.95 [95% confidence interval (CI): 0.91-0.99] (p< 0.001) and 0.96 (95% CI: 0.93-0.99) (p<0.001), respectively. For distinguishing different degrees of steatosis, TAI showed values of 0.75, 0.86, and 0.96 dB/cm/MHz, corresponding to sensitivities of 88%, 88%, and 100%, respectively, while TSI showed values of 92.44, 96.64, and 99.45, with sensitivities of 90%, 92%, and 91.7%. The correlation test between QUS measurements [TAI, TSI, EzHRI (Hepato-Renal Index with Automated regions of interest Recommendation)] and MR-PDFF indicated a concordance in TAI and TSI values, but not with EzHR.

Conclusions: The TAI and TSI tools can accurately measure liver fat content and can be used reliably in children for the assessment and grading of hepatosteatosis.

Keywords: Pediatric hepatosteatosis, hepatic fat quantification, tissue attenuation imaging, tissue scatter distribution imaging, magnetic resonance imaging-proton density fat fraction

ÖZ

Amaç: Bu çalışmanın amacı, çocuklarda karaciğer yağ içeriğinin manyetik rezonans görüntüleme proton yoğunluğu yağ fraksiyonu (MRI-PDFF) değerlerini referans alarak kantitatif ultrason (QUS) güvenilirliğini göstermek ve hepatosteatoz derecelendirilmesinde kantitatif US eşik değerlerini belirlemektir.

Yöntemler: Çalışma grubunu bilinen karaciğer hastalığı olmayan, 18 yaş altı çocuk hastalardan çalışmaya katılmaya gönüllü olanlar oluşturdu. Tüm hastalara MRI-PDFF taraması yapıldı ve doku zayıflama görüntüleme (TAI) ve doku saçılım dağılım görüntüleme (TSI) araçları kullanarak QUS görüntüleme yapıldı. MRI-PDFF'de ≥%5, ≥%16,3 ve ≥%21,7 kesme değerleri şu şekildedir: sırasıyla hafif, orta ve şiddetli steatoz için kullanıldı. Alıcı çalışma karakteristiği (AUROC) eğrilerinin altındaki alan farklı derecelerde hepatik steatozun saptanmasında TAI ve TSI'nın tanısal performansını değerlendirmek için kullanıldı.

Bulgular: Hepatosteatozun derecelendirilmesinde görülme sıklıkları S1;19 (%37), S2;5 (%10), S3;22 (%43). QUS ölçümleri tespitinde TAI ve TSI araçlarının AUROC'ları (MRI PDFF ≥%5), 0,95 idi [%95 güven aralığı (GA): 0,91-0,99] (p<0,001) ve 0,96 (%95 GA: 0,93-0,99) (p<0,001). Steatozun farklı dereceleri arasında ayrım yaparken, TAI aracı için 0,75, 0,86 ve 0,96 dB/cm/MHz değerleri sırasıyla %88, %88 ve %100 duyarlılığa sahiptir; ve değerleri 92,44, 96,64 ve 99,45, TSI aracı için sırasıyla %90, %92 ve %91,7 duyarlılığa sahiptir. QUS ölçümleri (TAI, TSI, EzHRI: otomatik ROI önerisi ile hepato-renal index) ve MR-PDFF değerleri arasındaki korelasyon testinde TAI ve TSI değerlerinde uyum olduğu ancak EzHRI ile uyumun olmadığı görüldü.

Sonuçlar: TAI ve TSI araçları karaciğer yağ içeriğini doğru bir şekilde ölçebilir ve hepatosteatozun değerlendirilmesi ve derecelendirilmesi için çocuklarda güvenilir bir şekilde kullanılabilir.

Anahtar kelimeler: Çocuk hepatosteatoz, quantitatif karaciğer yağ ölçümü, doku zayıflama görüntüleme, doku saçılım dağılım görüntüleme, manyetik rezonans görüntüleme-proton yoğunluğunun yağ fraksiyonu

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INTRODUCTION

Fatty liver is defined as the presence of intracellular fat content of 5% or more in hepatocytes[1]. Fatty liver has become the most common chronic liver disease worldwide, with publications reporting an incidence of up to 30% in the general population[2]. Early diagnosis is crucial, as the advanced stages of fatty liver can lead to serious complications such as steatohepatitis, portal hypertension, cirrhosis, and hepatocellular carcinoma.

Currently, the gold standard for the definitive diagnosis of liver fat quantification is liver biopsy. However, in cases of heterogeneous fat distribution in the liver, biopsy results may vary depending on the sampled location. Furthermore, because biopsies are an invasive procedure, it is challenging to repeat them for long-term monitoring of steatosis[3].

Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) is a non-invasive technique that offers accurate quantification of liver fat as an alternative to biopsy[4,5]. It also has advantages, such as being operator-independent and unaffected by body mass index (BMI). On the other hand, ultrasound (US) is a non-invasive, easily accessible, repeatable, and cost-effective method. With the addition of recent quantitative methods, US holds significant potential for diagnosis and monitoring in pediatric patients, particularly in the coming years.

In grayscale US examinations, fatty liver is subjectively classified and graded (grade 0-3). Conventional US has over 90% sensitivity in detecting hepatic steatosis (HS) when at least 20% of hepatocytes are affected. However, it has been reported to be less sensitive to detect lower degrees of steatosis. It is also known to be operator-dependent and subject to inter-operator variability[6].

For these reasons, a non-invasive, easy-to-apply, and quantitative US (QUS) method, similar to grayscale US, has been developed, particularly for use in pediatric patients. In the QUS device we use (Samsung Medison Co Ltd), tissue attenuation imaging (TAI) and tissue scatter distribution imaging (TSI), are utilized to measure hepatic fat content. This method provides users with numerical data on the degree of liver fat and allows for comparative analysis in follow-ups.

However, according to manufacturers, the cut-off values for steatosis grading differ between devices. Currently, there are insufficient studies to validate the accuracy of QUS and to establish standardized cut-off values, particularly in pediatric patients.

The aim of this study is to demonstrate the reliability of QUS in pediatric patients by referencing MRI-PDFF values and to determine the QUS cut-off values for the diagnosis of HS in children.

MATERIALS and METHODS

Approval of our single-center prospective study was obtained from the University of Health Sciences Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Board in accordance with the provisions of the Declaration of Helsinki (decision no: 2023/0889, date: 13.12.2023). Informed consent forms were obtained from the parents of all participating patients.

Patients who presented with a diagnosis or suspicion of HS and were referred for abdominal US examination between January and June 2024 were included in the study. Patients with homogeneous hepatosteatosis liver parenchyma were included in the study, and cases with heterogeneous and geographic-pattern hepatosteatosis were excluded. Demographic characteristics of the patients were recorded, and their BMI and body surface area (BSA) were calculated. Laboratory data (ALT, AST, GGT, albumin, total bilirubin, triglycerides, total cholesterol, LDL cholesterol) were retrieved from the hospital information system for pediatric patients under 18 years of age without known liver disease (Table 1).

Patients with primary or metastatic liver disease, a history of liver surgery, liver trauma, or hepatobiliary infectious-inflammatory diseases were excluded from the study.

Quantitative US Imaging

QUS imaging was performed on all patients after a minimum of 6 hours of fasting. Abdominal US examinations were conducted by a pediatric radiologist with over 15 years of experience (G.B) and a radiologist with 12 years of experience (M.A). The US device used was a Samsung RS Prestige 85 with a 1-7 MHz convex curved-array probe.

Patients were evaluated in the supine position. The cranio-caudal long axis of the liver was measured through the midclavicular line for each patient. Subsequently, QUS imaging was obtained through the right intercostal space by having patients place their right hand beneath their head.

Initially, a numerical EzHRI value was obtained by comparing the renal, and liver parenchyma. Next, TAI and TSI measurements were performed sequentially, ensuring measurements were taken from the same location. TAI and TSI values were measured from at least three different locations in the right liver lobe.

Table 1. Demographic characteristics of the patients, laboratory and physical examination findings.	
Variance	**n (%), mean ± SD**
Sex	
M	37(72.5)
F	14 (27.5)
Age	13.04±3.30
Liver KK lengh	147.45±21.71
ALT	43.27±36.08
AST	31.05±22.17
GGT	28.58±20.71
Albumin	47.64±4.56
Total bilirubin	0.47±0.32
LDL	89.11±21.33
TGS	118.41±62.93
HDL	44.45±10.38
Total cholesterol	151.41±28.60
BMI	29.56±7.81
BSA	1.78±0.39

CC: Cranio-caudal, ALT: Alanine aminotransferase, AST: Aspartat aminotransferaz GGT: Gamma-glutamyl transpeptidaz, LDL: Low-density lipoprotein, TGS: Trigliserid, HDL: High-density lipoprotein, BMI: Body mass index, BSA: Body surface area, SD: Standard deviation

Care was taken to exclude vascular structures from the measurements and to obtain measurements at least 3 cm deep from the liver capsule. Examinations were performed while the patients held their breath. Both QUS techniques were successfully and easily applied.

As shown in Figure 1, TAI is a tool that measures energy loss due to the attenuation of US signals from the liver, depending on liver fat concentration[7,8]. For accurate measurements, the ROI should be kept away from major vascular structures and artefactual areas, with measurements taken at least 3 cm below the liver capsule.

Measurement reliability was ensured by selecting optimal areas with an R^2 value of 0.6 or higher, as determined by the manufacturer. In areas with an R^2 value below 0.6, the device issued a warning, and measurements could not be taken. This feature facilitates standardization among operators.

TSI, on the other hand, is a tool that measures signal distribution based on backscattered signals, as shown in Figure 2. The distribution of scattering signals changes depending on hepatic fat content[9,10].

For both TAI and TSI, at least three measurements were obtained in a single breath-hold. The mean, median, and interquartile range (IQR) values of the measurements were recorded (Figure 3).

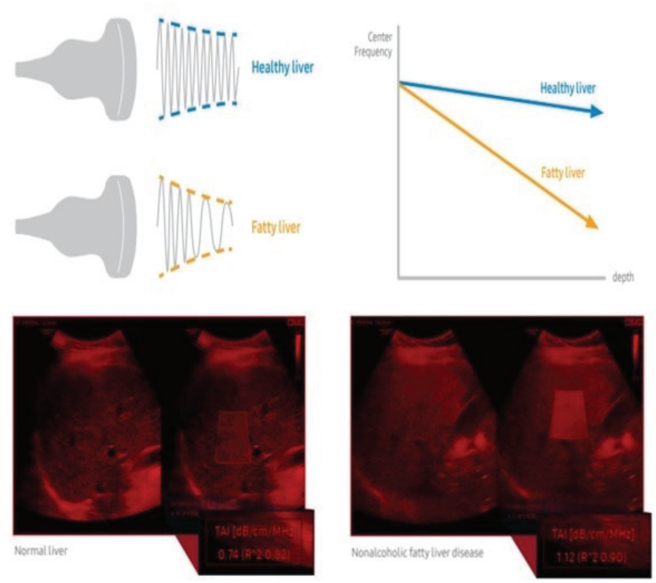

Figure 1. TAI, the quantitative tool that measures the attenuation of signals from the liver, shows that attenuation, as shown in Figure 1 above, causes a change in center frequency at greater depth, while a more severe fatty liver is associated with greater attenuation.

TAI: Tissue attenuation imaging

Magnetic Resonance Imaging-Proton Density Fat Fraction Method

After US imaging, all patients underwent MRI-PDFF scans on the same day using a 1.5 Tesla MRI scanner (GE, 360 Explorer) equipped with a body coil. A single breath-hold 3D volumetric imaging sequence, MRI-PDFF (IDEAL IQ), was performed with the following scanning parameters: TR 17.1 ms, TE 3.8 ms, imaging matrix 224x192, slice thickness 10 mm, field of view 40 cm, and bandwidth 100 kHz in the axial plane. A low flip angle of 8 degrees was set.

Elliptical regions of interest (ROIs) of 3 cm² were used for MRI-PDFF measurements. At least three ROI values were taken from the right liver lobe (segments 5, 6, 7, and 8), and their averages were recorded. The images were independently reviewed by two radiologists blinded to the US findings, and the average of their measured values was calculated.

Based on previously published studies, the accepted MRI-PDFF cut-off values for HS were as follows: mild (S1) ≤5%, moderate (S2) 16.3%, and severe (S3) 21.7% steatosis[11].

Statistical Analysis

The Kolmogorov-Smirnov test was used to show the normal distribution of the data. Frequency and percentage were used for categorical data, and mean standard deviation and maximum and minimum values were used for continuous data. Spearman correlation analysis was used to evaluate the correlation between QUS values such as TSI, TAI, EzHRI, and MRI-PDFF values. ROC curve analysis was performed to determine the diagnostic performance of QUS data in detecting hepatosteatosis grades from S0 to S3, corresponding to grades S0, S1, and S2 of ≥5%, ≥16.3% and ≥21.7%, respectively. The p-value less than 0.05 was considered statistically significant. The SPSS 24.0 software (IBM Corp, Armonk, NY) was used to perform statistical analyses.

RESULTS

The study included 51 patients [37 male (72.5%)]. The mean age of the patients was 13.04±3.30 (range: 5-17 years). Demographic values, laboratory findings showing liver function tests, and physical examination findings (such as BMI, BSA) of the patients are shown in Table 1.

According to MRI-PDFF values, steatosis was not detected in 8 patients [S0: 5 (10%)]. Steatosis grading was done from S1 to S3, and the values of this grading were ≥5%, ≥16.3%, and ≥21.7%, respectively. Their frequency was found as follows in our patient group: S1: 19 (37%), S2: 5 (10%), S3: 22 (43%). In the correlation test between QUS measurements (TAI, TSI, EzHRI) and MRI-PDFF values, it was seen that there was agreement in TAI and TSI values, but no agreement with EzHRI (Table 2).

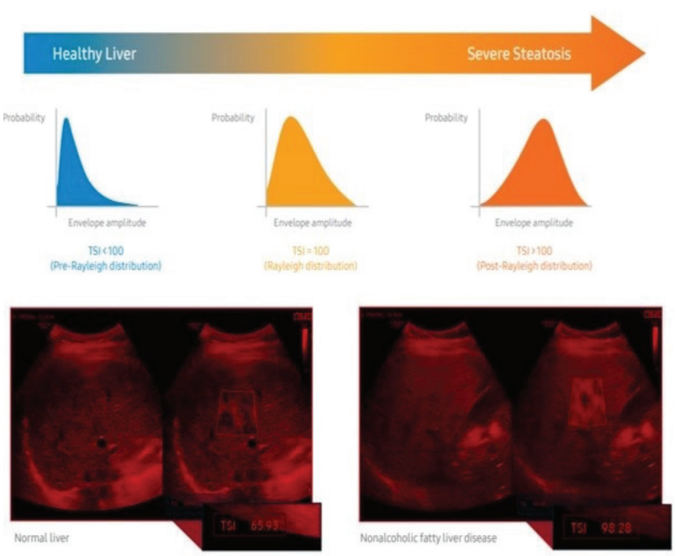

Figure 2. Figure 2 below shows TSI, which measures the correlation between the backscattered signals and the Rayleigh distribution to assess the scattered signal distribution.

TAI: Tissue attenuation imaging

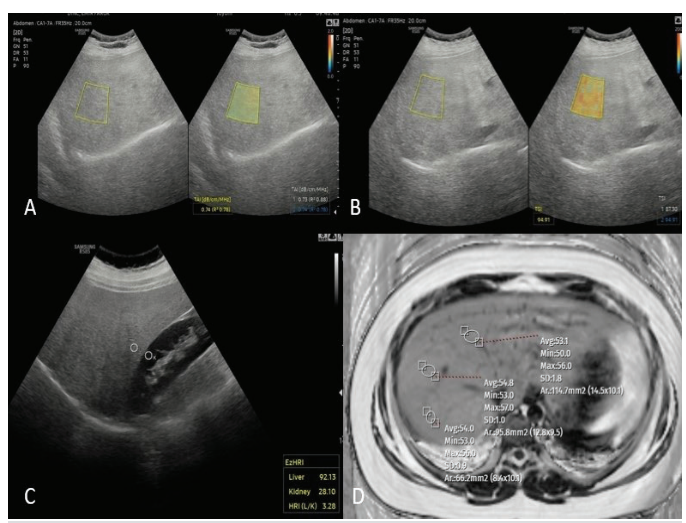

Figure 3. The median values of measurements were 0.74 dB/cm/ MHz and 94.91 for TAI (Figure 3A) and TSI (Figure 3B) techniques in a 10-year-old male patient with grade 1 hepatosteatosis. EzHRI value (Figure 3C) is 3.28. MRI-PDFF value is 9.38 % (Figure 3D).

TAI: Tissue attenuation imaging, TSI: Tissue scatter distribution imaging, MRI: Magnetic resonance imaging, PDFF: Proton density fat fraction

Table 2. QUS measurements with MRI PDFF.				
MRI-PDFF hepatosteatosis grade	TAI (dB/cm/MHz) Median (IQR)	TSI median (IQR)	EzHRI median (IQR)	n (%)
S0 (<%5)	0.64 (0.61-0.66)	83.87 (71.14-87.44)	2.29 (1.85-2.55)	5 (10)
S1 (≥5%-<16.3%)	0.70 (0.67-0.77)	89.24 (88.41-96.00)	2.63 (2.64-3.03)	19 (37)
S2 (≥16.3%-<21.7)	0.82	98.97 (97.02-100.01)	3.47 (3.34-3.55)	5 (10)
S3 (≥21.7%)	0.84	101.94 (100.85-102.65)	3.68 (3.57-3.85)	22 (43)

TAI: Tissue attenuation imaging, QUS: Quantitative Ultrasound, MRI: Magnetic resonance imaging, PDFF: Proton density fat fraction, IQR: Interquartile range, TSI: Tissue scatter distribution imaging

In the correlation analysis, it was seen that there was a correlation between TAI (r=0.790, p<0.001) and TSI (r=0.591, p<0.001) measurements and MRI-PDFF values, while there was no correlation between EzHRI (r=0.294, p=0.36) value and MRI-PDFF.

According to the evaluation made with ROC curve analysis, the results of TAI and TSI in diagnosing hepatosteatosis (accepted MRI-PDFF ≥5%) were as follows: AUROC: 0.817, 95% CI: (0.73-0.93) (p=0.005) and AUROC: 0.628, 95% CI: (0.70-0.88) (p=0.047).

The sensitivity and specificity of the TAI value of 0.67 dB/cm/MHz in diagnosing hepatosteatosis (MRI-PDFF ≥5%) were found to be 77% and 75%, respectively. In the TSI measurement, the sensitivity at the value of 88.03 was 70% and the specificity was 73%.

DISCUSSION

In recent years, the terminology of HS has evolved, and it is now internationally recognized as fatty liver disease associated with metabolic syndrome, which includes dyslipidemia, obesity, and insulin resistance. This metabolic syndrome is well-known to be linked to cardiovascular risk[12,13]. Therefore, early diagnosis is crucial, and one of the primary non-invasive methods gaining prominence, especially in children, is QUS. In our study, the effectiveness of QUS in diagnosing HS in pediatric patients was demonstrated; showing strong correlation with MRI.

In our study, we demonstrated that QUS is an effective non-invasive method for diagnosing HS in pediatric patients, showing a strong correlation with MRI-PDFF. The Samsung Prestige RS85 device used in our study employed TAI and TSI parameters to calculate HS percentage, with cut-off values of 0.67 and 88.03, respectively. TAI demonstrated an AUROC value of 0.817, indicating good diagnostic performance with 77% sensitivity and 75% specificity. In contrast, TSI exhibited a lower AUROC value, highlighting differences in diagnostic performance. Additionally, the EzHRI parameter did not show a statistically significant results or a correlation with MRI-PDFF.

Interestingly, previous studies conducted in adult populations reported a strong diagnostic performance for EzHRI, identifying a cut-off value of 1.2 as optimal for detecting steatosis with 100% sensitivity[14]. Additionally, a recent pediatric study found a similar optimal cutoff value (AUROC 0.98, specificity 92.9), indicating good diagnostic performance[15]. The discrepancy between our findings and these previous studies might be attributed to differences in sample size, population characteristics, or study design.

The incidence of HS in children is increasing, largely due to sedentary lifestyles, fast-food consumption, and screen dependency. HS poses severe risks, including parenchymal inflammation and fibrosis (in about 20-25% of cases), carcinoma, and mortality. Therefore, accurate, non-invasive, and easily applicable diagnostic techniques are essential. Our findings suggest that QUS, particularly using TAI, is a reliable and practical tool for diagnosing HS in children, especially in settings where MRI is unavailable.

When comparing our findings with the literature, it is evident that studies have reported the growing role of QUS in liver fat quantification. The American Institute of US in Medicine and RSNA Quantitative Imaging Biomarkers Alliance have standardized US protocols for fat quantification. In 2022, Ferraioli et al.[16] reported attenuation-based QUS techniques with MRI-PDFF as the reference standard. In recent studies, the receiver operating characteristic (ROC) curves for QUS showed an area under the curve (AUC) of 0.84-0.93 for steatosis grade 1, 0.86-0.93 for grade 2, and 0.79-0.93 for grade 3 (17,18). Similarly, Labyed and Milkowski[19] reported a high correlation (r=0.87) between US-derived fat fraction and MRI-PDFF. Our results are consistent with these findings, emphasizing the robustness of QUS for pediatric HS diagnosis.

Guidelines published by the Expert Committee on HS and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend alanine aminotransferase (ALT) as the best screening test for detecting steatosis in children; however, B-mode US is not recommended due to insufficient sensitivity and specificity. In our study, elevated ALT levels were observed. However, serum markers such as aminotransferases are relatively insensitive and not specific for detecting HS. Liver enzyme tests systematically underestimate the true extent of disease and have low prognostic value for the development of non-alcoholic steatohepatitis[20].

Transient elastography via FibroScan, while effective, shows variability in threshold values and higher measurement failure rates in patients with high BMI. In contrast, QUS offers better accessibility and cost-efficiency without sacrificing diagnostic accuracy. Moreover, recent advancements in US-based technologies (such as ATI and TAI) are promising but vary in diagnostic performance, as shown by Zhu et al.[21] in a study comparing TAI, ATI, and controlled attenuation parameter (CAP). When compared with 1 proton MR spectroscopy (1H-MRS), TAI also demonstrated the highest correlation (the study). Their study showed moderate-to-good AUCs for detecting HS. However, in cases of severe HS, the significantly attenuated signals limit the system's ability to evaluate steatosis effectively.

On the contrary, in a steatosis study conducted on 305 children, the CAP demonstrated higher sensitivity (72%), compared to B-mode US (42%)[22]. Moreover, liver stiffness values in children with HS were significantly higher (approximately 0.5 kPa) than those without steatosis. While this increase may not be clinically significant, it underscores that steatosis is not always a benign condition due to the potential risk of steatohepatitis. Indeed, advanced fibrosis was present at diagnosis in 15% of children, suggesting that the disease may be more severe in children than in adults[23]. Therefore, early diagnosis is of great importance in the management of children.

In 2021, Bende et al.[24] conducted studies on US-guided attenuation parameter measurements, which showed a strong correlation with CAP, with a correlation coefficient of 0.73. The AUROC values for predicting S1, S2, and S3 steatosis were above 0.83 and up to 0.90, indicating high accuracy.

Similarly, a study by Tada et al.[25] involving 126 participants used MRI-PDFF to assess chronic liver disease, reporting AUROC values of 0.92, 0.87, and 0.92 for predicting S1, S2, and S3 steatosis, respectively. Several studies have also validated MRI-PDFF or H-MRS as reference standards in numerous clinical trials[26].

Despite their high sensitivity, these techniques are expensive and not routinely utilized for HS quantification[27]. Consequently, US remains the most preferred method for clinical screening and follow-up due to its accessibility and affordability.

In a recent study, TAI demonstrated high diagnostic performance and a strong correlation in differentiating degrees of HS, whereas TSI did not show a linear dependence on the severity of steatosis[28]. According to the literature and the aforementioned studies that used MRI-PDFF as a reference, it is evident that when MRI is unavailable, there is a need for less expensive and non-invasive imaging techniques, such as US, which is more practical and easier to perform in children.

The limitations of our study include its single-center nature and the small sample size of patients. Another limitation is that potential confounding factors such as inflammation or fibrosis cannot be completely eliminated.

CONCLUSION

In conclusion, as the prevalence of fatty liver disease continues to rise and associated complications become more apparent, the need for reliable non-invasive diagnostic methods has grown. Our study demonstrated that QUS, particularly using TAI and TSI parameters, provides a practical and accessible alternative to MRI-PDFF in diagnosing HS in children. The strong agreement between TAI and TSI values and MRI enhances the reliability of QUS. In contrast to previous studies showing good diagnostic performance, the inconsistency of EzHRI suggests that further large-scale research is necessary to evaluate the consistency and applicability of this parameter across different populations.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Clinical Research Ethics Committee of the Istanbul Medeniyet University Göztepe Training and Research Hospital of the Health Sciences University (decision no: 2023/0889, date: 13.12.2023).

Informed Consent: Informed consent forms were obtained from the parents of all participating patients.

Footnotes

Author Contributions

Concept: S.G.B., M.A., Design: S.G.B., M.A., Data Collection and/or Processing: S.G.B., M.A., Analysis and/or Interpretation: S.G.B., M.A., Literature Search: S.G.B., M.A., Writing: S.G.B., M.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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