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ORIGINAL RESEARCH

Diagnostic Performance of Ultrasound in Detecting Hepatic Steatosis in Non-Alcoholic Fatty Liver Disease Considering MRI Proton Density Fat Fraction as the Reference Standard

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Abstract

Introduction: The increasing incidence of Non-Alcoholic Fatty Liver Disease (NAFLD) will burden the health care system. There is a pressing need to devise an accurate non-invasive method to detect and quantify hepatic steatosis (HS) in NAFLD.

Goal: To evaluate the diagnostic efficacy of conventional ultrasound (US) to predict the presence and degree of HS in NAFLD considering MRI Proton Density Fat Fraction (PDFF) as the reference standard.

Methods: The study comprised sixty subjects with high clinical suspicion of NAFLD. The US was performed to assess four defined signs (abnormal echogenicity of liver, loss of echogenicity of portal vein, poor diaphragm visualization and posterior beam attenuation). MRI IDEAL IQ software-generated fat-fraction maps were used to measure PDFF values as the average of 24 regions of interest (ROIs) in eight liver segments. The sensitivity, specificity, NPV, PPV and diagnostic accuracy of US signs and their combinations were calculated with the MRI PDFF values (≥6.5 % vs <6.5 %) as the reference standard.

Results: The presence of posterior beam attenuation and obscuration of the diaphragm in the US showed excellent sensitivity and NPV (100%) for detecting grade 3 HS. The presence of altered liver echotexture and loss of echogenicity of the portal vein showed excellent sensitivity and NPV (100%) for detecting grade 2 HS.

Conclusion: The sensitivity and negative predictive value of various US signs and their combinations for detecting hepatic steatosis were excellent. Thus, the conventional ultrasound must be considered a satisfactory screening tool for the exclusion of NAFLD.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is known as an exuberance of fat in the liver (steatosis) that is not caused by exorbitant alcohol consumption or any other accessory cause (1). Quantitatively, NAFLD is diagnosed when liver fat quantity exceeds 5% of the weight of the liver, and that exuberance of fat is not caused by alcohol consumption, pharmaceutical products, toxoids, infectious diseases, or any other attributable cause (2).

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The clinical entity of NAFLD has shown a universal rise with prevalence rates of 10-46% in the United States, 6-35% in the rest of the world, and 9-32 % in India (3, 4). Delineating a gamut of disorders from simple steatosis to lobular inflammation with uncertain degrees of fibrosis, and non-alcoholic steatohepatitis, NAFLD can be a precursor of cirrhosis and hepatocellular carcinoma, situations coupled with very poor clinical outcomes.

The risk factors for NAFLD include style of living, like high-fat diet, lack of physical activity, accompanied by metabolic syndrome which comprises central abdominal obesity, hypertension, dyslipidaemia etc. NAFLD is apparently the hepatic manifestation of metabolic syndrome and insulin resistance plays a major role in its etiopathogenesis. Many studies have reported that a rise in the prevalence of NAFLD is related with an increased prevalence of pre-diabetes, diabetes, and cardiovascular diseases. It is also known that NAFLD is associated with gender, age, ethnicity, and pathological conditions such as hypothyroidism, hypopituitarism, hypogonadism, sleep apnea, and polycystic ovarian syndrome (2).

Conventional ultrasound (US) has been the primary imaging method used for NAFLD because it is safe, free of radiation, available at hand, and cost-effective. However, it has substantial inter-observer variability. Recently, MRI Proton density fat fraction (PDFF) is being suggested as a non-invasive biomarker of HS. PDFF is known as the ratio of mobile triglyceride protons to the sum of mobile triglyceride and water protons. Thus MRI-quantified PDFF postulates an objective, countable, quantitative, and non-invasive judgement of the degree of hepatic steatosis. However, its use in scientific probe and clinical set-up is limited due to cost factors and restricted access (3).

Liver biopsy is still considered to be the gold standard for the diagnosis of NAFLD. However, liver biopsy is an unsuitable tool for most screening, and research purposes due to its invasive nature and other constraints such as sampling error. Over the past few years, MRI PDFF of the liver has demonstrated high diagnostic accuracy with histological grades of steatosis and therefore has been accepted as a reference standard in diagnostic radiology (3).

Conventional US signs of HS have been extensively studied in the literature, but there are very few studies comparing US signs with MRI PDFF (5,6,7). The purpose of this study is to weigh the diagnostic efficacy of US signs and their combinations in detecting the presence and extent of HS in NAFLD, considering MRI PDFF as the reference standard.

Methods

A cross-sectional observational study was conducted on 60 adult subjects with approval from an institutional ethical committee (S No. IEC/VMMC/SJH/Thesis/October/2019-10/161). Written informed consent was obtained from the subjects. Adult subjects more than 18 years of age who had a clinical suspicion of NAFLD with associated risk factors like diabetes, obesity and incidentally detected fatty liver on ultrasound were included in the study. Those who had a history of alcohol consumption of >20g/day for men and >10g/day for women, acute/chronic liver diseases, severe biliary obstruction due to any other cause, pregnant/breastfeeding women, drug intake that cause steatohepatitis, including Tamoxifen, Glucocorticoids, Isoniazid, Amiodarone, Methotrexate, HAART, Estrogen, Sodium Valproate etc., sudden weight loss or weight gain, patients on total parenteral nutrition and patients with a history of gastric bypass, jejunoileal bypass surgeries, surgeries related to liver mass, and patients who had congestive hepatomegaly due to congestive heart failure were excluded from the study.

Age, gender, body weight, height, and body mass index (BMI) were documented for each subject at the time of the study. Based on their BMI, subjects were categorized into normal, overweight, and obese as per revised body mass index categories for Asian Indians based on consensus guidelines (8). BMI of 23 was considered normal, 23-24.9 as overweight and more than 25 as obese. The correlation between BMI and fatty liver was also studied.

Conventional ultrasound (US) was performed by one radiologist with eight years of experience to identify fatty liver using a curvilinear transducer of frequency 3-5 Hz on Siemens S3000 ultrasound scanner. The presence or absence of the four ultrasound signs was noted which were described as abnormal echogenicity of the liver, loss of echogenicity of the portal vein, poor diaphragm visualization, and posterior beam attenuation.

After the US, all the subjects underwent an MRI scan on a 3T MRI scanner (Discovery™ MR750, GE Medical Systems) with a torso coil. IDEAL IQ software-generated images of separated water and triglyceride fat, relative triglyceride fat fraction map, and tissue transverse magnetization relaxation. The relative triglyceride fat fraction map was quantitative and it reflected the proton density (number of protons per unit volume) of triglyceride fat, divided by the sum of the proton density of triglyceride fat and the proton density of water, on a voxel-by-voxel basis. The scanning parameters were: Scan Plane = Axial, Slice Thickness = 10, Frequency Direction = R/L, # of slabs = 1, Locs per Slab = 24. Detail parameters: Number Shots = 2, TE = Minimum Full, Flip angle = Auto, Echo Train Length = 3, Frequency = 224, Phase = 160, NEX = 0.75, Bandwidth = 125.

MRI PDFF measurement

For MRI PDFF measurement, three non-superimposed circular ROIs of 100 mm2 area within each Couinaud liver segment were marked, avoiding large vessels, biliary ducts, focal liver lesions, and imaging artifacts if any (Figure 1). A total of 24 ROIs per subject were obtained from eight segments, and the averages of all readings were defined as the mean PDFF (9). A PDFF value of ≤ 6.5% was considered normal, > 6.5 % and ≤ 17.4 % were considered a grade 1 HS, > 17.4 % and ≤ 22.1 % as grade 2 HS and > 22.1 % as grade 3 HS (10) (Figures 2,3). Taking MRI PDFF results as the reference standard, the accuracy of ultrasound signs and their consolidations in detecting the presence and severity of HS in NAFLD were determined.

Statistical analysis

The data was entered in the MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. Categorical variables were presented in number and percentage. Continuous variables were presented as mean ± SD and median. MRI PDFF values were used to calculate sensitivity, specificity, NPV, PPV and diagnostic accuracy of US signs and their various combinations.

Results

The present study comprised 60 adult subjects, including 25 males and 35 females; ages ranging from 23-70 years with a median age of 38.5 yrs. The study subjects were divided into five subgroups in terms of US findings (normal & four US signs) and four subgroups in terms of MRI fat fraction based on PDFF values (normal & grades of HS 1-3). No significant association was found between age/gender and these subgroups based on US & MRI findings.

The mean BMI (kg/m2) of study subjects was 25.3 (ranging from 19.4-40.5). There was a significant disparity between the five US subgroups in terms of BMI ($\chi2 = 22.357$, p = <0.001), with the median BMI being the highest (27.3 kg/m2) in the subgroup showing obscuration of the diaphragm on the US. The strength of association was (Kendall's Tau) = 0.38 (medium effect size). Similarly, there was an affirmative, statistically significant positive correlation between MRI fat fraction and BMI (rho = 0.62, p = <0.001). For every one unit increase in MRI fat fraction, the BMI would increase by 0.12 units. Conversely, for every one unit increase in BMI, the MRI fat fraction would increase by 2.95 units. There was a convincing correlation between the BMI of 4 MRI subgroups ($\chi2= 20.088$, p = <0.001), with the median BMI being highest in the MRI fat fraction: Grade 3 subgroup; strength of association (Kendall's Tau) = 0.45 (medium effect size).

Table 1. Baseline Demographic and Imaging Findings.

All Parameters	**Mean ± SD || Median (IQR) || Min-Max || Frequency (%)**
Age (Years)	39.87 ± 10.72 || 38.50 (32.00-45.25) || 23.00 - 70.00
Male	25 (41.7%)
Female	35 (58.3%)
Height (m)	1.66 ± 0.09 || 1.68 (1.57-1.73) || 1.49 - 1.84
Weight (Kg)	69.37 ± 9.21 || 70.00 (61.00-75.00) || 54.00 - 98.00
BMI (Kg/m^2)	25.31 ± 2.26 || 25.55 (23.88-26.55) || 19.40 - 30.50
18.5-22.9 Kg/m^2	7 (11.7%)
23.0-24.9 Kg/m^2	16 (26.7%)
≥25.0 Kg/m^2	37 (61.7%)
Ultrasound Findings	
Normal	5 (8.3%)
Altered Liver Echotexture	25 (41.7%)
Loss Of Periportal Echogenicity	10 (16.7%)
Posterior Beam Attenuation	14 (23.3%)
Obscuration Of Diaphragm	6 (10.0%)
Fat Fraction (MRI) (%)	15.10 ± 11.26 || 11.45 (5.75-23.60) || 4.00 - 44.00
Normal	19 (31.7%)
Grade 1	20 (33.3%)
Grade 2	3 (5.0%)
Grade 3	18 (30.0%)
Fatty Liver on MRI (Present)	41 (68.3%)

Figure 1. US and MRI PDFF of the liver of a patient with grade 1 HS with positive ultrasound signs-altered liver echotexture and MRI PDFF value of 12.7.

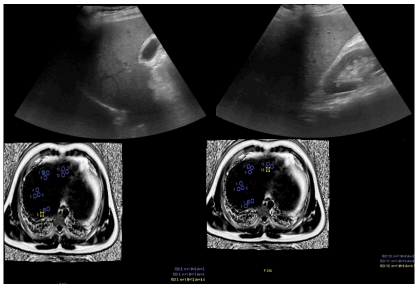


Figure 2. US and MRI PDFF of the liver of a patient with grade 2 HS with positive ultrasound signs-altered liver echotexture, loss of periportal echogenicity and MRI PDFF value of 18.4.

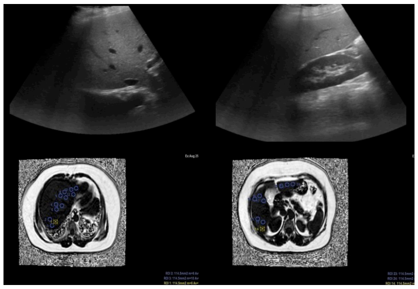


Figure 3. US and MRI PDFF of the liver of a patient with grade 3 HS with positive ultrasound signs-altered liver echotexture, loss of periportal echogenicity, posterior beam attenuation and obscuration of the diaphragm and MRI PDFF value of 39.1.

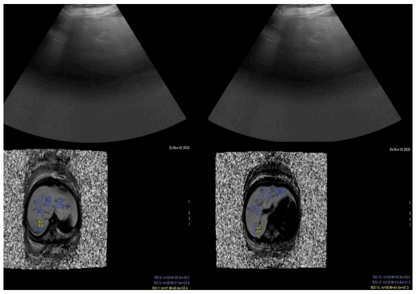


Table 2. Association between ultrasound findings and Grades of hepatic steatosis based on MRI fat fraction.

Grades of the fatty liver based on MRI fat fraction	Ultrasound Findings						Chi-Square Test*	
	Normal	Altered Liver Echotexture	Loss Of Periportal Echogenicity	Posterior Beam Attenuation	Obscuration Of Diaphragm	Total	χ2	P Value
Normal	3 (60.0%)	16 (64.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (31.7%)	77.984	<0.001
Grade 1	2 (40.0%)	9 (36.0%)	7 (70.0%)	2 (14.3%)	0 (0.0%)	20 (33.3%)		
Grade 2	0 (0.0%)	0 (0.0%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	3 (5.0%)		
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (85.7%)	6 (100.0%)	18 (30.0%)		
Total	5 (100.0%)	25 (100.0%)	10 (100.0%)	14 (100.0%)	6 (100.0%)	60 (100.0%)		

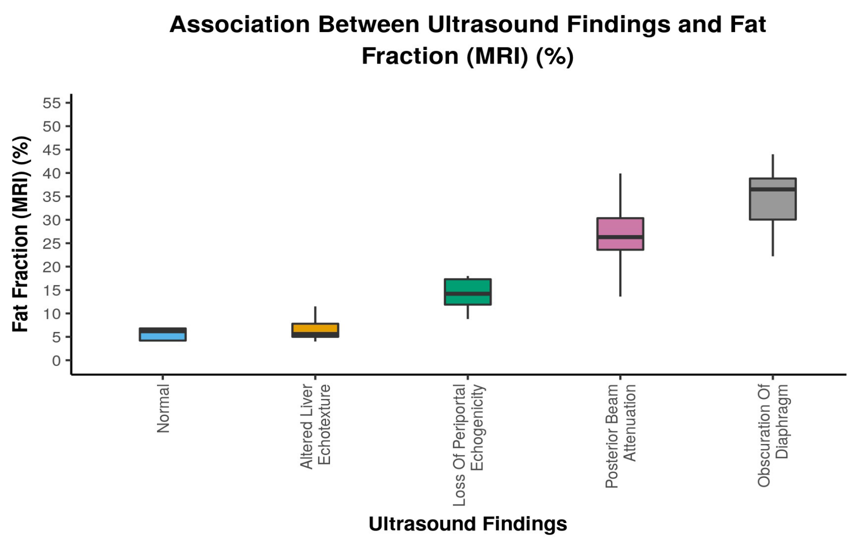
*A chi-square test was used to explore the association between "Ultrasound Findings" and "MRI fat fraction."

The conventional US was done to assess the presence and degree of hepatic steatosis in all the subjects, which was normal in five, and showed the presence of altered liver echotexture in 25, loss of periportal echogenicity in ten, posterior beam attenuation in 14 and obscuration of the diaphragm in six subjects. MRI fat fraction was assessed using PDFF values which were normal in 19, grade 1 in 20, grade 2 in 3 and grade 3 in 18 subjects. These findings have been tabulated in Table 1.

There were significant differences between the five US subgroups in terms of MRI fat fraction (χ2 = 47.845, p = <0.001), with the median MRI fat fraction being the highest (34.5%) in the subgroup showing obscuration of the diaphragm on the US (Figure 4). The strength of association (Kendall's Tau) was 0.74 (large effect size). Also, there was a significant difference between the various US subgroups in terms of grades of hepatic steatosis based on MRI fat fraction (χ2 = 77.984, p = <0.001) and in the strength of association between the two variables (Bias Corrected Cramer's V) = 0.62 (high association) (Table 2).

The primary diagnostic performance of ultrasound signs in predicting the presence of HS in NAFLD, considering MRI as the reference standard, proved to be good (Table 3). Among the four US signs, altered liver echotexture had the highest sensitivity of 95.1% and diagnostic accuracy of 70%. The combination of altered liver echotexture and periportal echogenicity proved to be excellent with a sensitivity of 73.2%, specificity and PPV of 100% and diagnostic accuracy of 81.6%. The rest of the ultrasound signs had similar sensitivity of 5-29% and specificity of 82-100% in the prediction of HS.

Figure 4. The box and whisker plot showing association between ultrasound findings and MRI fat fraction.



The diagnostic accuracy of ultrasound signs in predicting the grades of HS in NAFLD was not as good: the diagnostic accuracy ranged from 30-70% (Table 4). The sensitivity and NPV of altered liver echotexture in detecting grade 1 HS or higher were 81.8% and 60% respectively. However, with the presence of both altered liver echotexture and loss of periportal echogenicity, both sensitivity and NPV in detecting grade 2 HS or higher were excellent (100%). Also, the sensitivity and NPV for detecting grade 3 HS were exceptional (100%) when posterior beam attenuation and obscuration of the diaphragm were present.

Discussion

NAFLD, which is considered to be the hepatic manifestation of the metabolic syndrome due to its association with obesity,

Table 3. Diagnostic performance of US signs and their combinations in predicting hepatic steatosis in NAFLD with MRI PDFF as the reference standard.

Variables	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Altered liver echotexture	95.1%	15.7%	70.9%	60%	70%
Loss of periportal echogenicity	73.1%	100%	100%	63.3%	81.6%
Posterior beam attenuation	48.7%	100%	100%	47.5%	65%
Obscuration of diaphragm	14.6%	100%	100%	35.19%	41.67%
Altered liver echotexture + loss of periportal echogenicity	73.2%	100%	100%	63.3%	81.6%
Altered liver echotexture + posterior beam attenuation	48.78%	100%	100%	47.5%	65%
Altered liver echotexture + obscuration of diaphragm	14.63%	100%	100%	35.19%	41.67%
Loss of periportal echogenicity + posterior beam attenuation	48.7%	100%	100%	47.5%	65%
Loss of periportal echogenicity + obscuration of diaphragm	14.6%	100%	100%	35.1%	41.6%
Posterior beam attenuation + obscuration of diaphragm	14.63%	100%	100%	35.2%	41.7%
Altered liver echotexture + loss of periportal echogenicity + posterior beam attenuation	48.8%	100%	100%	47.5%	65%
Altered liver echotexture + loss of periportal echogenicity + obscuration of diaphragm	14.63%	100%	100%	35.2%	41.7%
Altered liver echotexture + posterior beam attenuation + obscuration of diaphragm	14.6%	100%	100%	35.2%	41.7%
Loss of periportal echogenicity + posterior beam attenuation + obscuration of diaphragm	14.6%	100%	100%	35.2%	41.7%
Altered liver echotexture + loss of periportal echogenicity + posterior beam attenuation + obscuration of diaphragm	14.63%	100%	100%	35.19%	41.67%

Table 4. Diagnostic performance of US signs and their combinations in predicting grades of hepatic steatosis in NAFLD with MRI PDFF as the reference standard.

MRI	US Signs	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Normal	None	15.8%	95.1%	60.0%	70.9%	70.0%
≥ Grade I	Altered liver echotexture	81.8%	15.8%	36.0%	60.0%	40.0%
≥ Grade II	+Loss of periportal echogenicity	100.0%	13.5%	8.6%	100.0%	20.0%
≥ Grade III	+Posterior beam attenuation	100.0%	11.9%	24.5%	100.0%	31.5%
≥Grade IV	+Obscuration of diaphragm	100.0%	11.9%	32.7%	100.0%	38.3%

insulin resistance, and type 2 Diabetes Mellitus (DM), is a commonly encountered condition that may be a harbinger of early liver parenchymal disease. To date, liver biopsy is the gold standard for establishing the diagnosis of NAFLD, however, there is a compelling need to devise a non-invasive technique for accurate identification, quantification, and follow-up of hepatic steatosis in NAFLD. In the recent past, MRI PDFF has proved to have precise diagnostic accuracy with histological grades of hepatic steatosis and therefore has been accepted as a reference standard in diagnostic radiology.

In the present study subjects, it was found that 70% were aged between 23-65 years, consistent with the study results of Chalasani N et al., in which NAFLD was common between the third to sixth decade of life. Secondly, no correlation between age and ultrasound signs of HS or fat fraction was found in the present study ($\chi 2 = 4.174$, $p = 0.383$) which was again, consistent with the results of this previous study (11).

In the present study, subjects with HS had a mean BMI above the normal range of 18.5-22.9 kg/m2. Being overweight and obese are important predisposition factors for the onset of NAFLD, as mentioned in previous studies by Boza et al. and Harnois et al. (12,13). We found that 26.7 % of subjects with HS were overweight, and 61.7 % of them were obese, confirming that overweight and obesity are important risk factors and predictors of NAFLD.

The current study found a positive correlation between some combinations of US signs and MRI PDFF values. In addition, the ability of 'altered liver echotexture' in predicting the presence of fatty liver (≥6.5% MRI PDFF) was high with a sensitivity of 95.12% and NPV of 60%, respectively, fairly comparable to the study by Kim Mimi et al. which showed altered liver echotexture to have a sensitivity and NPV of 96.6 % and 97.9 % respectively (14). Loss of periportal echogenicity had a sensitivity and NPV of 73.17 % and 63.33 %, respectively, which was again comparable to the study by Kim Mimi et al., which found 72.9% and 88.2 % respectively (14).

The statistical analysis of various combinations of US signs in the present study revealed that the combination of altered liver echotexture and periportal echogenicity was excellent in predicting the presence of HS with a sensitivity and specificity of 73.2% and 100% respectively, consistent with the results of a study in the recent past (72.9% and 96.8 % respectively) (14).

A meta-analysis of 46 studies that compared the diagnostic performance of US to detect grade 2 HS or higher was excellent, with a sensitivity of 85.7% and a specificity of 85.2%. (15). However, the sensitivity of US for detection of grade 1 HS was relatively low at 12-49.8% (16,17). In contradiction, previous studies by Bohte A. E et al. and Hernaez R. et al. have shown that the sensitivity and specificity of US for detecting HS of 10% or less in histology were 73.3% and 84.4%, respectively. (15,18)

A previous study by Ryan C. K. et al. stated that the sensitivity of US was only 12% with a histologic liver fat content of 5–10%(17). However, the present study demonstrated that the sensitivity and NPV of "altered liver echotexture" in detecting grade 1 HS or higher were excellent (sensitivity 81.8% and NPV 60%). The present results were as per the threshold used by Kim Mimi et al. and Ryan C.K et al. (>6.5 MRI PDFF as fatty liver) (14,17).

We found that when both altered liver echotexture and loss of periportal echogenicity were present, the sensitivity and specificity in detecting grade 2 or higher steatosis were 73.17% and 100%, respectively, which were comparable to a previous study (72.9 % and 96.8% respectively). Furthermore, in the present study, the presence of posterior beam attenuation showed excellent (100%) sensitivity and NPV for detecting grade 3 HS, which was superior to that of the study by Kim Mimi et al. (82 % sensitivity for the same) (14).

In a previous study by Lee, J. Y. et al. and Ryan C. K. et al. with liver transplantation donors, the sensitivity of US was low in participants with HS less than or equal to 30% by histology. (16,17) Similarly, other subsequent studies by Dasarathy, S. et al. and Bril F. et al. demonstrated that sensitivity was low in those with HS less than or equal to 20% and 12.5% by histology, respectively (5,19). This was in contradiction to the results of the present study.

Simon Strauss et al., in another study, concluded that subjective visual judgement of fatty liver on US had significant inter-observer variability. The mean inter-observer and intra-observer agreement rates for the presence of fatty liver were 72% ($\kappa = 0.43$) and 76% ($\kappa = 0.54$). The severity of fatty liver showed an intra-observer agreement of 55% to 68% ($\kappa = 0.51$-0.63)(20). In the present study, we tried to improvise upon the objectivity of US assessment of HS. Altered liver echotexture was observed in 26.6% of subjects (16/60) showing normal MRI fat fraction, which suggests that the NPV to detect HS using altered liver echotexture was high, while the PPV was low. High sensitivity and NPV are essential for screening, given their benefit when excluding HS. Thus, the US can be a very efficient modality to rule out NAFLD in routine clinical practice.

There were several limitations to our study. Firstly, this study did not evaluate the operator dependency of US signs and longitudinal follow-up of hepatic steatosis. In addition, the small sample size was an important limitation, which was majorly reduced due to COVID-19 pandemic in the study duration. Multicentric longitudinal studies with a standardized technique, a much larger sample size of subjects, and a wider spectrum of the population across diverse ages, socioeconomic backgrounds, and ethnicity are needed for the corroboration of these results.

Conclusion

MRI PDFF provides an objective, non-invasive quantification of hepatic steatosis and has been recently accepted as a reference standard in diagnostic radiology, instead of liver biopsy for the diagnosis of NAFLD. However, the limited access and affordability pose a challenge to its use. The findings of the present study suggest that conventional ultrasound can be used as a screening tool for the diagnosis of NAFLD, particularly in resource-limited settings.

Conflicts of Interest

The authors report no conflicts of interest.

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