

# Quantification of Liver Fat by MRI-PDFF Imaging in Patients with Suspected Non-alcoholic Fatty Liver Disease and Its Correlation with Metabolic Syndrome, Liver Function Test and Ultrasonography

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**Background:** Magnetic resonance imaging (MRI)-estimated proton density fat fraction (PDFF) has emerged to be a promising tool in quantification of liver fat. Aim of this study was to quantify liver fat using MRI-PDFF in patients with suspected non-alcoholic fatty liver disease (NAFLD) and to correlate it with the presence of metabolic syndrome (MetS), ultrasonography (USG) and liver function test (LFT). **Methods:** We included 111 consecutive patients who were suspected to have NAFLD on the basis of clinical, laboratory or USG findings. A 3 Tesla Philips MRI machine was used with a software named “mDixon Quant” for quantification of the liver fat. **Results:** MRI-PDFF revealed hepatic steatosis grading as Grade 0 in 31 patients (28%), Grade I in 40 (36%), Grade II in 19 (17.1%) and Grade III in 21 patients (18.9%). MetS patients had higher proportion of advanced steatosis (Grades II and III) as compared to those without MetS ( $P < 0.001$ ). ALT (alanine transaminase) was found to be significantly elevated ( $>1.5$  times) in the patients with advanced steatosis as compared to patients with Grades I and 0 fatty liver on MRI-PDFF ( $P < 0.001$ ). The Kappa measure of agreement between USG and MRI-PDFF was found to be 0.2, which suggests a low level of agreement between the two tests. **Conclusion:** MetS patients have higher proportion of advanced steatosis (Grades II and III) at MRI-PDFF as compared to those without MetS. Patients with advanced steatosis at MRI-PDFF had higher proportion of abnormal LFTs as compared to those with Grades 0 and I hepatic steatosis. There was a dis-correlation between MRI-PDFF and USG in the evaluation of NAFLD. (J CLIN EXP HEPATOL xxxx;xxx:xxx)

Non-alcoholic fatty liver disease (NAFLD) has been an emerging major health problem and is now considered as a global epidemic. NAFLD is characterised by steatosis in  $>5\%$  of hepatocytes in patients who do not consume excessive alcohol ( $<20$  g/day for women and  $<30$  g/day for men).<sup>1</sup> It involves a spectrum of disease from simple steatosis and steatohepatitis to advanced fibrosis and cirrhosis.

The prevalence among the general population in India varies from 9% to 35%.<sup>2-5</sup> The prevalence not only differs as per the geographical distribution across the country but also depends on the modality chosen to assess the subjects. The various methods for non-invasive quantification of liver fat are ultrasonography (USG), controlled attenuation parameter (CAP), computed tomography hydrogen-1 magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI).<sup>6</sup> A recently modified MRI technique, magnetic resonance imaging-estimated proton density fat fraction (PDFF) has shown to have a strong correlation and equal efficacy with MRS.<sup>7</sup> Higher liver fat content measured by MRI-PDFF is associated with fibrosis progression and the mortality risk increases exponentially as fibrosis increases from Stage 0-4.<sup>8,9</sup>

EASL-EASD-EASO Clinical Practice Guidelines 2016 states that “Patients with IR and/or metabolic risk factors should undergo diagnostic procedures for the diagnosis of NAFLD, which relies on the demonstration of excessive liver fat”.<sup>1</sup> Approximately, 90.0% of NAFLD subjects have at least one feature and 33.0% have all features of the metabolic syndrome (MetS).<sup>10</sup>

The aim of this study was to quantify liver fat using MRI-PDFF in patients with suspected NAFLD and to

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**Abbreviations:** ALT: alanine transaminase; BMI: body mass index; CAP: controlled attenuation parameter; HDL: high-density lipoprotein; LFT: liver function test; MetS: metabolic syndrome; MRI: magnetic resonance imaging; MRS: magnetic resonance spectroscopy; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PDFF: proton density fat fraction; ROI: region of interest; ULN: upper limit of normal; USG: ultrasonography

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correlate it with the presence of MetS, USG and liver function test (LFT).

## MATERIALS AND METHODS

This was an observational prospective study from April 2019 to February 2020, in which 1200 patients were screened. Patients less than 12 years of age suspected for NAFLD on the basis of clinical, laboratory and USG findings as mentioned below were included in the study.

### Clinical:

- History of diabetes mellitus and/or hypertension
- Abdominal obesity

### Laboratory:

- Hypertriglyceridemia
- Low high-density lipoproteins (HDL)
- Raised transaminases

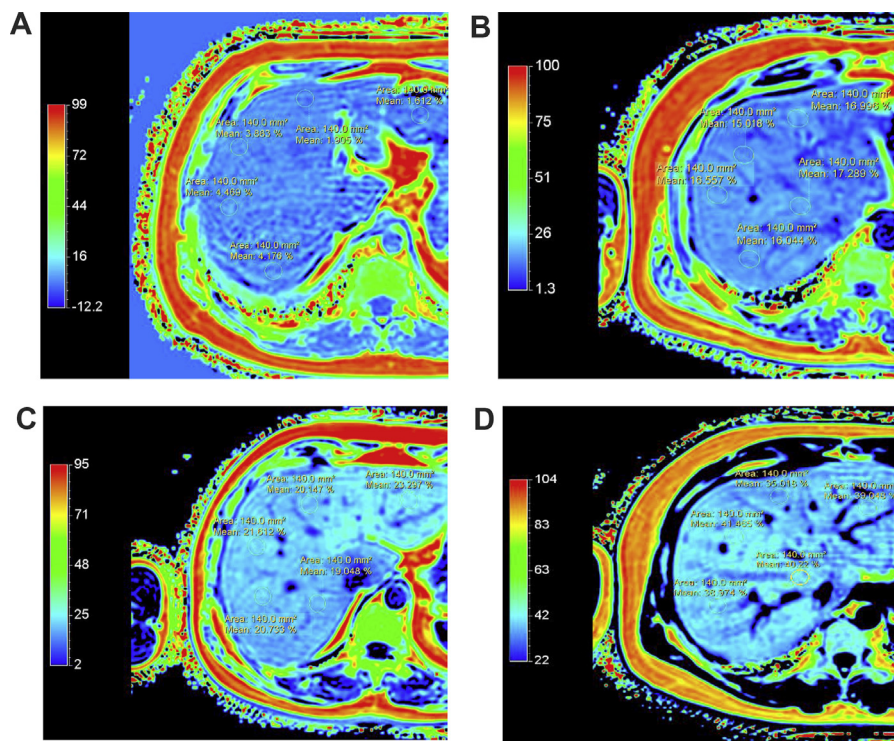
### Ultrasonography:

- Fatty liver

Patients with significant alcohol intake, autoimmune hepatitis, hepatitis B surface antigen or anti-HCV positive, diagnosed case of chronic liver disease, pregnant females, genetic or acquired disorders and major systemic illnesses were excluded from the study. Patients who were not able

to undergo MRI because of any contraindication/claustrophobia were also excluded from the study. In total, 111 consecutive patients who met the inclusion criteria were evaluated.

All patients underwent a standardized clinical evaluation in the form of history taking and anthropometric examination, which included age, sex, height, weight, body mass index (BMI) and waist circumference. Asian-Indian cut offs for BMI were used: normal: 18–22.9 kg/m<sup>2</sup>, overweight: 23–24.9 kg/m<sup>2</sup>, obese: >25 kg/m<sup>2</sup>.<sup>11</sup> Patients were evaluated for all the features of MetS, including diabetes mellitus, hypertension, HDL and waist circumference. Lower cut-offs for waist circumference were taken as recommended for Asia-Pacific/Indian population: ≥90 cm in men and ≥80 cm in women.<sup>12</sup> USG and LFT reports were noted, including aspartate transaminase (AST) and alanine transaminase (ALT). ALT >1.5 times the upper limit of normal (ULN) was considered as abnormal and has been used as an indirect marker for non-alcoholic steatohepatitis (NASH).<sup>13</sup> USG grading as mild, moderate and severe was considered as Grades I, II and III, respectively, for this study. When the echogenicity of the liver is just increased, it is considered as Grade I fatty liver. In Grade II fatty liver, the echogenic liver obscures the echogenic walls of portal vein branches and in Grade III, the echogenic liver obscures the diaphragmatic outline.<sup>14</sup>



**Figure 1** (A) MRI-PDFF showing normal liver (PDFF value < 6.5%). (B) MRI-PDFF showing Grade I fatty liver (PDFF value > 6.5 and < 17.4%). (C) MRI-PDFF showing Grade II fatty liver (PDFF value > 17.4 and < 22.1%). (D) MRI-PDFF showing Grade III fatty liver (PDFF value > 22.1%).

**Table 1 MRI-PDFF percentage and grades.**

|                       |          |            |
|-----------------------|----------|------------|
| Grade 0 (Figure 1A)   | Normal   | 0–6.4%     |
| Grade I (Figure 1B)   | Mild     | 6.5–17.4%  |
| Grade II (Figure 1C)  | Moderate | 17.5–22.1% |
| Grade III (Figure 1D) | Severe   | >22.1%     |

MRI-PDFF, magnetic resonance imaging–estimated proton density fat fraction.

## MRI-PDFF

A 3 Tesla Phillips MRI machine was used with a software named “mDixon Quant” for quantification of the liver fat. The MRI-PDFF technique uses a gradient echo sequence with low flip angle, which helps to reduce the T1 bias. Multiples echoes are acquired at echo times at which fat and water signals are nominally in-phase or out-of-phase compared to each other. The data then undergo correction of T2 effects and fat signal modelling, after which the fat content is calculated. The different steps in processing of the MRI-PDFF images help to increase the accuracy and robustness of fat quantification.

Nine circular regions of interest (ROIs) of same size (140 sq.mm) corresponding to the Couinaud liver segments (Segment I, II, III, IVA, IVB, V, VI, VII and VIII) on the MRI-PDFF maps in each subject were analysed.<sup>15</sup> Circular ROIs were placed avoiding large vessels or bile ducts. Recommended MRI-PDFF thresholds are shown in Table 1.<sup>15</sup>

## Statistical analysis

EPI info (version 7.2) was used to compile and analyse the data. The qualitative variables were indicated in terms of percentages, and the quantitative variables were both classified and indicated in terms of percentages or in terms of mean and standard deviations. Chi square or Fisher exact

test was used to analyse the difference between two proportions. The difference between two means were tested using ‘Student t’ test. To identify the different predictors, we used logistic regression analysis. Agreement between two tests was measured using Kappa statistics. All analysis was found to be two-tailed and the significance value was set at 0.05.

## RESULTS

In this prospective study, 111 patients were evaluated for features of MetS, LFT, USG and MRI-PDFF other than the baseline characteristics. Table 2 shows the patient’s characteristics. Of the 111 patients, 58 fulfilled the diagnostic criteria for MetS (ATP III criteria) and had at least three of five components, namely central obesity, diabetes mellitus, hypertension, low HDL and high triglycerides. The MRI-PDFF grading in patients who did not meet MetS criteria and in those who met at least three components are shown in Table 3. MetS patients had higher proportion of advanced steatosis (Grades II and III) as compared to those without MetS ( $P < 0.001$ ), as shown in Table 4.

Patients with advanced steatosis (Grades II and III) at MRI-PDFF had higher proportion of abnormal ALT levels as compared to those with Grades 0 and I hepatic steatosis ( $P < 0.001$ ), as shown in Table 5. ALT levels were elevated >1.5 times in 15 of 21 patients with Grade III hepatic steatosis on MRI-PDFF. It was further seen that patients with MetS and advanced steatosis (Grades II and III) at MRI-PDFF had higher proportion of abnormal ALT levels as compared to patients without MetS but with advanced steatosis ( $P = 0.0241$ ).

USG correlation with MRI-PDFF was very poor as in nine of the 22 patients with normal USG had either Grade I or II hepatic steatosis at MRI-PDFF. Of the 21 patients with Grade III hepatic steatosis on MRI-PDFF, only two

**Table 2 Baseline Characteristics.**

| Parameter                               | All Patients (n = 111) | Male (n = 73) | Female (n = 38) | P value |
|---|------------------------|---------------|-----------------|---------|
| Age                                     | 45.81 ± 11.45          | 48.66 ± 10.14 | 44.33 ± 11.87   | 0.0582  |
| BMI                                     | 28.25 ± 4.32           | 28.27 ± 4.19  | 28.42 ± 4.45    | 0.9701  |
| Abdominal obesity                       | 95 (85.5%)             | 57 (78%)      | 38 (100%)       | 0.0023  |
| Diabetes mellitus                       | 48 (43.2%)             | 28 (38.3%)    | 20 (18%)        | 0.0348  |
| Hypertension                            | 48 (43.2%)             | 29 (39.7%)    | 19 (50%)        | 0.0322  |
| Low HDL                                 | 60 (54%)               | 38 (52%)      | 22 (57.8%)      | 0.0441  |
| High triglycerides                      | 55 (49.5%)             | 41 (56.1%)    | 14 (36.8%)      | 0.0572  |
| Elevated serum ALT levels (>1.5 normal) | 46 (41.4%)             | 31 (42.4%)    | 15 (39.4%)      | 0.6723  |
| PDFF percentage                         | 14.03 ± 9.31           | 13.10         | 13.00           | 0.7655  |

BMI, body mass index; HDL, high density lipoprotein; ALT, alanine transaminase; PDFF, proton density fat fraction.



**Table 3 MRI-PDFF grading in Patients with without MetS.**

|                           | Patients with MetS (ATP III criteria) (n = 58) | Patients without MetS (n = 53) | P Value |
|---------------------------|--|--------------------------------|---------|
| <b>MRI-PDFF Grade 0</b>   | 5 (8.6%)                                       | 26 (49%)                       | <0.001  |
| <b>MRI-PDFF Grade I</b>   | 21 (36.2%)                                     | 19 (35.8%)                     | 0.965   |
| <b>MRI-PDFF Grade II</b>  | 16 (27.5%)                                     | 3 (5.6%)                       | <0.001  |
| <b>MRI-PDFF Grade III</b> | 16 (27.5%)                                     | 5 (9.4%)                       | 0.007   |

MetS, metabolic syndrome; MRI-PDFF, magnetic resonance imaging–estimated proton density fat fraction.

were diagnosed as severe (Grade III) on USG. In 44 patients, USG was reported as fatty liver and no grade of hepatic steatosis was mentioned. After excluding these 44 patients, the measure of agreement was calculated between the USG and MRI-PDFF grades (Table 6A). The Kappa measure of agreement was found to be 0.2, which suggested a minimal level of agreement between the two tests (Table 6B).

## DISCUSSION

NAFLD is considered as the hepatic component of MetS and approximately 90.0% of NAFLD subjects have at least one feature of MetS.<sup>10</sup> In this study, patients suspected for NAFLD underwent MRI-PDFF and the fat fraction in all segments of the liver was calculated in a breath-hold. Four MR-based diagnostic methods are currently available for liver fat quantification: (1) Dixon MRI technique; (2) modified Dixon type (mDixon); (3) single proton-MR spectroscopy; and 4) PDFF.<sup>16</sup> There are a number of studies that have reported excellent diagnostic performance of MRS to detect and quantify the hepatic steatosis.<sup>17–20</sup> MRS measures the chemical composition within liver tissue and displays multiple peaks at different locations according to the chemical composition of protons in their corresponding frequency domains. However, MRS samples only a portion of the liver and it is time consuming.<sup>21</sup> The spatial distribution of fat in the entire liver is non-uniform and difficult to understand by MRS as only a portion of the liver is being evaluated.<sup>22</sup>

MRI-PDFF is a recently innovated MRI technique with the advantage of obtaining complete data in a single breath-hold and allowing calculation of fat fraction in any segment of the liver.<sup>23</sup> Kang et al. compared the accuracy between MRI-PDFF and MRS-PDFF and the results showed that the former is more accurate compared against the latter.<sup>23</sup> Tang et al. validated the previously proposed

MRI-PDFF thresholds using histologic findings as a reference in an independent cohort of adults with NAFLD.<sup>15</sup> One of the shortcomings of MRI-PDFF is that the hepatic fibrosis can reduce the correlation between biopsy results and MRI-PDFF.<sup>19</sup>

We have shown that MetS patients have higher proportion of advanced steatosis (Grades II and III) on MRI-PDFF imaging as compared to those without MetS ( $P < 0.001$ ). These findings are consistent with the previous studies, which have shown that liver fat quantification measured by CAP values is closely associated with MetS and its components.<sup>24,25</sup> MRI-PDFF performed in adolescent girls and young women also showed that a low threshold on MRI-PDFF is predictive of MetS.<sup>26</sup> Abnormal LFTs have been used as a non-invasive marker of NASH. ALT >1.5 times the ULN identified the patients with NASH.<sup>13</sup> In our study, we found that patients with advanced steatosis had a significantly higher number of patients with abnormal LFTs ( $P < 0.001$ ). This suggests that higher the fatty liver grade on MRI-PDFF, higher are the chances of NASH, although it is not conclusive for NASH. Approximately, 82% of the patients with MetS and Grade III hepatic steatosis on MRI-PDFF had elevated ALT levels.

Abdominal USG has unanimously been the first-line examination to diagnose hepatic steatosis in patients with altered liver enzymes or suspected fatty liver disease, in daily clinical practice. USG, although a simple technique for evaluation of fatty liver, has several limitations, which are as follows: (1) subjective nature of the criteria used to differentiate fatty from normal liver and a lack of sonographic criteria for different degrees of steatosis; (2) sensitivity and specificity of B-mode sonography decreases as BMI increases; and (3) sensitivity is limited when there are few steatotic hepatocytes.<sup>27,28</sup> In this study, all the included patients underwent MRI-PDFF for accurate estimation of hepatic fat content. MRI-PDFF is not only

**Table 4 Advanced steatosis at MRI-PDFF in Patients with and without MetS.**

|  | Patients with MetS (ATP III criteria) (n = 58) | Patients without MetS (n = 53) | P Value |
|--|--|--------------------------------|---------|
| <b>MRI-PDFF Grades 0 &amp; I</b>                         | 26 (44.8%)                                     | 45 (85%)                       | <0.001  |
| <b>MRI-PDFF Grades II &amp; III (advanced steatosis)</b> | 32 (55.2%)                                     | 8 (15%)                        |         |

MetS, metabolic syndrome; MRI-PDFF, magnetic resonance imaging–estimated proton density fat fraction.

**Table 5 Advanced steatosis at MRI-PDFF and ALT correlation.**

|                           | MRI-PDFF Grades 0 & I (n = 71) | MRI-PDFF Grades II & III (advanced steatosis; n = 40) | P Value |
|---------------------------|--------------------------------|---|---------|
| Normal ALT                | 53 (74.6%)                     | 12 (30%)  | <0.001  |
| Elevated ALT (>1.5 times) | 18 (25.4%)                     | 28 (70%)  |         |

ALT, alanine transaminase; MRI-PDFF, magnetic resonance imaging–estimated proton density fat fraction.

**Table 6A USG (fatty liver grade) and MRI-PDFF grade crosstabulation.**

|                         |        | MRI-PDFF Grade |    |    |     | Total |
|-------------------------|--------|----------------|----|----|-----|-------|
|                         |        | Normal         | I  | II | III |       |
| USG (fatty liver grade) | Normal | 13             | 6  | 3  | 0   | 22    |
|                         | I      | 5              | 10 | 3  | 2   | 20    |
|                         | II     | 4              | 6  | 4  | 8   | 22    |
|                         | III    | 0              | 0  | 2  | 1   | 3     |
| Total                   |        | 22             | 22 | 12 | 11  | 67    |

**Table 6B USG and MRI-PDFF symmetric measures.**

|                      |       | Value | Asymptotic Standard Error <sup>a</sup> | Approx. T <sup>b</sup> | Approx. Sig. |
|----------------------|-------|-------|--|------------------------|--------------|
| Measure of agreement | Kappa | 0.200 | 0.078                                  | 2.797                  | 0.005        |
| No. of valid cases   |       | 67    |  |                        |              |

USG, ultrasonography; MRI-PDFF, magnetic resonance imaging–estimated proton density fat fraction.

<sup>a</sup>Not assuming the null hypothesis.

<sup>b</sup>Using the asymptotic standard error assuming the null hypothesis.

accurate in quantifying hepatic fat content, but also has a high degree of precision and reproducibility, as well as greater reliability than histologic assessments.<sup>29</sup> We feel that as MRI-PDFF will be widely available, it will be preferred over USG. In this study, the Kappa measure of agreement between USG and MRI-PDFF was found to be 0.2, which suggests a low level of agreement between the two tests.

However, there are certain limitations of this study as liver biopsy was not conducted and CAP score at fibroscan was not evaluated. USG was read by only one radiologist. Use of MRI-PDFF in patients with more advanced liver disease is limited by the severity of fibrosis present, which is a drawback of this test.<sup>19,30</sup> Patients with claustrophobia will not be able to undergo the test. It can also be argued that MRI-PDFF only evaluates the fat content of liver, whereas it is steatohepatitis and fibrosis, which are important prognosticator of NASH. However, as shown by Ajmera et al and Dulai et al, higher amount of liver fat as measured by MRI-PDFF is associated with progression of fibrosis.<sup>8,9</sup>

In conclusion, MetS patients have higher proportion of advanced steatosis (Grades II and III) at MRI-PDFF as compared to those without MetS. Patients with advanced steatosis at MRI-PDFF had higher proportion

of abnormal LFTs as compared to those with Grades 0 and I hepatic steatosis. There was a dis-correlation between MRI-PDFF and USG in the evaluation of NAFLD.

## AUTHOR'S CONTRIBUTION

Gajanan Rodge: Data curation, Writing- Original draft preparation, Investigation, Software, Mahesh Goenka: Conceptualization, Methodology, Supervision, Software, Usha Goenka: Visualization, Investigation, Supervision, Software, Shivaraj Afzalpurkar: Reviewing and Editing, Bhavik Shah: Reviewing and Editing.

## CONFLICTS OF INTEREST

The authors have none to declare.

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