Research Article

Assessment of Segmental Hepatic Fat Distribution using Magnetic Resonance Proton Density Fat Fraction MR-PDFF in Non-alcoholic Fatty Liver Disease (NAFLD)

Muhammad Salman Rafique[*,1], Ayesha Ayub[2], Ahmad Karim Malik[2], Tahir Malik[1], Sana Kundi[1], Abdullah Saeed[1]

[1]*Department of Radiology, Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan.*

[2]*Department of Gastroenterology, Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan.*

Abstract: Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is a significant healthcare challenge. MR proton density fat fraction (MR-PDFF) is a quantitative imaging parameter that allows a precise estimation of hepatic steatosis. Determination of segmental and lobar fat distribution is also important since underestimation or overestimation may lead to hurdles in patient management and may also alter outcomes during liver donor assessment for living donor liver transplant.

Objective: To determine the heterogeneity of hepatic fat distribution across different liver segments and both lobes in patients with non-alcoholic fatty liver disease (NAFLD).

Materials and Methods: This cross-sectional descriptive study included 35 patients of NAFLD. MR-PDFF sequence was performed, two regions of interest (ROI) were drawn at the periphery of each hepatic segment and their mean was taken. We calculated mean values, ranges, and standard deviations for individual segments, both lobes and the entire liver. Pearson's correlation was used to assess the relation between MR-PDFF and MR-PDFF variability. Paired sample t-test was utilized to compare the means of the right and the left lobe of the liver.

Results: The fat fraction in segment I was the lowest and in segment VII the highest. The right and left lobes showed a significant difference in fat fraction with values of 14% and 11.4% respectively (paired sample t-test, $p<0.005$). The left lobe showed a greater MR-PDFF variability than the right lobe (1.9 vs 1.6%).

Conclusion: In patients with NAFLD, segments VII and VIII show the greatest while segments I and IV show the least fat infiltration. Hepatic fat preferentially gets deposited more in the right lobe of the liver.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Magnetic resonance imaging (MRI), Proton density fat fraction, Hepatic fat, Variability of hepatic fat distribution, Healthcare.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is a significant healthcare challenge in modern Hepatology with a 15% prevalence in Pakistan [1, 2]. It is defined as an abnormal accumulation of triglycerides in the liver, histologically beyond 5% [3, 4]. The disease can only be labeled as NAFLD if other causes of liver disease and an intake ≥30 and 20 g of alcohol per day for men and women respectively have been excluded [5]. NAFLD presents as a continuum from non-alcoholic steatohepatitis (NASH) to liver cirrhosis (NAFLD-related liver cirrhosis). A recent study concluded an increased risk for hepatocellular carcinoma in patients with NAFLD, with a hazard ratio (HR) of 1.22 [6].

Ultrasound is the most readily available radiological modality, but its ability to estimate hepatic steatosis of less than 20% is limited and is only qualitative [3].

Computed tomography (CT) poses the risk of exposure to ionizing radiation, and quantitative analysis is not very dependable since different scanning parameters differ amongst patients. Injection of IV contrast and deposition of hepatic iron or other substances also influence the CT attenuation measurements [7].

Liver biopsy is conventionally believed to be the gold standard to diagnose and quantify liver fat and can also differentiate between NAFLD and NASH [8]. However, it can result in complications including hemorrhage and rarely mortality. Multiple passes in one sitting may be necessary to avoid under sampling since in a single biopsy only about 1/50,000 of the liver is sampled [9]. All these limitations render follow-up liver biopsies difficult for disease monitoring [1, 2].

MRI is emerging as a valuable non-invasive instrument for hepatic fat quantification. Magnetic resonance spectroscopy (MRS) has shown promise for hepatic fat assessment and is reproducible but is unable to assess the entire liver [10]. On the other hand, MR proton density fat fraction (MR-PDFF) is a quantitative imaging parameter that allows a precise and reproducible estimation of hepatic steatosis while sampling the

*Address correspondence to this author at the Department of Radiology, Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan. Email: msalmanrafique@gmail.com

entire liver [11].

Determination of segmental and lobar fat distribution is also important. A recent study revealed a maximum negative predictive value with a single biopsy to be 0.74. It also showed a 41% discordance rate for 1 or more stages [12]. Another research employing MRS concluded that for the assessment of fat, the coefficient of variation (CV) was 14.5% within the liver [10]. Thus underestimation or overestimation of liver fat may lead to hurdles in patient management as well as disease monitoring. Such errors may also alter outcomes during liver donor assessment for living donor liver transplant.

To our knowledge, only one study has been performed to demonstrate the segmental distribution of liver fat using MR-PDFF, and no such study has been conducted in a Pakistani population [13]. Furthermore, the mentioned study used a 3T MRI system whereas the current study was performed on a 1.5T MRI unit to determine its generalizability across different magnetic field strengths.

Therefore, this study aims to determine segmental and lobar liver fat distribution while explaining the possible mechanisms underlying the heterogenous distribution of fat in NAFLD patients.

MATERIALS AND METHODS

This cross-sectional descriptive study was conducted at Pakistan Kidney and Liver Institute and Research Center, Lahore after approval from the institutional review board. The duration of the study was 1 month (January 24, 2023 to February 23, 2023). Sample size of 35 was calculated using WHO sample size calculator. A confidence interval of 95%, standard deviation of 9 and precision for mean (L) of 3 was used [14]. We included 35 patients according to the WHO sample size calculator (95% confidence interval and precision for mean of 1). We excluded all patients who had diseases other than NAFLD and patients who were unable to lie in MRI due to claustrophobia or other conditions. The included patients were clinically diagnosed as having NAFLD and were initially evaluated with ultrasound to detect a fatty liver. A complementary MR-PDFF sequence was then performed on these patients after obtaining informed consent.

MR Technique

All patients were imaged supine with a 16-channel surface coil which was centered upon the liver, on a 1.5T MRI (Signa Voyager; GE Medical Systems, Milwaukee, WI, USA). For MR-PDFF acquisition, multi-echo spoiled gradient-recalled-echo (SGRE) MR technique was employed. Images of the entire liver were acquired in a single breath-hold, axial plane. A low flip angle (7-10°) with a repetition time ≥12 ms (125–270 ms, default 200 ms) were used. The slice-thickness was 8 mm, with a 110-125 kHz receiver bandwidth.

Image Analysis

As shown in Fig. (**1**), two regions of interest (ROI) were drawn at the periphery of each of the hepatic Couinaud's segments (segment I, II, III, IV, V, VI, VII, VIII) to avoid the blood vessels and bile ducts, and their mean taken as the fat fraction for that segment. The area of each ROI was 200-400 mm^2. To remove bias, two radiologists having a greater than 5-year experience in hepatobiliary imaging calculated the MR-PDFF blinded to each other's findings. A mean of both the radiologists' values was taken as the final reading for a particular segment. Then across all 35 patients, we calculated mean values, ranges, and standard deviations for individual segments, both lobes and the entire liver.

STATISTICAL ANAYLSIS

Data was analyzed using SPSS version 20. Pearson's correlation was used to assess the relation between MR-PDFF and MR-PDFF variability (taken as the standard deviation for a segment/lobe/liver). Paired sample t-test was utilized to compare the means of the right and the left lobe of the liver.

RESULTS

There were 21 male and 14 female patients with an age range of 22-56 years (mean 39.2 years).

Table 1. Segmental, Lobar, and Entire Liver Mean Fat Fractions, Ranges, and Variability.

	Fat Fraction % (MR-PDFF)		**Variability**	
	Mean	Range	Mean	Range
Entire Liver	12.7	6-35.1	2.3	1.2-4.6
Right lobe	14.0	6.5-36.6	1.6	0.5-4.4
Left lobe	11.4	4.8-33.5	1.9	0.5-4.8
Segment 1	10.3	2.8-31.5	1.4	1.9-3.1
Segment 2	11.7	5.4-35	2.8	1.8-3.7
Segment 3	12.0	4.2-36.5	2.9	2.1-3.8
Segment 4	11.4	3.6-30.9	2.6	2.2-3.1
Segment 5	13.7	7.1-33.9	1.3	1.1-1.5
Segment 6	12.8	4.7-35.1	1.9	1.4-2.4
Segment 7	15.0	7.2-38.7	2.2	1.3-3.0
Segment 8	14.5	6.7-38.8	1.4	1.1-1.7

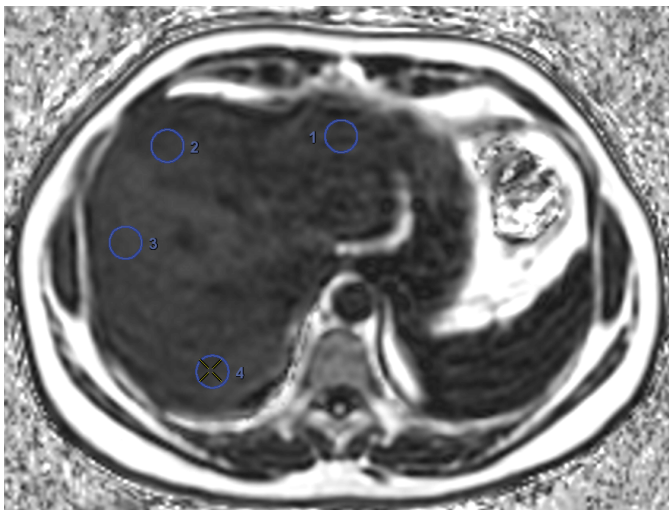

Fig. (1). ROIs for Fat Fraction Calculation Drawn over Different Liver Segments on the Workstation.

Segments

As shown in Table **1**, the fat fraction in segment I was the lowest (10.3%) whereas the fat fraction in segment 7 was the highest (15%). Segments IV and VIII had the second lowest and second highest fat fractions respectively.

Lobes

The right and left lobes showed a significant difference in fat fraction with values of 14% and 11.4% respectively (paired sample t-test, $p<0.005$). The left lobe showed a greater MR-PDFF variability than the right lobe (1.9% vs 1.6%). In all patients, the right lobe had a higher fat fraction than the left lobe, with a mean difference of 2.6% and a range of 0.4% to 6.6%.

Whole Liver

The whole liver fat content ranged from 6% to 35.1% with a mean of 12.7%. The variability ranged from 1.2% to 4.6% with a mean of 2.3%. The MR-PDFF variability showed a very weak positive correlation (for entire liver r=0.09, for right lobe r=0.27, for left lobe r=0.20). Age and gender did not influence the fat fraction.

DISCUSSION

Our primary objective was to determine the differences in hepatic mean segmental fat distribution and variability, in patients with NAFLD.

There are multiple reasons for considering MR-PDFF as a sequence of choice. Its advantages over MRS include the ability to assess fat fraction values over the entire liver unlike MRS which gives values only from a single voxel, a shorter image acquisition time, rapid and more convenient image post-processing [15]. On the other hand, liver biopsy despite being considered the gold standard for haptic fat quantification has the downside of being invasive, carrying multiple complications, and inability to sample the entire liver [16]. Finally, the American Association for Study of Liver Disease (AASLD) has also advocated MR-PDFF as a good non-invasive tool for quantifying hepatic fat content [17].

Our study showed significant differences in fat distribution between various hepatic segments. Segment I was the least and segment VII was the fattiest (mean fat fractions of 10.3% and 15%). These findings are in partial agreement with the study by Bonekamp *et al*. who determined segments I and VII as having the second lowest and second highest fat contents respectively. That study concluded that segment II had the lowest fat and segment VIII had the highest [13]. The highest and lowest variability was observed in segments III and V respectively which differs from the aforementioned research.

The lobar differences were also significant, the mean fat percentage in the right lobe being greater than that of the left lobe (values of 14% and 11.4% respectively), in keeping with Bonekamp *et al*. and Larson *et al*. [18]. The mean difference between the right and left lobe hepatic fat content was 2.63%. This was even more significant than revealed by Bonekamp *et al*. (0.58% mean difference between right and left lobes). There was a very weak positive correlation between the mean liver fat and liver fat variability (r= 0.09). This was in agreement with Hines *et al*. who also could not ascertain any relationship between mean hepatic fat and mean hepatic fat variability [14]. However, it disagrees with the study by Bonekamp *et al*. who showed a positive correlation between mean MR-PDFF and MR-PDFF variability (r=0.34).

For the entire liver fat content, our mean was 12.7% with a range of 6% to 35.1%. Thus, this also corresponds to a study by Di Martino *et al*. in which MRS and MR-PDFF were used for hepatic fat assessment [15]. They declared a value of 5% by MRS and 3.5% by MR-PDFF as safe cut-off values for hepatic steatosis.

Although the heterogeneity of hepatic fat distribution cannot be fully explained, some probable causes have been proposed in the past. One explanation is that the splenic blood preferentially flows into the left lobe of the liver, while the blood from the superior mesenteric vein that drains visceral fat predominantly perfuses the right lobe [19]. Another study using Doppler ultrasound to study postprandial changes in portal circulation found that blood flow to the right lobe increased more significantly than the left lobe [20]. While these are only theoretical explanations, they do provide insight into potential underlying mechanisms behind the observed heterogeneity of hepatic fat distribution.

LIMITATIONS AND RECOMMENDATIONS

Our study has a few limitations. Firstly, the sample only represents patients presenting to one center of one city in Pakistan and therefore lacks representation from different regions of the country. Secondly, we did not divide NAFLD patients into groups with low, intermediate, and high hepatic fat content,

which could have provided further in-depth analysis of hepatic fat distribution. Thirdly, our sample size was small and further studies with larger sample sizes may be needed for further validation of our findings.

Our findings highlight the need for future studies on larger and more diverse samples where hepatic blood flow and metabolic pathways are studied together to provide a more elaborate delineation of the mechanisms underlying differential hepatic fat distribution. Such studies can provide more comprehensive insights into the phenomenon and contribute to the development of clinical interventions to address this healthcare challenge.

CONCLUSION

In patients with NAFLD, segments VII and VIII show the greatest while segments I and IV show the least fat infiltration. Hepatic fat preferentially gets deposited more in the right lobe of the liver, with the mean MR-PDFF correlating strongly with the MR-PDFF variability.

AUTHORS' CONTRIBUTION

- **Muhammad Salman Rafique**: Conception of the research idea, Presentation in IRB, Writing of discussion.
- **Ayesha Ayub**: Data collection and Compilation in SPSS.
- **Ahmad Karim Malik**: Data analysis and Interpretation.
- **Tahir Malik**: Writing of introduction and Literature review.
- **Sana Kundi**: Literature review and Contribution to the intellectual content.
- **Abdullah Saeed**: Final revision of the draft and Critical analysis.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDEMENTS

My co-authors and I acknowledge the swift and efficient response from Ms. Maria Baig (In-charge Publications and Editorial Manager Publications, National Journal of Health Sciences). We are grateful to her for regular communications and expert advice.

REFERENCES

[1] Bhat V, Velandai S, Belliappa V, Illayraja J, Halli KG, Gopalakrishnan G. Quantification of liver fat with mDIXON magnetic resonance imaging, comparison with the computed tomography and the biopsy. J Clin Diagn Res 2017; 11(7): TC06-TC10.

[2] Abbas Z, Zaheer R. Non-alcoholic fatty liver disease: A real threat in Pakistan. J Pak Med Assoc 2020; 70(12(B)): 2437-40.

[3] Lee DH. Imaging evaluation of non-alcoholic fatty liver disease: Focused on quantification. Clin Mol Hepatol 2017; 23(4): 290-301.

[4] Zhang Y, Wang C, Duanmu Y, *et al*. Comparison of CT and magnetic resonance mDIXON-Quant sequence in the diagnosis of mild hepatic steatosis. Br J Radiol 2018; 91(1091): 20170587.

[5] Lv S, Jiang S, Liu S, Dong Q, Xin Y, Xuan S. Noninvasive quantitative detection methods of liver fat content in nonalcoholic fatty liver disease. J Clin Transl Hepatol 2018; 6(2): 217-21.

[6] Björkström K, Widman L, Hagström H. Risk of hepatic and extrahepatic cancer in NAFLD: A population-based cohort study. Liver Int 2022; 42(4): 820-8.

[7] Kramer H, Pickhardt PJ, Kliewer MA, *et al*. Accuracy of liver fat quantification with advanced CT, MRI, and ultrasound techniques: Prospective comparison with MR spectroscopy. Am J Roentgenol 2017; 208(1): 92-100.

[8] Iftikhar R, Kamran SM, Sher F, Wahla MS. Prevalence of non alcoholic fatty liver disease in patients with metabolic syndrome. PAFMJ 2015; 65(5): 616-9.

[9] Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014; 20(2): 475-85.

[10] van Werven JR, Hoogduin JM, Nederveen AJ, *et al*. Reproducibility of 3.0 Tesla magnetic resonance spectroscopy for measuring hepatic fat content. J Magn Reson Imaging 2009; 30(2): 444-8.

[11] Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology 2018; 68(2): 763-72.

[12] Ratziu V, Charlotte F, Heurtier A, *et al*. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005; 128(7): 1898-906.

[13] Bonekamp S, Tang A, Mashhood A, *et al*. Spatial distribution of MRI-Determined hepatic proton density fat fraction in adults with nonalcoholic fatty liver disease. J Magn Reson Imaging 2014; 39(6): 1525-32.

[14] Hines CD, Frydrychowicz A, Hamilton G, *et al*. T(1) independent, T(2) (*) corrected chemical shift based fat-water separation with multi-peak fat spectral modeling is an accurate and precise measure of hepatic steatosis. J Magn Reson Imaging 2011; 33(4): 873-81.

[15] Di Martino M, Pacifico L, Bezzi M, *et al*. Comparison of magnetic resonance spectroscopy, proton density fat fraction and histological analysis in the quantification of liver steatosis in children and adolescents. World J Gastroenterol 2016; 22(39): 8812-9.

[16] Ferraioli G, Calcaterra V, Lissandrin R, *et al*. Noninvasive assessment of liver steatosis in children: the clinical value of controlled

attenuation parameter. BMC Gastroenterol 2017; 17(1): 61.

[17] Chalasani N, Younossi Z, Lavine JE, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the study of liver diseases. Hepatology 2018; 67(1): 328-57.

[18] Larson SP, Bowers SP, Palekar NA, Ward JA, Pulcini JP, Harrison SA. Histopathologic variability between the right and left lobes of the liver in morbidly obese patients undergoing Roux-en-Y bypass. Clin Gastroenterol Hepatol 2007; 5(11): 1329-32.

[19] Serege H. Contribution a l'etude de la circulation du sang porte dans le foie et des localizations lobaires hepatiques. J Med Bordeaux 1901; 31: 271–5.

[20] Dauzat M, Lafortune M, Patriquin H, *et al*. Meal induced changes in hepatic and splanchnic circulation: A noninvasive Doppler study in normal humans. Eur J Appl Physiol Occup Physiol 1994; 68: 373-80.

Received: April 10, 2023 Revised: May 24, 2023 Accepted: May 26, 2023