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Role of MR as Non-Invasive Procedure in Assessment of Fatty Liver Infiltration in Potential Liver Donor Versus Biopsy

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Abstract

Background: *Significant hepatic steatosis can impact surgical results in the donor. Liver biopsy is the gold standard for hepatic steatosis diagnosis and assessment. Liver biopsy is not useful for screening or monitoring hepatic steatosis in living liver donors. MR spectroscopy and the proton density fat fraction (FF) approach have shown encouraging results in assessing hepatic steatosis.* ***Aim and Objectives:*** *is to correlate between the MRI-PDFF techniques as a non-invasive technique in pre-operative assessment of quantification of liver fat in comparison to the liver biopsy.* ***Patients and Methods:*** *This prospective control study was conducted at the National Hepatology and tropical medicine research institute including 42adult potential hepatic donors. The duration of the study ranged from 6-12 months.* ***Results:*** *regarding median fat percent for selected patients (n=42) We found that correlation between both reading was significant strong positive one (spearman correlation =0.960, p<0.001). despite the recorded liver fat percent through MRI PDFF was higher in males when compared to females, this was statistically insignificant. MRI PDFF true positive was 86.8% with false positive of 50% and true negative was 50% with false negative of 13.2%.* ***Conclusion:*** *Noninvasive MR hepatic PDFF technique with IDEAL sequence is a precise reliable technique for quantitative assessment of hepatic steatosis with high sensitivity, specificity and accuracy of It is recommended to be a part of preoperative liver evaluation in living donors and selectively performing liver biopsy in donor candidates diagnosed to have substantial steatosis based on MR PDFF findings.*

Keywords: *MRI, MRI-PDFF, Fatty Liver Infiltration, Biopsy.*

1. Introduction

Since 1963, when the first human liver transplantation (LT) was performed by Thomas Starzl, the world has witnessed 50 years of development in surgical techniques, immunosuppression, organ allocation, donor selection, and the indications and contraindications for LT. This has led to the mainstream, well-established procedure that has saved innumerable lives worldwide. Today, there are hundreds of liver transplant centres in over 80 countries. This review aims to describe the main aspects of LT regarding the progressive changes that have occurred over the years. We herein review historical aspects since the first experimental studies and the first attempts at human transplantation. We also provide an overview of immunosuppressive agents and their potential side effects, the evolution of the indications and contraindications of LT, the evolution of survival according to different time periods, and the evolution of methods of organ allocation **(1)**.

A living-donor liver transplant is a surgical procedure in which a portion of the liver from a healthy living person is removed and placed into someone whose liver is no longer working properly. The donor's remaining liver regrows and returns to its normal size, volume and capacity within a couple of months after the surgery. At the same time, the transplanted liver portion grows and restores normal liver function in the recipient **(2)**.

MRI are key imaging modalities that allow for a noninvasive and comprehensive evaluation of potential living liver donors, including the assessment of liver volumetric, biliary and hepatic vascular anatomy, and liver parenchyma. Awareness of the various anatomic variations and pathologic states, and the impact of such findings on donor and surgical planning is essential for the radiologists to generate a meaningful report and to become an integral part of the LDLT team **(3)**.

Hepatic steatosis in living donors for liver transplantation causes morbidity of both donor and recipient. This study aims at evaluating magnetic resonance proton density fat fraction technique (MR PDFF) in quantitative evaluation of living donor's hepatic steatosis compared to histopathology **(4)**.

The recently developed magnetic resonance imaging (MRI) proton density fat fraction (PDFF) allows measurement of the fat in all segments of hepatic tissue. However, it is time consuming and inconvenient to measure each segment repeatedly. Moreover, volume of each segment also should be adjusted with arithmetic mean of the selected segments when total amount of liver fat is estimated. Therefore, we try to develop a clinically-relevant and applicable method of estimating hepatic fat in PDFF image **(5)**. The aim of this work was to correlate between the MRI-PDFF techniques as a non-invasive technique in pre-operative assessment of quantification of liver fat in comparison to the liver biopsy

2. Materials and Methods

This prospective control study was conducted at the National Hepatology and tropical medicine research institute including 42adult potential hepatic donors. The duration of the study ranged from 6-12 months.

A total of 42 potential donors were eligible to participate in the study, participants (30 patients) were males, while (11 patients) were females. They were referred to the radiology department at National Hepatology and Tropical Medicine Institute (NHTMI) by the liver transplantation unit in the institute for pre-operative assessment. Over 2000 living donor's liver transplants were performed since the establishment of the NHTMI program in 2013 until the current time.

Inclusion criteria: All potential candidates for donation in living donor liver transplantation after passing step 1 assessment for labs, Adult more than 18 years old. And less than 45 years old and Both sexes.

1st step assessment for donor preparation: Blood group +ve RH factor, HCVab , HBs Ag , HBC Ag (Total), ALT , AST , ALKALIEN PHOSPHATASE , GGT, Total protein , Albumin, Renal Profile (urea , creatinin , uric acid , Na , K , Ca (total and ionized), CBC , PT , PC , PTT , INR, CRP , antibelharzial AB , cholesterol , triglycerides , LDL , HDL, ANA, Pelviabdominal US, Doppler US (portal vein , hepatic artery and hepatic veins), MRCP, Triphasic CT for (CT volumetry for potential donor) and Liver biobsy for histopathiology**.**

Exclusion criteria: Younger than 18 years old and more than 45 years old, Severe psychiatric disease, Claustrophobia, BMI >31 and +ve HBsAg, HVC Ab.

The selected donors were subjected to the full radiological survey of MRI Techniques for Evaluation of Hepatic Steatosis, MRI-PDFF Experimental newly introduced at the radiology department of NHTMI and Liver biopsy.

MRI Techniques for Evaluation of Hepatic Steatosis: The MRI techniques used for noninvasive evaluation of hepatic steatosis separate liver signal into its fat and water signal components first, and then calculate the hepatic fat fraction.

MRI PDFF: Fat quantification**,** Sequences, m Dixon – Quant (breath hold)**,** water only**,** fat only, T2W star, Fat frcation, Number of echoes: 6 echoes are enough for FF**,** mDixon – Quant post processing on con sole, Color overlay (blue for ped) and Every 20 intensity mean value = fat fraction.

Liver biopsy: All 42 living potential liver donors underwent liver biobsy in the) in the radiology department of the National Hepatology and tropical medicine research institute.

Laboratory parameters for a safe procedure: Complete (full) blood count and coagulation profile.

Statistical analysis

We analyzed the data using spss (statistical package of social sciences) version 24 software of windows for analyzing the data. Numerical data was described in terms of mean and standard deviations if normally distributed and median and interquartile range if non-normally distributed. Kolmogrov-Semornov test was used to test the normality of distribution of numerical variables. Pearson correlation was used to test the association between numerical variable if parametric while spearman was used if non-parametric variables were found. P value less than 0.05 was considered statistically significant.

3. Results and Discussion

Table 1: Showing the median fat percent for selected patients (n=42)

	Median (Q1 – Q3)	**Minimum**	**Maximum**	**Spearman correlation**	**P value**
Biopsy	3 (2 – 4)	1	10	0.960*	<0.001*
PDFF	5 (4 – 6)	2	15		

*** Spearman correlation**

On analyzing the fat percent, we found that the recorded fat percent ranges between 1 to 10% with a median of 3 (2 – 4). On the other hand, the recorded fat percent using MRI ranged between 2% and 15% with a median of 5 (4 – 6). We found that correlation between both reading was significant strong positive one (spearman correlation =0.960, p<0.001)

Table 2: showing the correlation between (age, BMI, height & weight) and recorded fat percent through biopsy

	Correlation coefficient	P value
Age	0.075	0.639
	Pearson correlation	
BMI	0.217	0.179
	Pearson correlation	
height	0.300	0.054 (insignificant)
	Pearson correlation	
Weight	0.267	0.088 (insignificant)
	Spearman correlation	

There was an insignificantly positive correlation between age of the participants and fat percent when recorded during biopsy examination (Pearson correlation =0.075, p=0.639). fat percent recorded through biopsy was insignificantly correlated with BMI of participants (p=0.179). there was an insignificantly positive correlation between patients' height and recorded fat percent through biopsy examination (Pearson correlation = 0.300, p=0.054). the correlation between recorded fat percent through biopsy examination and patients' weight was an insignificantly positive one (Pearson correlation = 0.267, p=0.088).

Table 3: Showing the difference between males and females concerning fat percent recorded by PDFF

	Male	Female	P value
Fat percent	5 (4 – 6)	4 (3 – 5)	0.804

Mann Whitney U test

We found that despite the recorded liver fat percent through MRI PDFF was higher in males when compared to females, this was statistically insignificant (p=0.804)

Table 4: Showing the correlation between (age, BMI, Height & weight) and recorded fat percent through PDFF

	Correlation coefficient	P value
Age	0.013	0.933
	Pearson correlation	
BMI	0.247	0.124
	Pearson correlation	
Height	0.340	0.027 (significant)
	Pearson correlation	
Weight	0.312	0.044 (significant)
	Spearman correlation	

There was an insignificantly positive correlation between age of the participants and fat percent when recorded through MRI PDFF (Pearson correlation =0.013, p=0.933). there was an insignificantly positive correlation between fat percent recorded through MRI PDFF and their BMI; (Pearson correlation = 0.247; p=0.124). the correlation between recorded fat percent through MRI and patients' height was a significant positive one (Pearson correlation = 0.340, p=0.027). the correlation between recorded fat percent through MRI and patients' weight was a significant positive one (Pearson correlation = 0.312, p=0.044)

Table 5: Showing the Agreement between biopsy and PDFF in detecting of fat percentage among participants

MRI PDFF	Biopsy		Total	P
	≤ 5%	> 5%		
≤ 5%	33 (86.8%)	2 (50%)	35 (83.3%)	
> 5%	5 (13.2%)	2 (50%)	7 (16.7%)	.060
Total	38	4	42	

We found that MRI PDFF true positive was 86.8% with false positive of 50% and true negative was 50% with false negative of 13.2%.

Table 6: Showing the diagnostic accuracy of PDFF in prediction of fat percentage among participants.

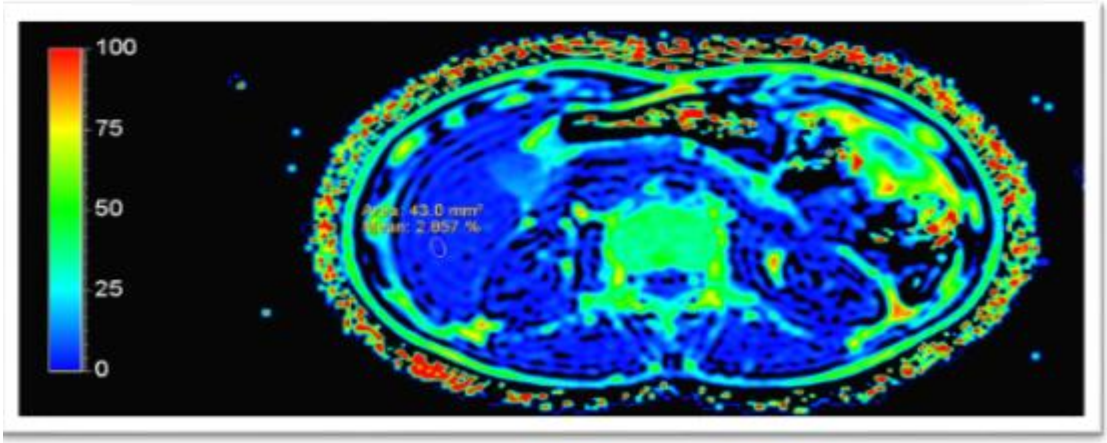
Statistic	**Value**	**95% CI**
AUC	0.684	0.523 - 0.819
Sensitivity	86.84%	71.91% - 95.59%
Specificity	50%	6.76% - 93.24%
Positive Predictive Value	94.29%	86.01% - 97.79%
Negative Predictive Value	28.57%	10.05% - 58.89%
Accuracy	83.33%	68.64% - 93.03%

We found that MRI PDFF is a good tool for detection of fat percentage among patients (AUC=0.684, 95% CI: 0.523 – 0.819) with a sensitivity of 86.8% and specificity of 50% with accuracy of 83.3%.

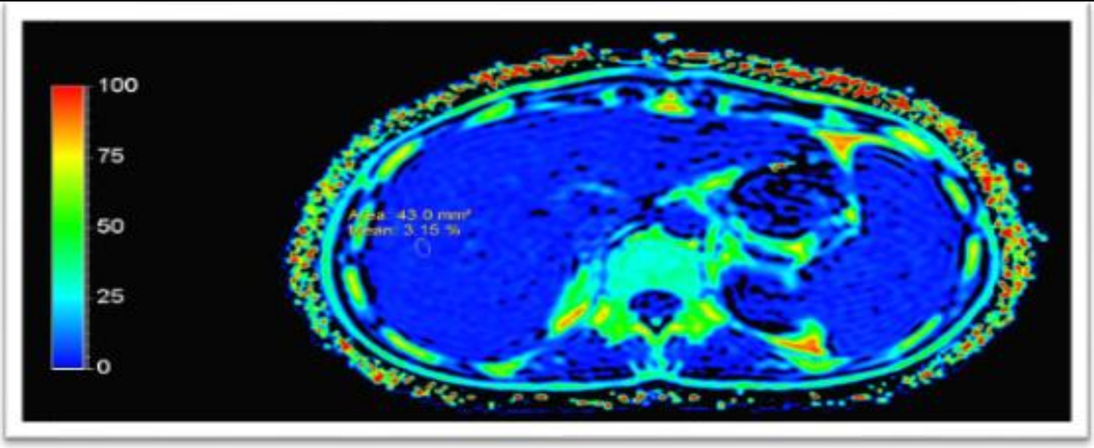
Case Presentation

Case 1)

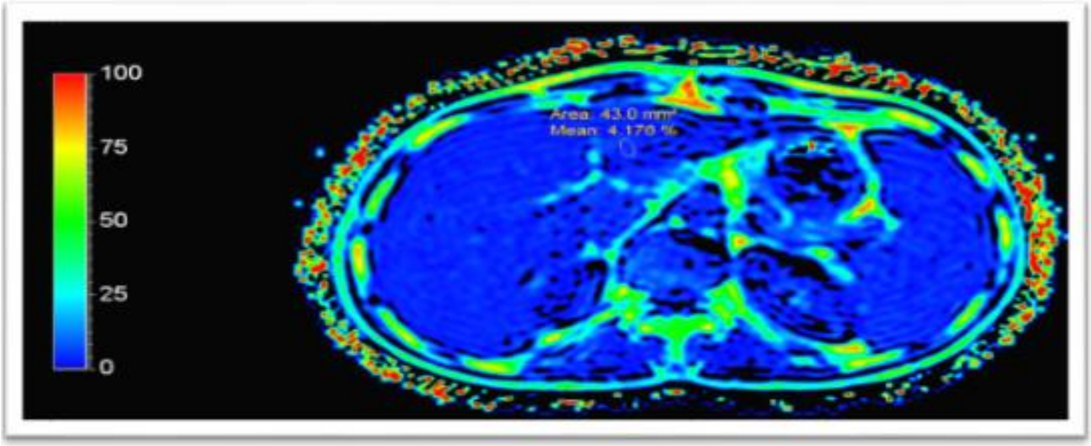
Donor Data: Age: 28 y Sex: Male Weight: 70 kg Height: 183 cms Body Mass Index: 20.1 Clinical Status: passed 1st step of investigations and clinically fit.


100
75
50
25
0
Area: 43.0 mm²
Mean: 2.857 %

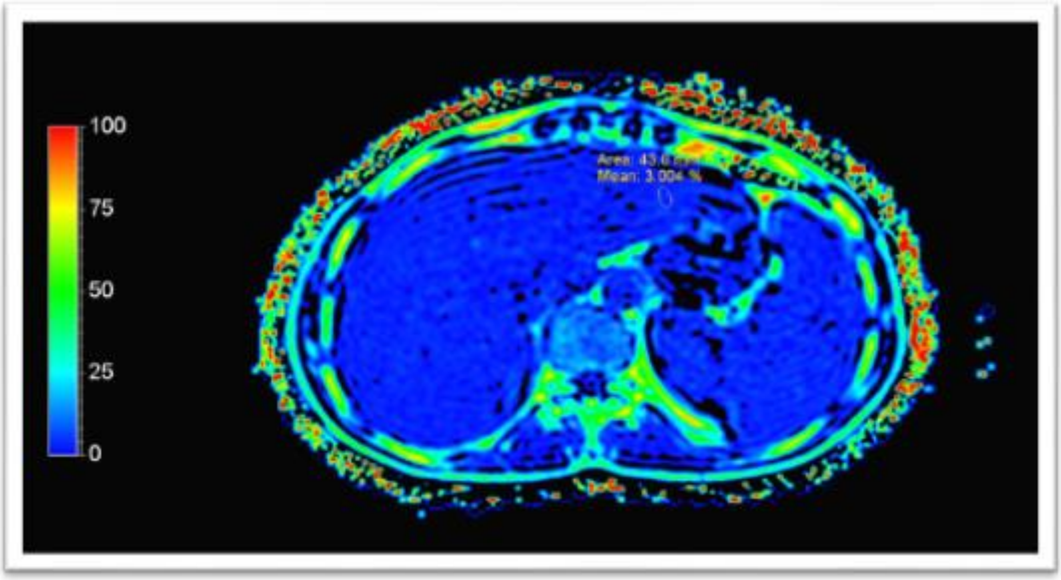
(A)


100
75
50
25
0
Area: 43.0 mm²
Mean: 3.15 %

(B)


100
75
50
25
0
Area: 43.0 mm²
Mean: 4.176 %

(c)



(D)

fig1: Multiple sequences of MRI PDFF of the liver from (a) to (d) MR imaging PDFF maps in, a 28-year-old man with grade 0 steatosis, (2.9% to 4.2%). One representative section acquired in the liver is shown for each subject. All maps were generated by using the same PDFF dynamic range (see scale bar at right). Overlaid on each Figure part is the mean PDFF calculated from ROIs placed in each liver segment.

Clinical: Potential donor for liver transplan at n: Liver biopsy for pathological examination.

Gross: Cores of tissue about 1.5 Cm. H&E, MT, Pb and MT stained slides were prepared.

Microscopic: Examination of the prepared slides revealed liver tissue wit ... racts with, intact architecture and no evidence of portal fibrosis, or inflamma or reaction, apart from one portal area showing minimal lymphocytic infiltrate with one eosinophil. No evidence of bile duct injury. No evidence of interface hepatitis. Parenchyma shows one cell thick plates, with no evidence of lobular necrosis.
No detected ground glass hepatocytes.
No evidence of steatosis, cholestasis or hemosiderosis.
No evidence of associated granulomatous inflammation or storage material.
No detected bilharzia! ova or hemozoin pigment.

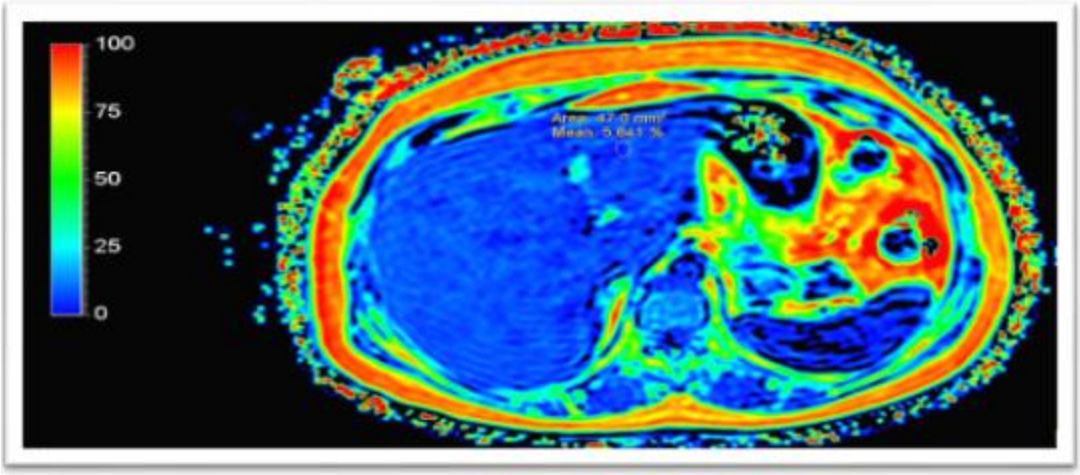
Diagnosis: Intact liver architecture with no evidence of portal fibrosis or significant necroinflammatory injury.
No evidence of steatosis(less than 5%).

Notes: Liver tissue within accepted average.

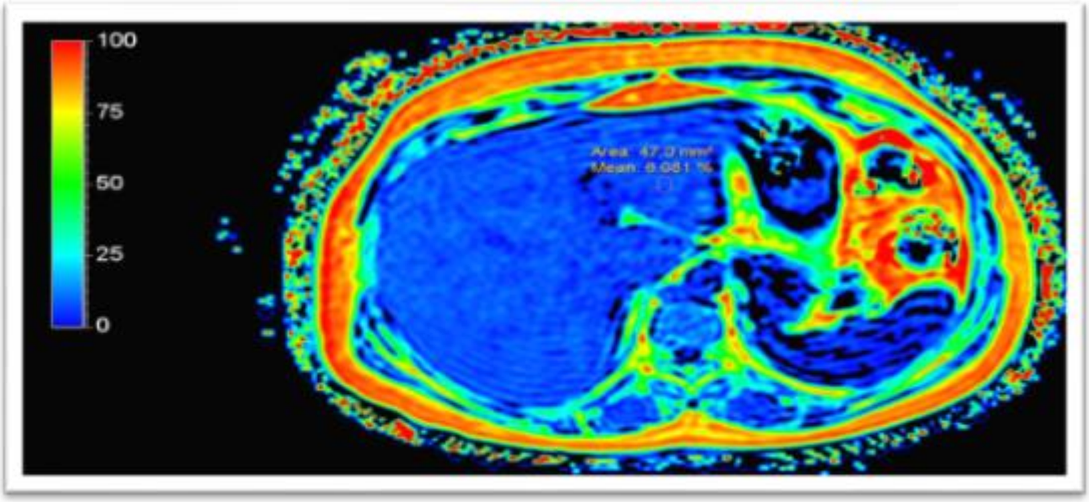
Fig 2: The pathology report of the case 1 shows no fatty liver and the donor with steatosis less than 5%

Case 2

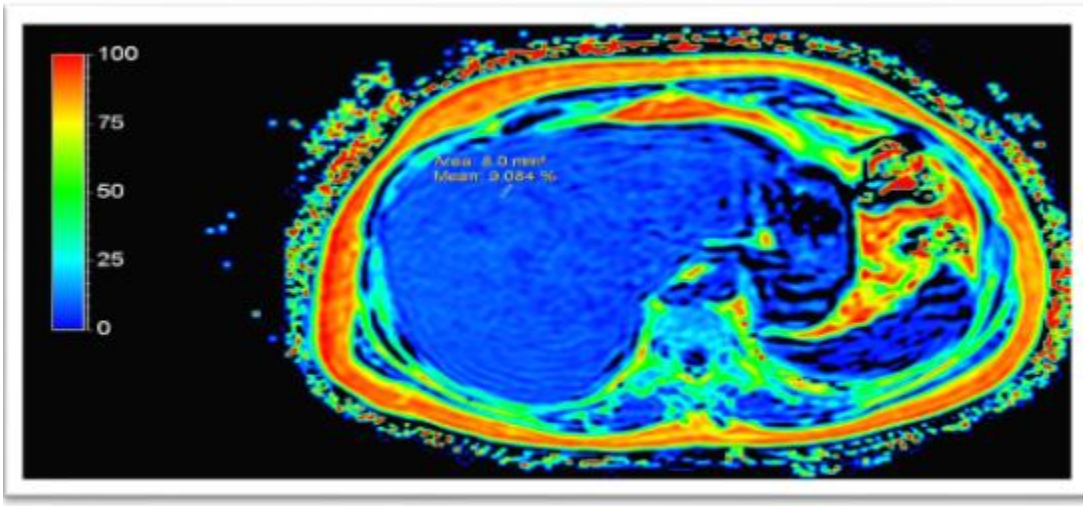
Donor Data: Age: 26 y Sex: female Weight: 67 kg Height: 165 cms Body Mass Index: 24 Clinical Status: passed 1st step of investigations and clinically fit.



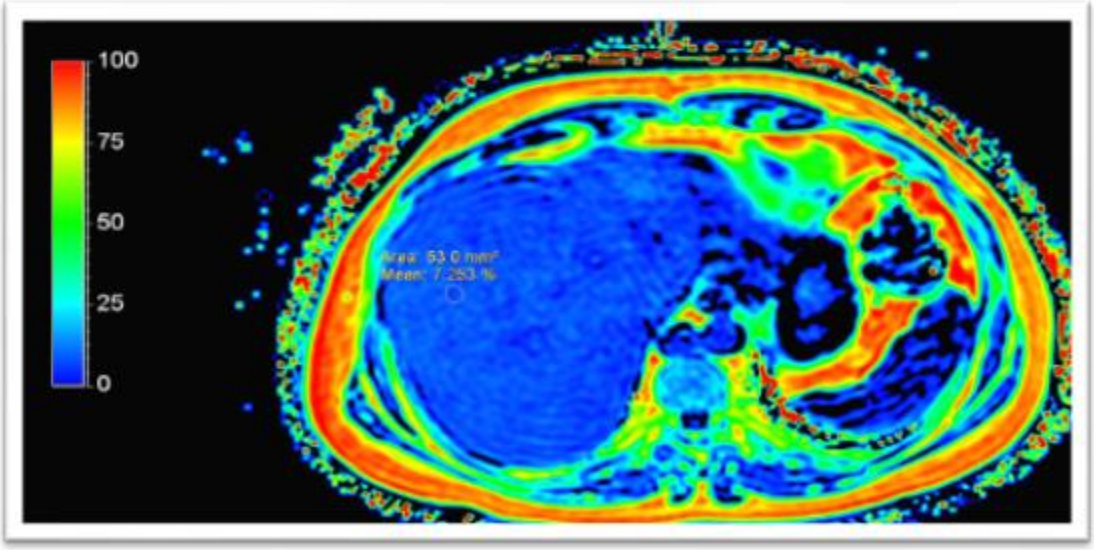
(A)



(B)

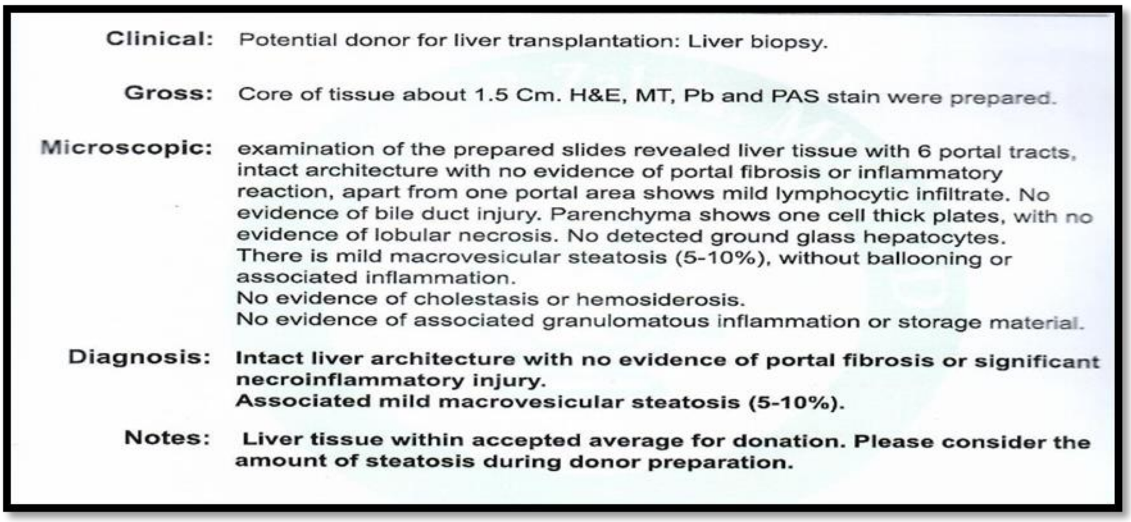


(C)



(D)

Fig 3: Multiple sequences of MRI PDFF of the liver from (a) to (d) MR imaging PDFF maps in, a 26-year-old man with grade 1 grade 1 steatosis, (5% to 9%). One representative section acquired in the liver is shown for each subject. All maps were generated by using the same PDFF dynamic range (see scale bar at right). Overlaid on each Figure part is the mean PDFF calculated from ROIs placed in each liver segment.



Clinical: Potential donor for liver transplantation: Liver biopsy.

Gross: Core of tissue about 1.5 Cm. H&E, MT, Pb and PAS stain were prepared.

Microscopic: examination of the prepared slides revealed liver tissue with 6 portal tracts, intact architecture with no evidence of portal fibrosis or inflammatory reaction, apart from one portal area shows mild lymphocytic infiltrate. No evidence of bile duct injury. Parenchyma shows one cell thick plates, with no evidence of lobular necrosis. No detected ground glass hepatocytes.
There is mild macrovesicular steatosis (5-10%), without ballooning or associated inflammation.
No evidence of cholestasis or hemosiderosis.
No evidence of associated granulomatous inflammation or storage material.

Diagnosis: **Intact liver architecture with no evidence of portal fibrosis or significant necroinflammatory injury.**
Associated mild macrovesicular steatosis (5-10%).

Notes: **Liver tissue within accepted average for donation. Please consider the amount of steatosis during donor preparation.**

Fig 4: The pathology report of the case 3 shows minimal to mild fatty liver and the donor with steatosis 5-10%

Hepatic steatosis in living donors for liver transplantation causes morbidity of both donor and recipient. The assessment of hepatic steatosis is essential for living liver donor selection because significant hepatic steatosis can affect postoperative outcomes in the donor. In addition, the development of primary dysfunction, early allograft dysfunction, poor overall graft survival, and other complications have been reported in recipients of steatosis grafts in liver transplantation **(6)**.

The main results of this study were as following

42 potential donors were eligible to participate in the study; we found that 73.8% of participants (31 potential donors) were males, while 26.2% of them (11 potential donors) were females. We found that their mean age ranged between 20 and 42 years old with a mean of 28.52 ± 5.55 years old.

Our results were supported by study of Broering et al. as they reported that 150 potential living liver donors were included in the analysis. The mean age of the cohort was 30.0±7.0 years, and 73.3% were males, giving a male to female ratio of 3:1 **(7)**.

The present study showed that on reviewing their BMI, we found that their BMI ranges between 19 and 30 kg/m2 with a mean of 25.21 ± 3.64 kg / m2 as shown in the table below. On reviewing patients' height, we found that their height ranged between 156 and 188 cm with a mean of 170.5 ± 7.72 cm. On reviewing weights of participants, we found that their weight ranges between 53 and 88 kilograms with a median level of 76 (67.75 – 80) kilo grams.

In accordance with our results, study of van Werven et al. as they reported that the mean body mass index was 27.1 kg/m2 (range, 20.2–40.6 kg/m2), with 26.2 kg/m2 (range, 20.8–34.0 kg/m2) in men and 28 kg/m2 (range, 20.2–40.6 kg/m2) in women. Considering a mean body mass between 20 and 25 kg/m2 to be normal, 41% (19 of 46) of the patients had normal weight and 59% (27 of 46) were overweight **(8)**.

In the study in our hands, we found that despite the recorded liver fat percent through liver biopsy was higher among males when compared to females, this was statistically insignificant (p=0.137). We also found that there was a moderate positive correlation between age of the participants and fat percent when recorded during biopsy examination (Pearson correlation =0.357). This was statistically significant (p=0.02). On the other hand, we found that fat percent recorded through biopsy was weakly correlated with BMI of participants. This was statistically insignificant. Similarly, we found that there was a weak positive correlation between patients' height and recorded fat percent through biopsy examination (Pearson correlation = 0.072). However, this was statistically insignificant (p=0.653). We also found that the correlation between recorded fat percent through biopsy examination and patients' weight was a weak positive one (Pearson correlation = 0.134, p=0.405).

While, in another study conducted by Rinella et al. used <25, 25-28, and >28 kg/m2 as BMI cutoffs and found that no patient with BMI <25 kg/m2 had hepatic steatosis, 33% of patients with BMI of 25-28 kg/m2 had steatosis on biopsy, and 76% of patients with BMI >28 kg/m2 had steatosis proven by liver biopsy **(9)**.

One recent study held by Adalı et al. with 264 living donor liver candidates used <25, 25-29.9, and ≥30 kg/m2 as BMI thresholds, and 83.3% of candidates with BMI <25 kg/m2 had no steatosis; however, this ratio was 51.5% among candidates with BMI of 25-29.9 kg/m2, and 31.9% among candidates with BMI ≥30 BMI kg/m2 on the liver biopsy **(10)**.

The present study showed that despite the recorded liver fat percent through MRI PDFF was higher in males when compared to females, this was statistically insignificant (p=0.204). We also found that there was a very weak negative correlation between age of the participants and fat percent when recorded through MRI PDFF (Pearson correlation =-0.006). this was statistically insignificant (p=0.968). We found that there was a weak positive correlation between fat percent recorded through MRI PDFF and their BMI; (Pearson correlation = 0.096; p=0.937). We also found that the correlation between recorded fat percent through MRI and patients' height was a weak positive one (Pearson correlation = 0.151, p=0.345). We also found that the correlation between recorded fat percent through MRI and patients' weight was a weak positive one (Pearson correlation = 0.192, p=0.224).

Moreover, Yoon et al. revealed that FF on MR images showed moderate correlation with macrovesicular fat in the specimen (r = 0.77, 95% CI: 0.73, 0.81; P <.001). Only a weak correlation was found between BMI and macrovesicular fat (r = 0.27, 95% CI: 0.17, 0.36; P <.0001) **(11)**.

4. Conclusion

Noninvasive MR hepatic PDFF technique with IDEAL sequence is a precise reliable technique for quantitative assessment of hepatic steatosis with high sensitivity, specificity and accuracy of It is recommended to be a part of preoperative liver evaluation in living donors and selectively performing liver biopsy in donor candidates diagnosed to have substantial steatosis based on MR PDFF findings.

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