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Original Article

Radiology Section

Correlation between Myosteatosis and Liver Fibrosis among Patients with Non Alcoholic Fatty Liver Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) is one of the major leading causes of liver diseases, comprising a spectrum of conditions ranging from simple steatosis to cirrhosis. In the era of preventive medicine, it is of utmost importance to recognise the subset of NAFLD patients at high risk of progressing to liver cirrhosis. A newly emerging concept of myosteatosis is now suspected to be an early manifestation of NAFLD disease progression.

Aim: To find the correlation between myosteatosis and liver fibrosis among patients with NAFLD.

Materials and Methods: This was a cross-sectional study conducted in the Department of Radiodiagnosis and Department of Gastroenterology at Amala Institute of Medical Sciences in Thrissur, Kerala, India, from January 2021 to June 2022. A total of 57 subjects with Magnetic Resonance Imaging-proven (MRI) NAFLD were included in the study. Body weight and height were measured. Liver fat and myosteatosis were measured using the MRI-derived Proton Density Fat Fraction (PDFF) method {Iterative Decomposition of Water and Fat with Echo (IDEAL-IQ sequence)}. Liver fibrosis was assessed using 2D shear wave elastography. The proportion of myosteatosis and liver fibrosis among NAFLD patients was estimated. Partial correlation, controlling for gender, was evaluated using partial Spearman's rho correlation coefficients. An Reciever Operating Characteristic (ROC) curve was plotted to assess muscle fat fraction in predicting liver fibrosis outcome among patients.

Results: Out of the 57 subjects studied, 17 were females and 40 were males. The median Interquartile Range (IQR) age of the subjects was 43.0 (16.5). The median MRI hepatic fat fraction was 10.8. The median muscle PDFF in males was 8.4, and in females, it was 16.9. The median H-PDFF was 18.8. Myosteatosis correlated positively with liver fibrosis ($r=0.558$; $p<0.001$). It also negatively correlated with hepatic steatosis ($r=-0.321$; $p=0.02$). A statistically significant correlation was not found between liver fat and liver fibrosis. An ROC curve was plotted to predict the liver fibrosis outcome by muscle fat fraction {Area Under Curve (AUC: 0.605; p-value: 0.204)}, which showed a sensitivity of 0.615 and a specificity of 0.389 at a cut-off score of 10.43.

Conclusion: Myosteatosis positively correlated with liver fibrosis and negatively with liver steatosis.

Keywords: Liver cirrhosis, Liver fat, Preventive medicine, Proton density fat fraction

INTRODUCTION

The NAFLD is defined as the accumulation of fat in the liver, which is proven by either histology or imaging, in a person with no other cause of fat accumulation such as significant alcohol use or steatogenic drugs [1]. It is one of the major causes of liver diseases worldwide, with a global prevalence of 32.4%. The overall incidence has been found to be higher in men than women [1]. NAFLD comprises a range of diseases, varying from simple steatosis called Non Alcoholic Fatty Liver (NAFL), a relatively harmless condition, to Non Alcoholic Steatohepatitis (NASH), which indicates hepatocyte injury in the form of hepatocyte ballooning. NASH can also involve varying levels of fibrosis, with progression to cirrhosis occurring in 30-40% of affected individuals [1-3]. Progressive liver fibrosis is a dreaded complication as it results in irreversible loss of hepatocytes and subsequent liver dysfunction [4].

The pathogenesis of NAFLD is multifactorial. One of the mechanisms is thought to be insulin resistance-mediated dysregulation of adipose tissue lipolysis, leading to increased circulating free fatty acids [5,6]. Skeletal muscle is considered to be the major site for the disposal of ingested glucose, which is insulin-stimulated. When there is excess fat infiltration in skeletal muscle, either within the myocytes or between the myofibres, it is termed as myosteatosis. This increased intramyocellular and intermyocellular fat content has been shown to play a pivotal role in the development of insulin resistance in skeletal muscle [5,6].

Little is known about the clinical implications of myosteatosis, but recent studies have shown that it is believed to be a precursor of insulin resistance and may be an early manifestation of NAFLD disease progression [6-8]. Since the authors could not find a study evaluating the correlation between myosteatosis and liver fibrosis in the South Indian population through online search, the present study was conducted with the aim of finding the correlation between myosteatosis and liver fibrosis.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Radiodiagnosis and the Department of Gastroenterology, Amala Institute of Medical Sciences, Thrissur, Kerala, India, from January 2021 to June 2022. All procedures adhered to the ethical standards of the Institutional Ethics Committee (Certificate number 17/IEC/21/AIMS-07). Prior to participation, all participants provided written informed consent.

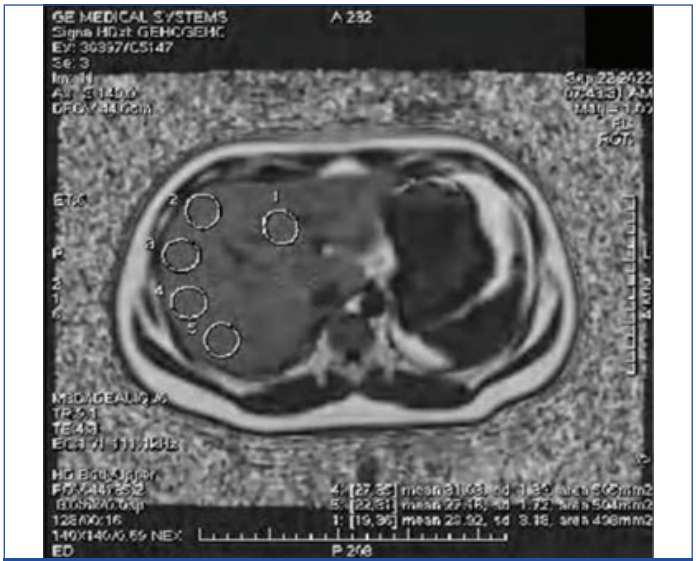
Inclusion and Exclusion criteria: The study included subjects between the ages of 25 to 72 years with confirmed NAFLD based on MRI (Liver PDFF >5%). Patients with significant alcohol use, the use of steatogenic drugs, uncompensated liver cirrhosis, pregnancy, known malignancies, and secondary causes of fat accumulation such as Wilson's disease, viral hepatitis, and parenteral nutrition were excluded.

Study Procedure

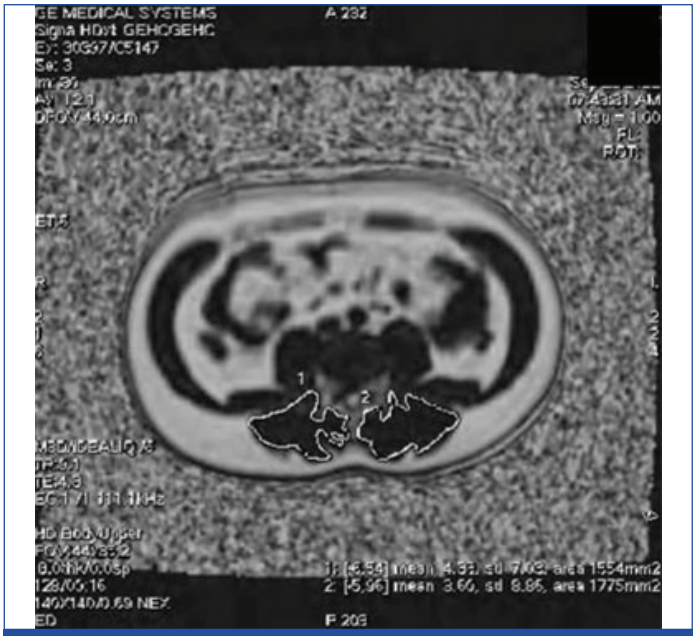
Body weight and height were measured to calculate the BMI for each subject. Liver fat and muscle fat quantification were performed using the MR PDFF sequence. Ultrasound elastography was used to assess liver fibrosis in each subject.

Quantification of Liver Fat and Muscle Fat [Table/Fig-1a,b]:

Liver and muscle fat quantification was conducted using the T2*-corrected 3D Multi Echo Dixon sequence with reconstruction on a GE HDxt-1.5 TESLA. The imaging protocol included an axial 3D IDEAL-IQ (DIXON-Fat Fraction, R2*, Water, and Fat). The IDEAL IQ sequence had the following parameters: TR-9.3, TE-4.4; Number of echoes-6; FOV-41.0×32.8 cm; Matrix size 128×128; Pixel bandwidth 111.11Hz; Flip angle 6; Slice thickness-8 mm. Data acquisition was completed during one breath hold (scan duration: 14.9 s).



[Table/Fig-1a]: Liver fat fraction calculation: Five circular ROIs drawn in one section of IDEAL IQ sequence. This step was repeated in two more sections.

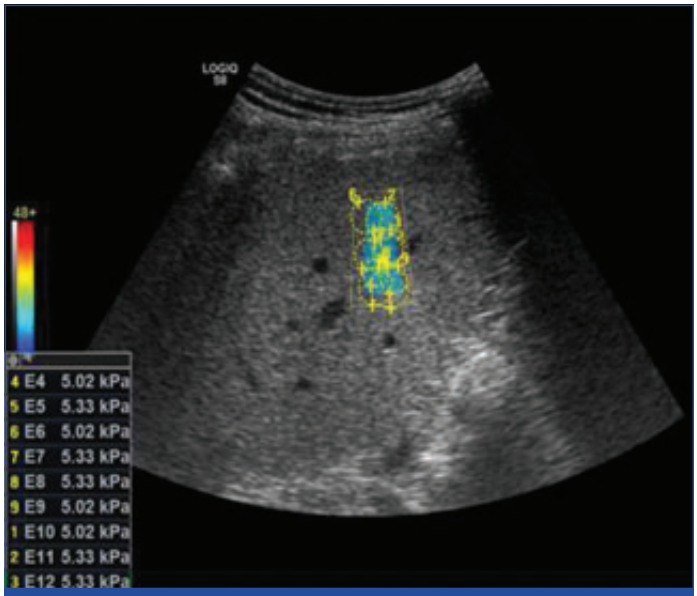


[Table/Fig-1b]: Muscle fat fraction calculation: Manual segmentation of the multifidus and erector spinae muscle. 1) Represents segmentation of the multifidus and erector spinae muscle at the L3 level on the right; and 2) Represents segmentation of the multifidus and erector spinae muscles on the left side.

The PDFF images were used to determine liver and muscle fat content, which were viewed on the imager console after image acquisition. On three MRI sections, five circular Region of Interests (ROIs) of 500 mm^2 were drawn in the liver while avoiding artifacts, vascular, and biliary structures. The average of the 15 values was taken as the hepatic PDFF, with a value of >5% considered significant steatosis [9]. Myosteatosis was assessed using the same sequence by manually segmenting the multifidus and erector spinae muscles bilaterally at the Lumbar 3 (L3) level. The large fat-filled 'tent' observed between the longissimus and iliocostalis muscles was not included in the ROI. The muscle PDFF was determined by taking the average value of the two readings, which were performed by a single observer. Liver PDFF and muscle PDFF measurements were each performed twice, and the average of the two measurements was taken.

Liver fibrosis assessment [Table/Fig-1c]:

All ultrasound examinations were conducted using the GE Healthcare LOGIQ S8 system. The patient was imaged in a supine or slight (30°) left lateral decubitus position, with the right arm elevated above the head to improve the acoustic window to the liver. The B-mode image was optimised for the best acoustic window, avoiding any mass lesions, vessels, and bile ducts. All elastography measurements were obtained by a single observer.



[Table/Fig-1c]: Liver fibrosis assessment using 2D Shear Wave Elastography (SWE).

The probe was placed on the skin surface after applying gel, and measurements were taken 4-5 cm deep from the skin and at least 1-2 cm away from the liver capsule to avoid reverberation artifacts. The patient was instructed to hold their breath at the end of normal expiration or inspiration, and 11 measurements were taken in a neutral position. The measurements were recorded in kilopascals (kPa). It is important to note that cut-off values for fibrosis staging may vary across ultrasound systems from different vendors.

According to the present system, the cut-off values and grading of fibrosis are provided as follows [Table/Fig-2].

Liver fibrosis staging	Metavir score	kPa
Normal-mild	F1	6.48-6.60
Mild-moderate	F2	6.60-8.07
Moderate-severe	F3	8.07-9.31
Cirrhosis	F4	>9.31

[Table/Fig-2]: GE LOGIQ S8 liver shear wave elastography.

STATISTICAL ANALYSIS

The data analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0. The results were expressed as the median and interquartile range. Partial correlations, controlling for gender, were evaluated using partial Spearman's rho correlation coefficients. An ROC curve was plotted to assess the predictive value of muscle fat fraction in determining the outcome of liver fibrosis among patients. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

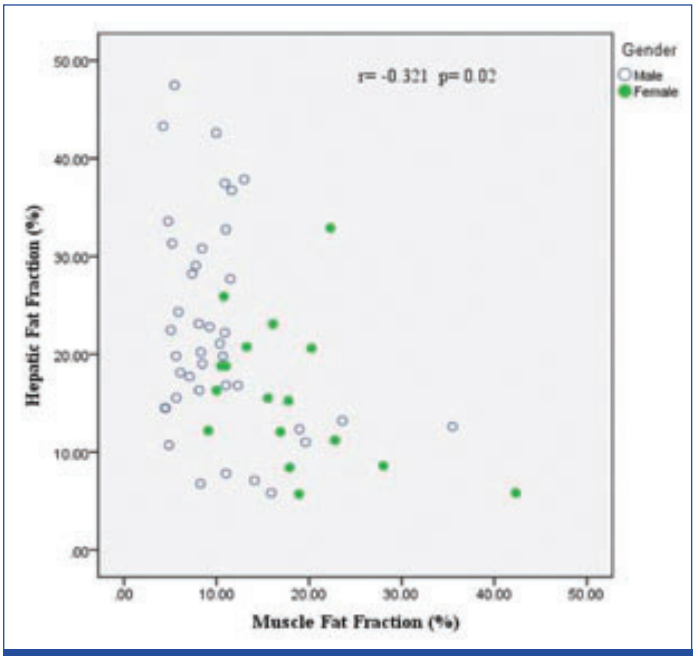
In total, 57 subjects with MRI-proven NAFLD were included in the study, with 17 being females and 40 being males. The median age for males was 37.5, while for females it was 45. The distribution of study subjects based on baseline characteristics is presented in

[Table/Fig-3]. Significant liver fibrosis (liver stiffness ≥6.60 kPa) was diagnosed in 39 NAFLD patients (68.4%).

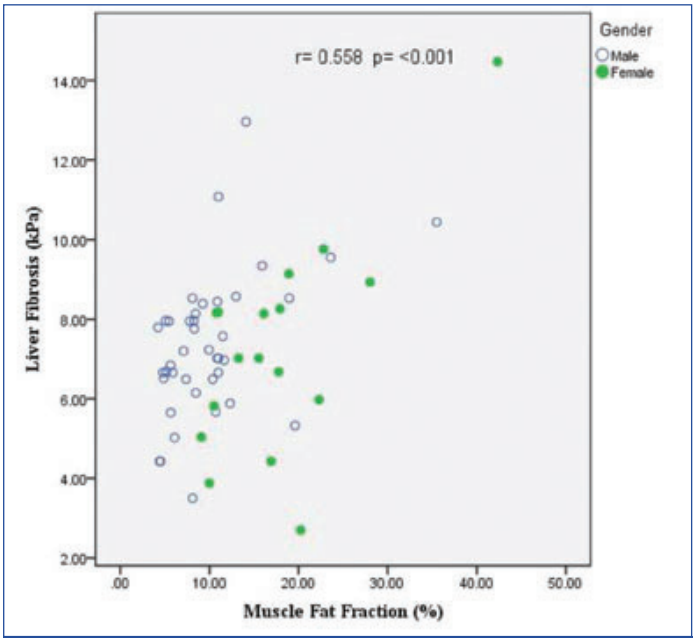
Variables	Male (n=40) Median (IQR)	Female (n=17) Median (IQR)	Total (n=57) Median (IQR)
Age (in years)	37.5 (17.0)	45.0 (15.0)	43.0 (16.5)
BMI (in kg/m^2)	28.2 (3.5)	28.7 (5.5)	28.4 (4.3)
Muscle fat fraction	8.4 (5.7)	16.9 (10.4)	10.8 (8.4)
Hepatic fat fraction	20.0 (15.9)	15.5 (10.8)	18.8 (14.3)

[Table/Fig-3]: Table showing baseline characteristics of the study population.

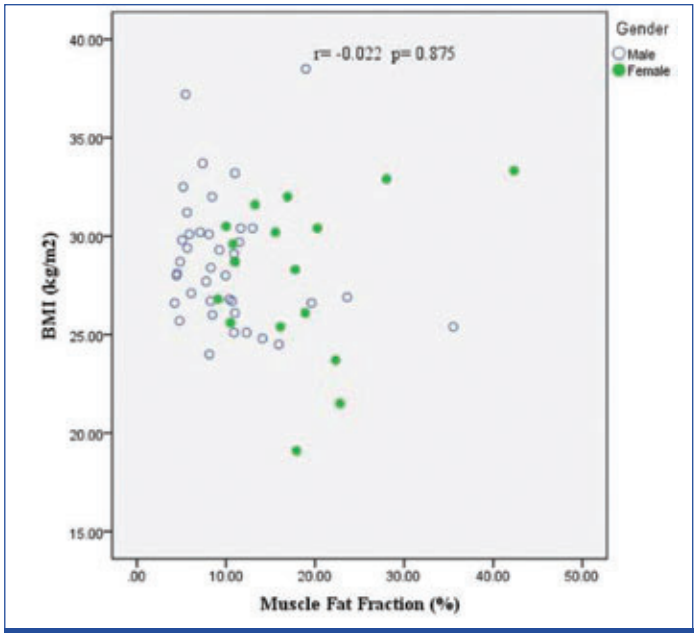
Myosteatosis showed a positive correlation with liver fibrosis (r=0.558; p<0.001) and a negative correlation with hepatic steatosis (r=-0.321; p=0.02), as shown in [Table/Fig-4a-d]. An ROC curve was performed to assess the muscle fat fraction test's ability to predict liver fibrosis. The Area Under Curve (AUC) was 0.605, indicating that it was considered a poor test for predicting liver fibrosis among patients (p-value=0.204). The cut-off value with the best sensitivity and specificity for muscle fat fraction was 10.43, with a sensitivity of 0.615 and specificity of 0.389, as presented in [Table/Fig-5].



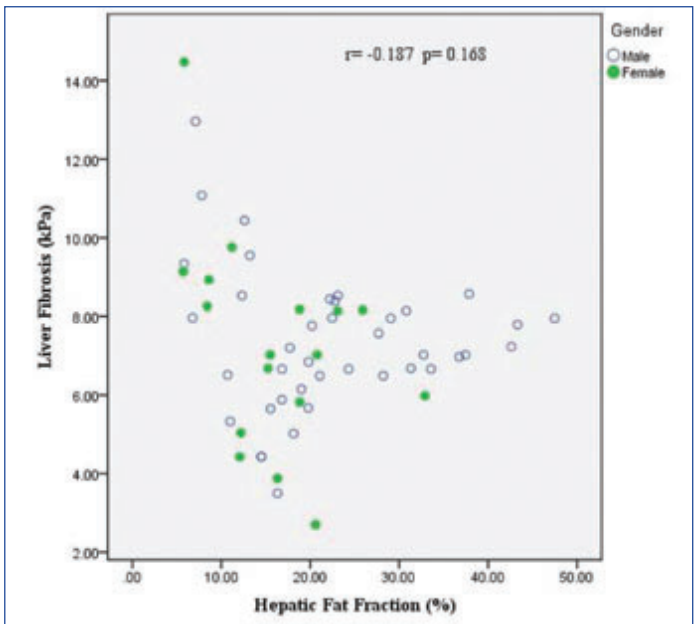
[Table/Fig-4a]: Partial correlation corrected for gender of muscle fat fraction and hepatic fat fraction showing negative correlation (r=-0.321, p=0.02).



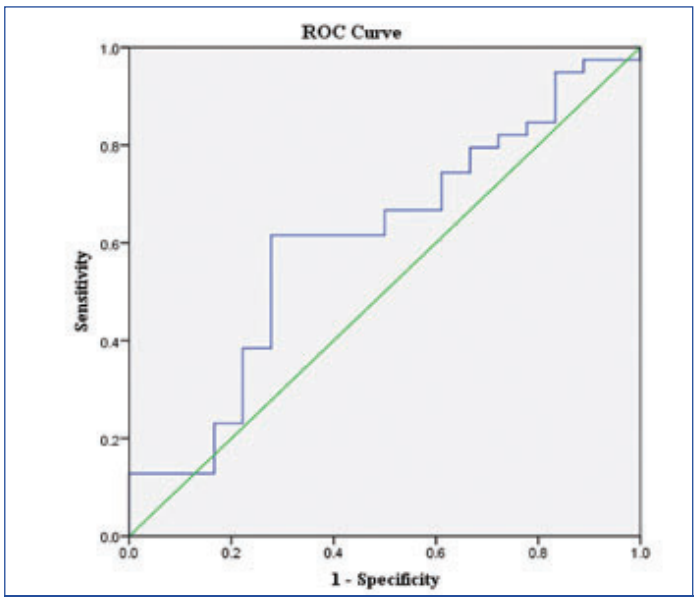
[Table/Fig-4b]: Partial correlation corrected for gender of muscle fat fraction and liver fibrosis showing positive correlation (r=0.558, p=<0.001).



[Table/Fig-4c]: No statistically significant correlation seen between BMI and myosteatosis.



[Table/Fig-4d]: No statistically significant correlation seen between liver fibrosis and steatosis.



[Table/Fig-5]: ROC curve to predict the liver fibrosis outcome by muscle fat fraction. AUC: 0.605, p-value: 0.204. Cut-off score: 10.43.

DISCUSSION

Myosteatosis is said to be an early sign of progression from simple steatosis to NASH [10]. In the present cross-sectional study, a moderately positive correlation was found between myosteatosis and liver fibrosis. These findings align with those of Nachit M et al., who found a significant correlation between liver stiffness and the skeletal muscle fat index calculated using CT in the psoas muscle. This correlation was also found to be independent of age, sex, liver steatosis, Alanine Transaminase (ALT), Glycated Haemoglobin (HbA1c), and hypertension. This relationship persisted in multivariate analysis when accounting for multiple confounders. Hence, myosteatosis was found to be strongly associated with liver stiffness [11].

To date, there is still no consensus on MRI-PDFF cut-off values for myosteatosis. Our study provided a cut-off value of 10.4, derived from the ROC curve between myosteatosis and liver fibrosis. Above this value, significant liver fibrosis (Metavir score ≥F2) was observed, making it a potential diagnostic marker for significant myosteatosis.

No statistically significant association was found between hepatic steatosis and liver fibrosis. However, the degree of myosteatosis showed a weak negative correlation with the amount of hepatic fat. Since higher grades of fibrosis were found in patients with high muscle PDFF, authors can indirectly assume an inverse relationship between liver fat and liver fibrosis. This can be explained by the histopathogenesis of liver fibrosis, where persistent hepatic injury leads to failed liver regeneration and the replacement of hepatocytes with excessive extracellular matrix, including fibrillar collagen [12].

A study by Permutt Z et al., examined the correlation between hepatic steatosis assessed by MRI-PDFF and liver steatosis and fibrosis assessed by histology [13]. They found that patients with stage-4 fibrosis on histology, compared to patients with stages 0-3 fibrosis, had significantly lower hepatic steatosis. Their study also showed an inverse correlation between MRI-determined hepatic PDFF and hepatic fibrosis [13]. Therefore, a low value of hepatic steatosis may not reliably indicate the severity of NAFLD, as it can also be present in advanced NASH with progression to cirrhosis. Additionally, to identify patients at risk of progression to advanced NASH, myosteatosis may be a better marker than liver fat content.

Furthermore, the present study shows no correlation between BMI and myosteatosis. This finding is consistent with the study conducted by Kitajima et al., [14], which examined 333 NAFLD patients and found a positive correlation between the multifidus muscle/subcutaneous fat ratio and age and visceral fat, but no significant correlation with BMI. One possible reason for this lack of correlation is that authors did not consider body fat percentage, which provides a more accurate depiction of body composition by differentiating fat-free mass. BMI has limitations as it does not distinguish between muscle, fat, bone, or vital organs. Therefore, individuals with high fat-free mass relative to stature may have a high BMI but not be obese [15].

The strength of the present study lies in the well-characterised adult NAFLD subjects, including both genders, and the use of imaging techniques (MRI-PDFF and 2D shear wave elastography) for assessment. The authors employed a validated MRI-determined PDFF technique that corrects for various biases, providing more reliable and accurate results compared to the conventional In-phase/Out-of-phase (IP/OP) Dixon method [16]. Additionally, the non invasive Shear Wave Elastography (SWE) technique used for hepatic fibrosis assessment has excellent diagnostic accuracy, serving as an alternative to liver biopsy [17]. Moreover, hepatic steatosis, myosteatosis, and fibrosis (E-median) were measured as continuous variables, which is ideal for correlation analysis.

The present study findings align with the study conducted by Kim HS et al., [18], which investigated 23,311 subjects and found a higher percentage of good-quality muscle to be associated with a lower likelihood of moderate to severe NAFLD in males and intermediate to high levels of liver fibrosis in both sexes among participants with NAFLD. These associations remained significant even after considering additional NAFLD risk factors. Further research is needed to establish causal relationships and determine the clinical significance of myosteatosis in predicting NAFLD outcomes, which would be valuable for future studies in this field.

Limitation(s)

One major limitation of the study was the inclusion of a low number of subjects, which can be seen as a limitation. Additionally, the study did not include insulin sensitivity in the assessment of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), despite its known impact on myosteatosis. Although the study established a cut-off value of 10.4 for myosteatosis, above which significant liver fibrosis was observed, it did not investigate the correlation with the severity of fibrosis. This can also be seen as a limitation of the study.

CONCLUSION(S)

The NAFLD has now become one of the most important causes of liver disease worldwide and may emerge as a leading cause of end-stage liver disease in the upcoming years. Early diagnosis is crucial to prevent various complications such as fibrosis. Recognising myosteatosis is important as it may contribute to early progression of fibrosis. The management of early NAFLD should also involve assessing the presence and severity of myosteatosis to prevent complications and predict the disease outcome. The authors cannot solely rely on the degree of liver steatosis to assess the severity of NAFLD.

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