DOI: 10.7860/JCDR/2023/63071.18450

Original Article

Radiology Section

Breast Arterial Calcification in Screening Mammograms and its Correlation with Carotid Intima Media Thickness: A Cross-sectional Study

ALEENA KHAN[1], VARUN NARAYAN[2], HAREESH JAYARAM[3], MANOJ KRISHNA SAJEEV[4], ROBERT P AMBOOKEN[5]

ABSTRACT

Introduction: Atherosclerosis is a leading cause of cardiovascular mortality worldwide. According to American Cancer Society (ACS) guidelines, screening mammography is optional for all women above the age of 40 years to detect breast cancer early. Incidentally, Breast Arterial Calcification (BAC) can be observed in mammograms. Women with BAC and additional risk factors like diabetes or hypertension may be referred for cardiovascular risk assessment in the future if there is a significant correlation between Carotid Intima Media Thickness (CIMT) and BAC.

Aim: To assess BAC among women undergoing screening mammography and determine the correlation between BAC and CIMT.

Materials and Methods: A cross-sectional study was conducted on 152 women who underwent screening mammography in the Department of Radiodiagnosis, Amala Institute of Medical Sciences, Thrissur, Kerala, India from May 2021 to October 2022. The presence and grading of BAC were determined using the Seimens Mammomat 1000 mammography unit, which captured two standard views: the Mediolateral Oblique (MLO) and Craniocaudal (CC) views. CIMT was measured using B-mode ultrasonography with an 8-13 MHz linear transducer, taking measurements from two contiguous sites at 1 cm intervals and calculating the average. Statistical significance was assessed at a 5% level, and the association was determined using Spearman's rho correlation.

Results: The mean age of the study population was 55.7±11.05 years. Among them, only 37 (24.3%) showed the presence of calcification in the breast arteries. The mean CIMT was 0.92±0.25 mm in the BAC (+) group and 0.72±0.24 mm in the BAC (-) group (p-value=0.001).

Conclusion: The authors developed a BAC grading method after studying various previous studies and the present study found a significant positive correlation between the presence of BAC and CIMT.

Keywords: American cancer society, Common carotid artery, Craniocaudal view, Mediolateral oblique view, Ultrasonography

INTRODUCTION

Atherosclerosis, the leading cause of cardiovascular mortality, is a chronic inflammatory disease caused by hyperlipidemia and lipid oxidation. It affects the intima of vessels, from the aorta to the coronary arteries, leading to the formation of intimal plaques [1]. Atherosclerosis can be detected through imaging techniques such as radiographs and Computed Tomography (CT), where arterial calcifications are observed, or through ultrasound, which shows an increase in Carotid Intima Media Thickness (CIMT) [2]. Screening mammograms are performed on asymptomatic women to detect breast malignancies at an early and treatable stage. According to ACS guidelines, average-risk women between the ages of 40 and 44 should undergo screening mammograms, while women aged 45 and above should have them annually. High-risk women should start screening from the age of 30 [3]. Breast Arterial Calcifications (BACs) are commonly seen as incidental findings on mammograms. They are benign dystrophic calcifications found in the tunica media of small to medium-sized muscular arteries in the breast. They are also known as Mönckeberg calcifications or arteriosclerosis [2]. CIMT is a well-established surrogate marker of atherosclerosis and is associated with cardiovascular risk factors and outcomes. It is a non-invasive measurement of the thickness of the innermost two layers of the arterial wall, the tunica intima and tunica media. CIMT is obtained through B-mode ultrasonography, which captures still images. Increased CIMT indicates diffuse arterial wall thickening, reflecting the presence of atherosclerosis [4]. It is also used to monitor the progression of atherosclerosis for early medical intervention. Vascular calcifications in the breast and increased CIMT have both been recognised as potential markers of a woman's risk for coronary artery disease. Therefore, for patients incidentally detected with BAC during screening mammography for breast cancer, the possibility of future cardiovascular events should be considered [4].

The aim of present study was to assess BAC, using the Grade system, and evaluate the association between BAC and CIMT in women undergoing screening mammography.

MATERIALS AND METHODS

A cross-sectional study was conducted on 152 women who underwent screening mammography at the Department of Radiodiagnosis, Amala Institute of Medical Sciences, Thrissur, Kerala, India from May 2021 to October 2022. Informed consent was obtained from all participants, and the study received approval from the Institutional Ethical Committee on 26/04/2021 (Ref. no. 17/ IEC/21/ AIMS-08). Consecutive sampling was performed.

Inclusion criteria: Women undergoing mammography between the ages of 31 years and 89 years.

Study Procedure

After obtaining relevant clinical and past history information, as well as informed consent, standard Mediolateral Oblique (MLO) and Craniocaudal (CC) views were obtained using the Siemens MAMMOMAT 1000 mammography unit. Breast Arterial Calcification

(BAC) was defined as the presence of tortuous, parallel linear calcified deposits along the vessel wall observed on at least one view of a mammogram, which is an incidental finding [2]. The mammogram images were assessed for the presence and grading of BAC. The scoring/grading system for breast arterial calcifications used in present study was developed by the authors after reviewing multiple articles [2-6]. For women with BAC, the number, length, and density of calcified vessels were evaluated using the following criteria:

The number of calcified vessels in each breast: (average of both breasts)

- Score 1: <2 vessels-1
- Score 2: 2-4 vessels- 2
- Score 3: >4 vessels-3

Length of the calcified vessels; (average of both breasts)

- Score 1: ≤3 cm-1
- Score 2: 4-6 cm-2
- Score 3: ≥7 cm-3

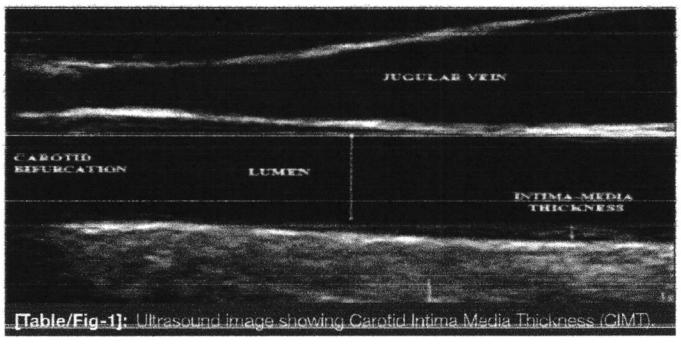
Density of a calcified vessel in its densest part;

- Score 1: BAC with clear lumen-1
- Score 2: BAC with clouded lumen-2
- Score 3: Dense BAC with non visualisation of lumen-3

The BAC grade was calculated by summing these three numbers and graded as:

- Grade-I (mild): Score ≤3
- Grade-II (moderate): Score 4-6
- Grade-III (severe): Score ≥7

Carotid Intima Media Thickness (CIMT) was assessed using an 8-13 MHz linear transducer. CIMT measurements were taken from two contiguous sites at 1 cm intervals, and the average of the two measurements was used for analysis. The CIMT measurement was reported as the average of the right and left Common Carotid Artery (CCA) [Table/Fig-1].



[Table/Fig-1]: Ultrasound image showing Carotid Intima Media Thickness (CIMT).

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 23.0. Continuous measurements were presented as mean±standard deviation, and categorical measurements were presented as number (%). Significance was assessed at a 5% level. The association between BAC and age was analysed using Fishers's-extract test. The association between different grades of BAC by mammography and CIMT was analysed using Spearman's rank correlation. The association between BAC and CIMT was analysed using the Chi-square test.

RESULTS

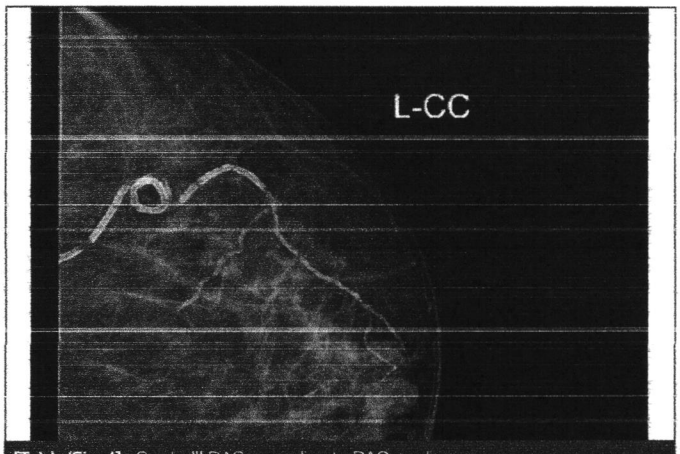
The mean age of the patients was 55.77±11.05 years. Among them, only 37 showed the presence of calcification in the breast arteries. The most commonly affected age group was 51-60 years [Table/Fig-2]. The majority of women showed a moderate grade of BAC [Table/Fig-3,4]. On the right side, the minimum CIMT noted was 0.3 mm, and on the left side, it was 0.1 mm. The maximum CIMT on the right side was 1.9 mm, and on the left side, it was 1.8 mm. The mean CIMT on the right side was 0.7 mm (0.4 sd), and on the left side, it was 0.7 mm (0.2 sd), with a total mean CIMT of 0.7 mm. Using a cutoff of ≤0.8 mm as normal CIMT [2], approximately 97 (63.8%) of the total subjects had CIMT ≤0.8 mm, and around 55 (36.2%) had CIMT > 0.8 mm [Table/Fig-5]. There was a significant difference in CIMT between the BAC positive and negative groups, with a p-value of <=0.05 [Table/Fig-6]. Logistic regression analysis between mean CIMT and BAC grades showed that there was no increase in CIMT with an increase in the grade of BAC [Table/Fig-7].

Age (years)	BAC		Total	p-value (Fisher-exact test)
	No	Yes		
31-40	10 (6.5%)	0	10 (6.5%)	0.0001
41-50	43 (28.3%)	1 (0.7%)	44 (28.9%)	
51-60	41 (26.9%)	10 (6.5%)	51 (33.6%)	
61-70	12 (7.9%)	15 (9.8%)	27 (17.8%)	
>70	9 (5.9%)	11 (7.2%)	20 (13.2%)	
Total	115 (75.7%)	37 (24.3%)	152 (100%)	

[Table/Fig-2]: Frequency of age distribution between BAC positive and BAC negative. Values presented as n (%).

Grading	Count	Percentage (%)
I	2	5.4
II	26	70.2
III	9	24.3

[Table/Fig-3]: Grading of BAC.



[Table/Fig-4]: Grade-III BAC according to BAC grading.

BAC	CIMT		Total	p-value (Chi-square test)
	≤0.8 (mm)	>0.8 (mm)		
Present	15 (40.5%)	22 (59.4%)	37 (24.3)	0.0001
Absent	82 (71.3%)	33 (0.28%	115 (75.6%)	
Total	97 (63.8%)	55 (36.18%)	152 (100%)	

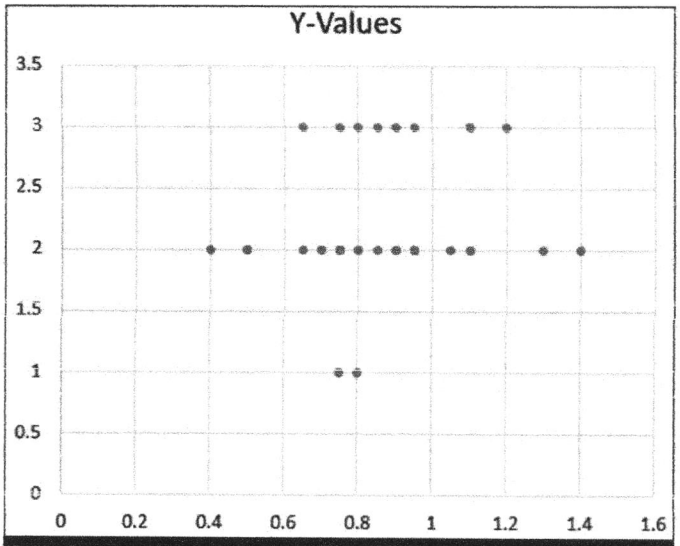
[Table/Fig-5]: CIMT in BAC positive and negative women.

Variables	BAC	N	Mean	Std. Deviation	p-value (Chi-square test)
CIMT right	No	115	0.759130	0.4516822	0.043
	Yes	37	0.921622	0.3038047	
CIMT left	No	115	0.717391	0.2103718	0.047
	Yes	37	0.808108	0.3165600	

[Table/Fig-6]: CIMT values in BAC + and – women.

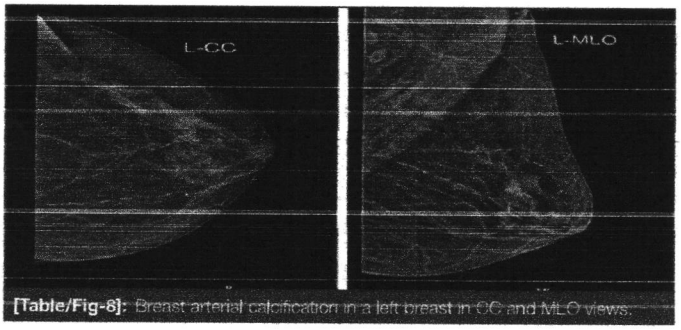
DISCUSSION

The BAC refers to calcium deposits along the vessel wall observed on mammograms, which is an incidental finding. These deposits



[Table/Fig-7]: r_s=0.16751, p (2-tailed)=0.3217.
There was a positive correlation between CIMT and BAC grade, but they are statistically insignificant. (No increase with an increase in grade)

occur in the middle layer of the vessel wall, leading to increased rigidity and stiffness of the vessel [Table/Fig-8] [2]. BAC detected on breast cancer screening mammograms may also be associated with disorders related to increased or accelerated atherosclerosis [7]. In the early stages, medial arterial calcifications appear punctate and then coalesce and become thicker, leading to linear tramtrack calcifications [8].



[Table/Fig-8]: Breast arterial calcification in a left breast in CC and MLO views.

The BAC is incidentally detected in only 9.1% of mammograms and is uncommonly seen before the age of 50 years [7]. The prevalence of BAC ranges from 9-17% and increases with age, particularly in women above 65 years of age. Increased parity has also been associated with an increase in BAC [9]. Kemmeren JM et al., recorded BAC in 9% of women who participated in a breast cancer screening program [5]. In present study, BAC was detected in only 24.3% of subjects, and there was only one case of BAC below the age of 50 years. Maas AH et al., demonstrated that the prevalence of BAC increased with advancing age, from 5% in the first quartile to 6% in the second quartile, 14% in the third quartile, and 20% in the fourth quartile. The odds ratio of women in the highest quartile of age having BAC was 4.7 (95% CI: 2.9-7.6) compared to women in the lowest quartile [10]. In present study, BAC was noted to increase with age and was mostly seen in women above 60 years of age.

Sankaran P et al., in their study on 100 women, found that there is an independent association between BAC in mammography and CIMT. Additionally, they found a statistically significant positive connection with CIMT, independent of age and menopausal state [2]. In the present study, CIMT did not show an increase in thickness with an increase in the grade of breast vessel calcification. Hanafi MG et al., in a study of 454 participants, showed that although individuals with BAC had a higher CIMT than the control group, there was no relationship between the grade of this calcification and carotid artery thickness [11].

Kadioglu A and Bahadir S, in their multi-modality study investigating the association of BAC, coronary artery calcification, and CIMT, found that BAC is strongly associated with aging. High BAC scores showed correlation with high CAC scores and also found a statistically significant correlation between BAC and cardiac risk factors like diabetes. Furthermore, in women younger than 60 years old, they suggested that the BAC scoring system can be used as an indicator of the presence of cardiovascular disease [12].

Akinola RA et al., in their study on 54 Nigerian women, found that although the presence of BAC in a mammogram is related to age, it may not be a reliable indicator or a relevant marker for cardiovascular diseases in women living in their environment [7]. Ali EA et al., in their study on 100 female patients, concluded that women over 60 who have BAC discovered accidentally via mammography should have their coronary atherosclerotic condition and risk of developing significant coronary artery disease further assessed [13]. In the present study, moderate grades of BAC were found to increase with age over 50 years. Since the majority of women over 40 years of age undergo screening mammography annually according to guidelines, our study suggests that the measurement of BAC may offer a non-invasive approach to risk stratify women for cardiovascular disease without additional radiation. Therefore, the inclusion of incidentally detected BAC in mammogram reports may help clinicians counsel and recommend lifestyle changes, cardiovascular risk assessment, and prevention of future cardiovascular events.

Limitation(s)

However, present study included a relatively small number of subjects, and most patients were post-mastectomy follow-up cases, which was a major limitation. The absence of a universally accepted method of grading BAC is another limitation.

CONCLUSION(S)

Hence, authors developed a BAC grading method after studying various previous studies. The effect of co-morbidities on CIMT thickness was not considered. This scoring criteria is only applied in a small population; therefore, before commenting on its accuracy, it needs to be tested in different settings or in different populations. Further, studies are warranted to determine the accuracy of this objective scoring system.

REFERENCES

[1] Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, et al. Atherosclerosis: Basic mechanisms: Oxidation, inflammation, and genetics. Circulation. 1995;91(9):2488-96.
[2] Sankaran P, Prajeeth N, Koteshwara P. Association of vascular calcification of breast with carotid intima media thickness. Pol J Radiol. 2019;84:335-59.
[3] Smith RA, Andrews K, Brooks D, DeSantis CE, Fedewa SA, Lortet-Tieulent J, et al. Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2016;66(2):95-114.
[4] Yildiz S, Yildiz A, Ertug N, Kaya I, Yilmaz R, Yuksel E, et al. Association of breast arterial calcification and carotid intima-media thickness. Heart Vessels. 2008;23(6):376-82.
[5] Kemmeren JM, Beijerinck D, van Noord PA, Banga JD, Deurenberg JJ, Pameijer FA, et al. Breast arterial calcifications: Association with diabetes mellitus and cardiovascular mortality. Radiology. 1996;201:75-78.
[6] Hannawi SMA, Hannawi H, Al Salmi I. Carotid intima media thickness as a surrogate measure for cardiovascular disease in rheumatoid arthritis: Literature review. J Integr Cardiol. 2018;4(4):01-05. Doi: 10.15761/jic.1000252.
[7] Akinola RA, Ogbera OA, Onakoya JA, Enabulele CE, Fadeyibi IO. Mammograms and breast arterial calcifications: Looking beyond breast cancer: A preliminary report. BMC Res Notes. 2011;4(1):01-06.
[8] Cetin M, Cetin R, Tamer N, Kelekci S. Breast arterial calcifications associated with diabetes and hypertension. J Dia Comp. 2004;18:363-66.
[9] Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature. 1993;362:801-09.
[10] Maas AH, van der Schouw YT, Beijerinck D, Deurenberg JJ, Mali WP, van der Graaf Y. Arterial calcifications seen on mammograms: Cardiovascular risk factors, pregnancy, and lactation. Radiology. 2006;240(1):33-38.
[11] Hanafi MG, Sarikhani S, Sahraeizadeh A. An investigation into the association between arterial calcification in mammography and carotid intima-media thickness. Pharmacophore. 2017;8(5):47-53.

[12] Kadioğlu A, Bahadır S. Breast arterial calcifications as an indicator of atherosclerotic cardiovascular disease: Comparative analysis of coronary computed tomography scoring systems and carotid intima-media thickness. Quant Imaging Med Surg. 2022;12(1):457-69.

[13] Ali EA, Fouad H, Razek NA, Saeed OM, Helmy SM. Evaluation of mammography detected breast arterial calcifications as a predictor of coronary cardiac risk. Egypt J Radiol Nucl Med. 2019;50(1). Doi: 10.1186/s43055-019-0095-7.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
2. Associate Professor, Department of Radiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
3. Assistant Professor, Department of Radiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
4. Senior Resident, Department of Radiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
5. Professor and Head, Department of Radiology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Aleena Khan,
Junior Resident, Department of Radiology, Amala Institute of Medical Sciences, Thrissur-680555, Kerala, India.
E-mail: khanalina3@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al]
- Plagiarism X-checker: Feb 04, 2023
- Manual Googling: Apr 27, 2023
- iThenticate Software: Jul 22, 2023 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jan 30, 2023**
Date of Peer Review: **Apr 15, 2023**
Date of Acceptance: **Jul 27, 2023**
Date of Publishing: **Sep 01, 2023**

AMALA INSTITUTE OF MEDICAL SCIENCES THRISSUR

Betsy

Dr. BETSY THOMAS
MD, FRCOG, DNB, MICOG
PRINCIPAL
AMALA INSTITUTE OF MEDICAL SCIENCES
AMALA NAGAR, THRISSUR-680 555

DOI: 10.7860/JCDR/2023/65204.18655

Original Article

Radiology Section

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

SAMHITA ANKALA[1], VARUN NARAYAN[2], SOJAN GEORGE[3], TONY JOSEPH KATTAKKAYAM[4], ROBERT P AMBOOKEN[5]

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.

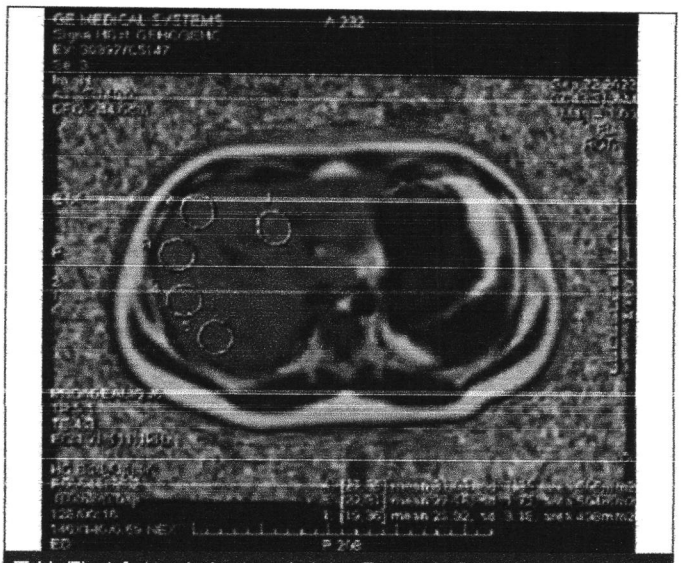
Inclusion and Exclusion criteria: The study included subjects between the ages of 25 to 72 years with confirmed NAFLD based on MRI (Liver PDFF >5%). Patients with significant alcohol use, the use of steatogenic drugs, uncompensated liver cirrhosis, pregnancy, known malignancies, and secondary causes 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).



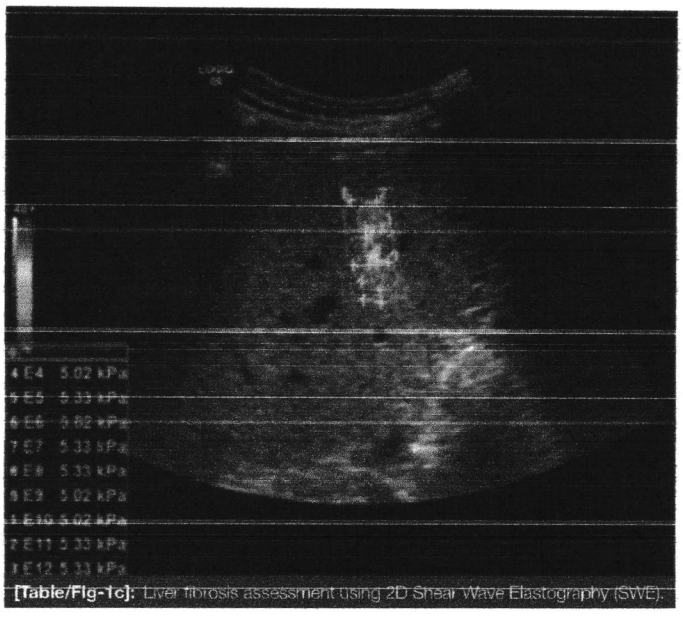
[Table/Fig-1a]: Liver fat fraction calculation: Five circular ROIs drawn in one section of IDEAL IQ sequence. This step was repeated in two more sections.

[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 mm² 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

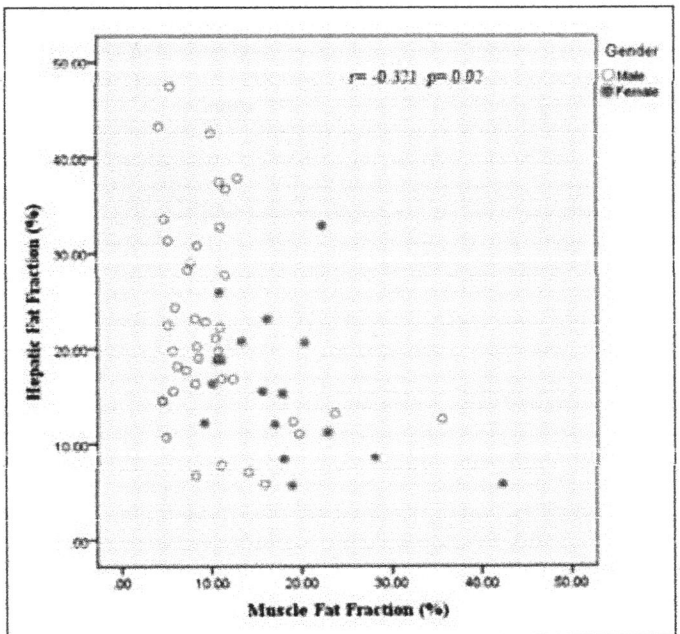
In total, 57 subjects with MRI-proven NAFLD were included in the study, with 17 being females and 40 being males. The median age for males was 37.5, while for females it was 45. The distribution of study subjects based on baseline characteristics is presented in

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

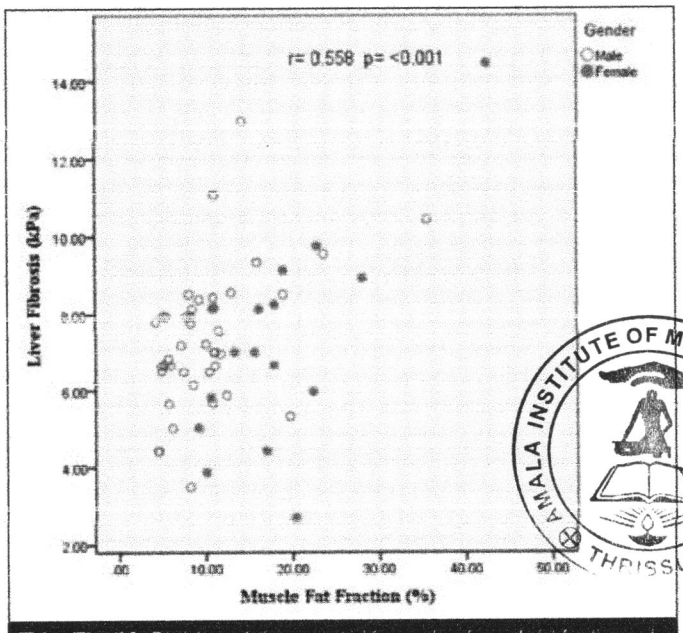
Variables	Male (n=40) Median (IQR)	Female (n=17) Median (IQR)	Total (n=57) Median (IQR)
Age (in years)	37.5 (17.0)	45.0 (15.0)	43.0 (16.5)
BMI (in kg/m²)	28.2 (3.5)	28.7 (5.5)	28.4 (4.3)
Muscle fat fraction	8.4 (5.7)	16.9 (10.4)	10.8 (8.4)
Hepatic fat fraction	20.0 (15.9)	15.5 (10.8)	18.8 (14.3)

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

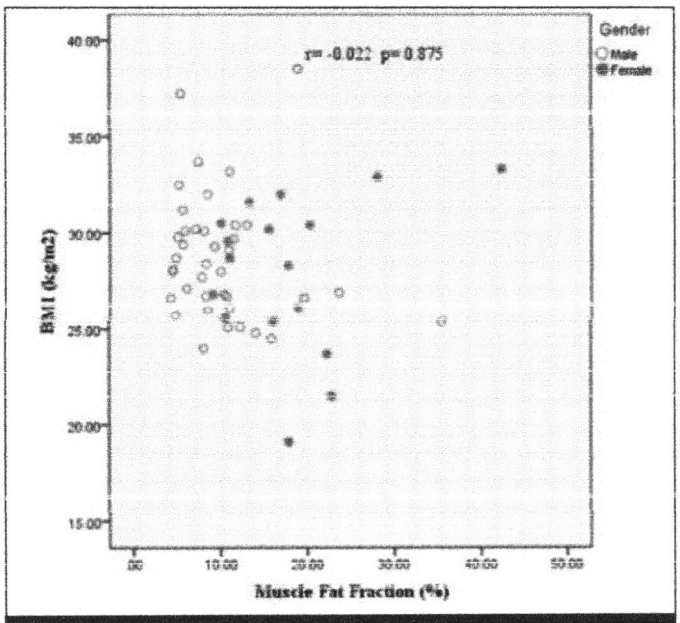
Myosteatosis showed a positive correlation with liver fibrosis (r=0.558; p<0.001) and a negative correlation with hepatic steatosis (r=-0.321; p=0.02), as shown in [Table/Fig-4a-d]. An ROC curve was performed to assess the muscle fat fraction test's ability to predict liver fibrosis. The Area Under Curve (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].



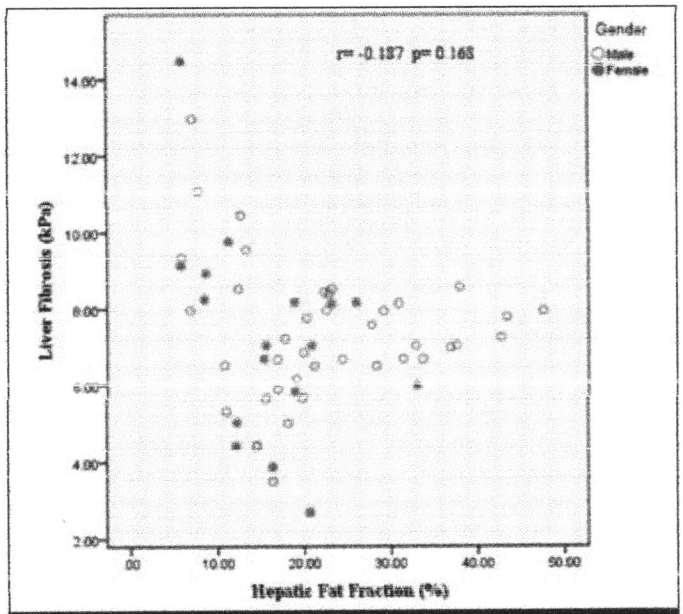
[Table/Fig-4a]: Partial correlation corrected for gender of muscle fat fraction and hepatic fat fraction showing negative correlation (r=-0.321, p=0.02).



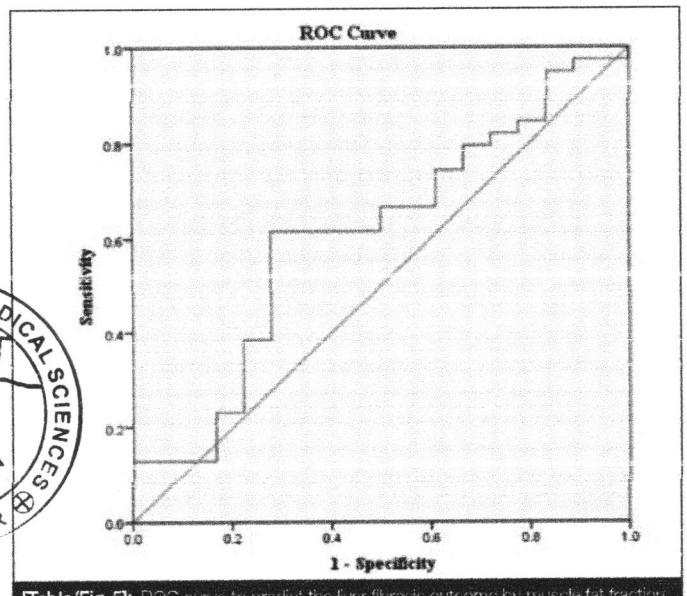
[Table/Fig-4b]: Partial correlation corrected for gender of muscle fat fraction and liver fibrosis showing positive correlation (r=0.558, p=<0.001).



[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.

REFERENCES

[1] Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: A systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology. 2022;7(9):851-61.

[2] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, 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.

[3] Sharma B, John S. Nonalcoholic Steatohepatitis (NASH). 2023 Apr 7. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan. PMID: 29262166.

[4] Aydin MM, Akçalı KC. Liver fibrosis. Turk J Gastroenterol. 2018;29(1):14-21. Doi: 10.5152/tjg.2018.17330.

[5] Abdul-Ghani MA, DeFronzo RA. Pathogenesis of insulin resistance in skeletal muscle. J Biomed Biotechnol. 2010;2010:476279.

[6] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908-22.

[7] Boettcher M, Machann J, Stefan N, Thamer C, Häring HU, Claussen CD, et al. Intermuscular adipose tissue (IMAT): Association with other adipose tissue compartments and insulin sensitivity. J Magn Reson Imaging. 2009;29(6):1340-45.

[8] Bosma M, Kersten S, Hesselink MKC, Schrauwen P. Re-evaluating lipotoxic triggers in skeletal muscle: relating intramyocellular lipid metabolism to insulin sensitivity. Prog Lipid Res. 2012;51(1):36-49.

[9] Petäjä EM, Yki-Järvinen H. Definitions of normal liver fat and the association of insulin sensitivity with acquired and genetic NAFLD- A systematic review. Int J Mol Sci. 2016;17(5):633.

[10] Nachit M, Leclercq IA. Emerging awareness on the importance of skeletal muscle in liver diseases: Time to dig deeper into mechanisms! Clin Sci (Lond). 2019;133(3):465-81.

[11] Nachit M, Lanthier N, Rodriguez J, Neyrinck AM, Cani PD, Bindels LB, et al. A dynamic association between myosteatosis and liver stiffness: Results from a prospective interventional study in obese patients. JHEP Rep. 2021;3(4):100323.

[12] Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005;115(2):209-18.

[13] Permutt Z, Le TA, Peterson MR, Seki E, Brenner DA, Sirlin C, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease- MRI accurately quantifies hepatic steatosis in NAFLD. Aliment Pharmacol Ther. 2012;36(1):22-29.

[14] Kitajima Y, Eguchi Y, Ishibashi E, Nakashita S, Aoki S, Toda S, et al. Age-related fat deposition in multifidus muscle could be a marker for nonalcoholic fatty liver disease. J Gastroenterol. 2009;45(2):218-24. Doi: 10.1007/s00535-009-0147-2.

[15] Wellens RI, Roche AF, Khamis HJ, Jackson AS, Pollock ML, Siervogel RM. Relationships between the body mass index and body composition. Obes Res. 1996;4(1):35-44.

[16] Eskreis-Winkler S, Corrias G, Monti S, Zheng J, Capanu M, Krebs S, et al. IDEAL-IQ in an oncologic population: Meeting the challenge of concomitant liver fat and liver iron. Cancer Imaging. 2018;18(1):51.
[17] Fu J, Wu B, Wu H, Lin F, Deng W. Accuracy of real-time shear wave elastography in staging hepatic fibrosis: A meta-analysis. BMC Med Imaging. 2020;20:01-09.
[18] Kim HS, Kim HK, Jung CH. Association of myosteatosis with nonalcoholic fatty liver disease, severity, and liver fibrosis using visual muscular quality map in computed tomography (diabetes Metab J 2023;47:104-17). Diabetes Metab J. 2023;47(2):304-05. Doi: https://doi.org/10.4093/dmj.2023.0058.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiodiagnosis, Amala Institue of Medical Sciences, Thrissur, Kerala, India.
2. Associate Professor, Department of Radiodiagnosis, Amala Institue of Medical Sciences, Thrissur, Kerala, India.
3. Associate Professor, Department of Gastroenterology, Amala Institue of Medical Sciences, Thrissur, Kerala, India.
4. Assistant Professor, Department of Radiodiagnosis, Amala Institue of Medical Sciences, Thrissur, Kerala, India.
5. Head, Department of Radiodiagnosis, Amala Institue of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Tony Joseph Kattakkayam,
Assistant Professor, Department of Radiodiagnosis, Amala Institute of Medical Sciences, Amala Nagar, Thrissur-680555, Kerala, India.
E-mail: tonykatts@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 06, 2023
- Manual Googling: Aug 02, 2023
- iThenticate Software: Aug 21, 2023 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: May 03, 2023
Date of Peer Review: Jul 28, 2023
Date of Acceptance: Aug 23, 2023
Date of Publishing: Nov 01, 2023

AMALA INSTITUTE OF MEDICAL SCIENCES THRISSUR

Betsy

Dr. BETSY THOMAS
MD, FRCOG, DNB, MICOG
PRINCIPAL
AMALA INSTITUTE OF MEDICAL SCIENCES
AMALA NAGAR, THRISSUR-680 555