Original Article

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Radiology Section

Non Invasive Assessment of Fibrosis in Non Alcoholic Fatty Liver Disease by Shear Wave Elastography and NAFLD Fibrosis Score: A Cross-sectional Study

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ABSTRACT

Introduction: The major consequence of Non Alcoholic Fatty Liver Disease (NAFLD) is the inflammation and fibrosis of hepatic tissue resulting in cirrhosis, portal hypertension, and eventually hepatocellular carcinoma. Presently, the distinction between simple steatosis, steatohepatitis, and cirrhosis stages of NAFLD is largely dependent on liver biopsy. Since, liver biopsy is invasive, it is not suitable for screening purposes. To overcome this limitation, elastography and NAFLD fibrosis score have been studied as non invasive objective substitutes for liver biopsy.

Aim: To evaluate the diagnostic accuracy of Shear Wave Elastography (SWE) as a method to diagnose significant-advanced fibrosis in patients with NAFLD by using NAFLD fibrosis score as a reference standard.

Materials and Methods: This hospital based cross-sectional study was conducted at JSS Hospital, Mysuru, Karnataka, India over a period of 18 months from September 2018 to November 2019. Total 154 participants underwent ultrasound abdomen to assess the presence and grade the degree of steatosis. All patients underwent 2D shear wave elastography and the values were compared with NAFLD fibrosis scores. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistics version 23.0.

Results: The age of this study group ranged from 20-76 years, mean age was 42.8±10.8 years including 51 (33.1%) females and 103 (66.9%) males. The level of agreement for assessment of fibrosis between SWE and NAFLD fibrosis score was good (score of 0.71). Using a predictive shear stiffness threshold of 6.1 kPa, shear stiffness distinguished low (fibrosis stage 0-2) from high (fibrosis stage 3-4) fibrosis stages with a sensitivity of 83% and a specificity of 92.5% (area under the curve of 0.879).

Conclusion: Two-dimensional shear wave elastography showed a good diagnostic performance for detection of fibrosis.

Keywords: Cirrhosis, Liver biopsy, Steatosis, Ultrasound

INTRODUCTION

Due to recent changes in lifestyle and diet, there has been a global rise in incidence of Non Alcoholic Fatty Liver Disease (NAFLD) creating a public health crisis, particularly in south Asia with a prevalence of approximately 9-32% within the general population of India [1].

Non alcoholic fatty liver disease is a spectrum of liver disease characterised by intracellular deposition of lipids within the hepatocytes, inflammation leading to hepatocytes injury which is accompanied by varying degree of fibrosis in the absence of secondary causes such as alcohol, drugs, toxins, hepatitis etc. Histologically the disease spectrum ranges from the benign hepatic steatosis to Non Alcoholic Steatohepatitis (NASH) with progressive fibrosis ultimately leading to cirrhosis [2]. Patients with NAFLD have a higher incidence of cardiovascular diseases and liver-disease related morality such as cirrhosis and hepatocellular carcinoma as compared to control population [3,4]. Various studies have shown that early intervention in NAFLD patients such as diet control, exercise and weight loss leads to an improvement in the histological grade of NAFLD [5]. Hence, early identification of fibrosis in NAFLD is vital.

Among the various techniques available to assess liver fibrosis, liver biopsy remains the gold standard. However, its utility as a screening test is impractical and unwarranted due to invasive nature. Moreover, it is prone to sampling errors, interobserver and intraobserver variability in the interpretation of histopathological slides thereby limiting its accuracy [6]. To overcome this limitation numerous non invasive biochemical and radiological tools have been developed to assess the degree of fibrosis of liver in NAFLD patients.

The serum non invasive methods are Alanine aminotransferase/Aspartate aminotransferase ratio, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), Fibrosis-4 index for hepatic fibrosis, NAFLD fibrosis score and BARD {Body mass index ≥ 28=1 point, Aspartate transaminase/Alanine transaminase Ratio (AAR) ≥ 0.8=2 points, type 2 Diabetes mellitus=1point} score. Of these the NAFLD fibrosis score is the most validated for assessment of fibrosis in NAFLD. It utilises six variables which include age, body mass index, hyperglycaemia, platelet count, albumin and AST/ALT ratio [7]. Advanced fibrosis can be ruled out with high accuracy by using a low cut-off point (-1.455) with a negative predictive value of 93%, thereby avoiding biopsies in these patients [8].

In radiology, elastography is used as a non invasive tool for assessment of liver fibrosis. Various elastography techniques include the transient elastography, shear wave elastography, supersonic shear wave elastography, Real time elastography and MRI Elastography. The most widely accepted and easily available techniques are transient elastography and 2D shear wave elastography [9].

In this study, we have assessed the shear wave elastography scores and NAFLD fibrosis score in normal and varying grade of fatty infiltration of liver as assessed by 2D ultrasound. The Shear wave elastography score and NAFLD fibrosis score were compared to assess the degree of agreement between the two. Further, diagnostic accuracy of Shear Wave Elastography (SWE) as a method to diagnose significant-advanced fibrosis in NAFLD was assessed by using NAFLD fibrosis score as a reference standard.

MATERIALS AND METHODS

This hospital based cross-sectional study was conducted at JSS Hospital, Mysuru, Karnataka, India over a period of 18 months from September 2018 to November 2019. Total 154 participants underwent ultrasound abdomen to assess the presence and grade of Steatosis. Informed consent from the enrolled participants and approval from Institutional Ethics Committee (IEC No-JSS/MC/PG/4623/2018-19) were obtained.

Sample size calculation: Based on previous hospital records (last five years), the prevalence of NAFLD among patients visiting the hospital was found to be 11%. Sample size was calculated by the formula; $N=z^2pq/d^2$ (N-Sample size, z-Standard deviation (1.96 for 95% confidence), p- prevalence, q-(1-p), d-margin of error of 5. A total of 154 subjects who met the inclusion and exclusion criteria referred were enrolled in the study.

Inclusion criteria: The inclusion criteria for enrollment was 2D ultrasound evidence of presence of steatosis with the absence of excessive alcohol consumption which was defined as alcohol consumption more than 20 g/day for women and 30 g/day for men.

Exclusion criteria: Alcoholics, pregnant women, Wilson's disease, iron overload and patients with known common secondary causes of fatty liver like drugs, chronic hepatitis B, chronic hepatitis C were excluded from the study.

Philips iu22 Ultrasound (USG) machine using curved array transducer of 3-5 MHz frequency was used for grey scale imaging of liver.

Fatty infiltration of liver grading [10]:

Grade 0: Normal echogenicity of Liver. Isoechoic to renal cortex.

Grade I: Minimal diffuse increase in the fine echoes. Liver appears bright compared to the cortex of the kidney. Normal visualisation of diaphragm and intrahepatic vessel borders.

Grade II: Moderate diffuse increase in the fine echoes. There is slight impaired visualisation of the intrahepatic vessels and diaphragm.

Grade III: Marked increase in the fine echoes. There is poor or no visualisation of intrahepatic vessels and diaphragm with poor penetration of the posterior segment of the right lobe of the liver.

Point shear wave elastography quantification: Shear wave elastography of the right lobe of liver was done following grey scale Ultrasound (USG) using curved array transducer of 3-5 MHz frequency on the Phillips iU22 US scanner. The participants were studied in supine with the right arm in maximum abduction. The right lobe of liver was subjected to shear wave elastography using the intercostal approach. Region of interest was elected free of vessels and ducts, within 2 cm from liver capsule. The participants were asked to stop breathing for a second in order to curtail breathing motion. All dimensions were performed by the same radiologist and described in kilopascals (kPa).

Study Procedure

Total of ten valid readings were taken. More than 60% of the measurements had to be good measurements; if not, a value was not reported. A "good" measurement was one where a numerical result is obtained, not an "x.xx" or "0.00". Median value was selected out of the total readings obtained. The shear wave speed was presented in kilopascals using Young's modulus [11].

The liver stiffness was categorised into different stages of fibrosis such as significant fibrosis (F>2), advanced fibrosis (F>3), and cirrhosis (F=4), respectively, using cut-off values of 6.43 kPa, 9.54 kPa, and 11.34 kPa, respectively, as given by Ferraioli G et al., [12].

Serum Liver fibrosis indices: The age, height, weight, Body Mass Index (BMI), platelet count, presence or absence of diabetes mellitus and liver function tests were obtained to calculate NAFLD score. The NAFLD fibrosis score was calculated as follows:

NAFLD fibrosis score=1.675×0.037 age (years)×0.094 BMI (kg/m^2)×1.13×IFG/diabetes (yes 1, no 0)×0.99 AST/ALT ratio 0.013 platelet ($10^9/L$) 0.66 albumin (g/dL) [8].

Based on NAFLD fibrosis score the participants were grouped into three groups a described below [8].

< -1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)

≥ -1.455 to ≤ 0.675: indeterminate score

> 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistics version 23.0 (IBM, Armonk, NY, USA). Continuous variables were summarised as the mean±standard deviation. The Student's t-test, Chi-square test and Fisher's-exact test were used as appropriate. Statistical significance was set at a two-sided p-value <0.05. The mean values of patients with sonographic findings of NAFLD were calculated. The level of agreement between SWE and serum fibrosis indices (NAFLD fibrosis score) was measured using the Kendall tau correlation coefficient. The diagnostic performance of SWE for staging liver fibrosis compared with NAFLD fibrosis score (reference standards), was assessed using Receiver-Operator Characteristic (ROC) curve and the Area Under Receiver Operating Characteristics Curve (AUROC) analysis.

RESULTS

The age of this study group ranged from 20-76 years, mean age was 42.8±10.8 years [Table/Fig-1]. This study population consisted of 51 females (33.1%) and 103 males (66.9%).

Age distribution (years)	Number	Percentage
<30 years	12	7.8%
31-40 years	61	39.6%
41-50 years	45	29.2%
51-60 years	28	18.2%
>60 years	8	5.2%
Total	154	100%

[Table/Fig-1]: Age-wise distribution of patients.

Based on 2D ultrasound grading of fatty infiltration of liver, among the study population, 50 (32.5%) did not have fatty infiltration of liver, 51 (33.1%) of them had grade I fatty infiltration of liver. While 23 (14.9%) of the study group had grade II fatty infiltration and 30 (19.5%) of the study group had grade III fatty infiltration [Table/Fig-2].

Study group	Frequency	Percentage
Grade 0	50	32.5%
Grade I	51	33.1%
Grade II	23	14.9%
Grade III	30	19.5%

[Table/Fig-2]: Distribution of participants in various sonographic grades of Fatty Liver.

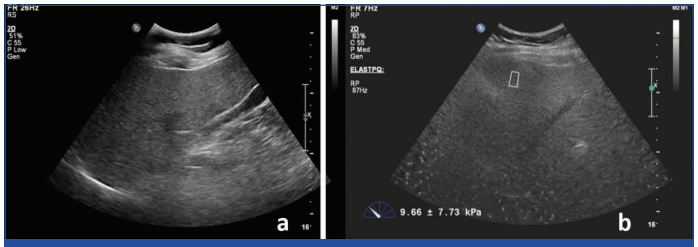
Comparison of SWE measurements with sonographic findings: On shear wave elastography quantification of liver stiffness, the mean liver stiffness in participants without 2D ultrasound evidence of fatty infiltration was found to be 4.6±1.1 kPa.

In this study, there is progressive rise in liver stiffness with increase in severity of fatty infiltration. The mean liver stiffness for grade I fatty infiltration was 6.7±0.94 kPa, grade II fatty infiltration was 9.3±1.28 kPa and grade III fatty infiltration was 10.7±2.06 kPa [Table/Fig-3].

Fatty liver grading	Mean SWE (kilopascals)	Standard deviation
Grade 0	4.60	1.17
Grade I	6.7	0.94
Grade II	9.3	1.28
Grade III	10.74	2.06

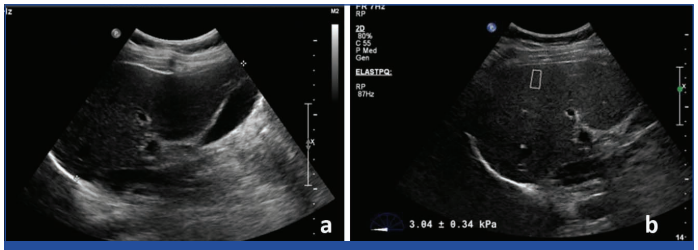
[Table/Fig-3]: Shear wave elastography measurements based on ultrasonography grades of fatty infiltration.

A 47-year-old female with Grade III fatty infiltration of liver on B-mode USG was moderately increased echo pattern of liver with slight impairment of visualisation of intrahepatic vessels and blurring of diaphragmatic margin [Table/Fig-4a]. On SWE, value of 9.6 kPa was obtained [Table/Fig-4b]. Her NAFLD fibrosis score was 0.046.



[Table/Fig-4]: a) and b) 2D USG - Grade III fatty liver; Shear wave elastography of 9.6 kPa. NAFLD Fibrosis score was 0.046.

A 20-year-old male with normal echo pattern of liver B-mode USG was without sonological evidence of fatty infiltration [Table/Fig-5a]. On SWE value of 3.04 kPa was obtained [Table/Fig-5b]. His NAFLD fibrosis score was -0.758.



[Table/Fig-5]: a) and b): Grade fatty liver- Normal echo pattern of liver. Shear wave elastography was 3.04 kpa. NAFLD Fibrosis score was -0.758.

Distribution of fibrosis among the NAFLD groups based on Shear wave elastography estimation: Among the 104 subjects with fatty infiltration of liver, 10 (9.6%) had no significant fibrosis, 64 (61.5%) had significant fibrosis, 19 (18.2%) had advanced fibrosis and 11 (10.5%) had cirrhosis. Among the 50 participants with sonological normal liver had 46 (92%) had no significant fibrosis on elastography and 4 (8%) had significant fibrosis.

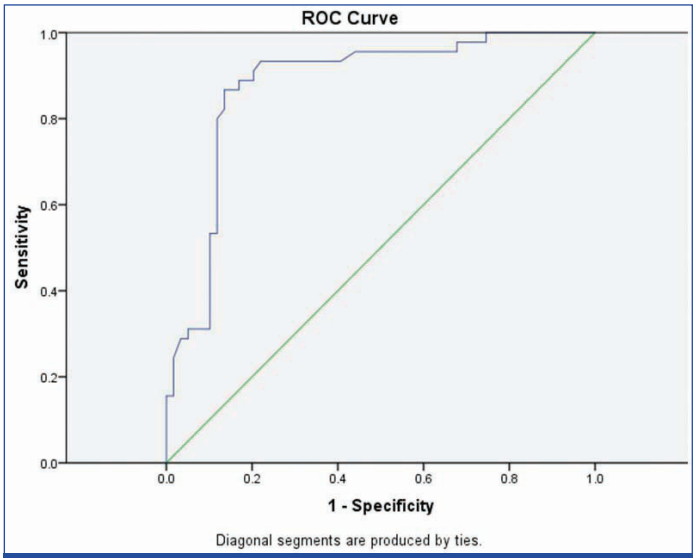
Distribution of fibrosis among the NAFLD groups based on NAFLD fibrosis score: Based on NAFLD fibrosis score, out of the 154 participants, 16% had low risk of fibrosis i.e., advanced fibrosis could be excluded with high accuracy, 27.9% had an intermediate score and 56.5% of them had significant fibrosis (F3 and F4) [Table/Fig-6].

NAFLD fibrosis score	Number	Percentage
Low risk- Advanced fibrosis can be excluded with high accuracy	24	16%
Intermediate score	43	27.9%
Advanced fibrosis (F3 and F4)	87	56.5%

[Table/Fig-6]: Distribution of fibrosis among study participants based on NAFLD fibrosis score.

Performance of SWE in the estimation of fibrosis: The level of agreement for staging of fibrosis between SWE and NAFLD fibrosis score was assessed using the Kendall's tau correlation test. Good agreement was obtained between the SWE and serum NAFLD fibrosis score with a score of 0.71 achieving a highly statistical significance (p-value <0.001).

The diagnostic ability of SWE to differentiate the stage of fibrosis was evaluated by ROC curve analysis. Patients were divided into a lack of significant fibrosis (F0-F1) and presence of significant-advanced fibrosis (F2-F4) taking NAFLD fibrosis score values as the reference standard with NAFLD fibrosis score of > - 1.455 used as cut-off for the presence of significant-advanced fibrosis. The ROC curves were plotted using SWE measurements for prediction of presence of significant-advanced fibrosis (F2-F4) over a lack of significant fibrosis (F0-F1). The Area Under Receiver Operating Characteristics Curve (AUROC) was 0.879 for the prediction of significant-advanced fibrosis (F2-F4) over a lack of significant fibrosis (F0-F1) using SWE measurements. The best discriminating cut-off value of liver stiffness to diagnose significant-advanced fibrosis was 6.1 kPa [Table/Fig-7]. This cut-off was associated with a sensitivity and specificity of shear wave elastography in detecting advanced fibrosis of 83% and 92.5%, respectively. The positive predictive rate was 90.5% and negative predictive rate of 70.4%.



[Table/Fig-7]: The Receiver Operator Characteristic (ROC) curve for the prediction of significant fibrosis (F2-F4) over no significant fibrosis (F0-F1) using shear wave elastography measurements. A cut-off value of 6.1 kPa was obtained with sensitivity and specificity of 83.0% and 92.5%, respectively.

DISCUSSION

In this study, based on 2D USG grading of fatty infiltration of liver, out of 154 participants included in the study, 50 (32.5%) did not have fatty infiltration of liver, 51 (33.1%) of them had grade 1 fatty infiltration of liver, 23 (14.9%) of them had grade II fatty infiltration and 30 (19.5%) of them had grade III fatty infiltration.

On shear wave elastography, a mean liver stiffness of 4.6±1.1 kPa was obtained in subjects without 2D ultrasound evidence of fatty infiltration. Similar such normal liver stiffness values were published in a study by Huang Z et al., [13]. In their study, mean value of the SWE measurements in 502 individuals without fatty infiltration of liver was 5.10±1.02 kPa. Suh CH et al., provided a range of normal elastography value of 2.6-6.2 kPa and in a study by Arda K et al., mean elasticity value for the right lobe of liver was determined as 4 kPa ±2.2 kPain 127 healthy volunteers [14,15].

In this study, there was progressive rise in liver stiffness with increase in severity of fatty infiltration. This finding was consistent with study done by Li YY et al., which showed a positive correlation between rise in liver stiffness with increasing grade of fatty liver with correlation coefficient of 0.822 [16]. However, this result is in conflict with study conducted by Yoneda M et al., where there was lower stiffness in mild steatosis as compared to normal liver [17]. The effect of steatosis and inflammation on measurement of liver stiffness to assess fibrosis has been evaluated by various studies with varied results. Most studies have concluded that steatosis and inflammation affects transient elastography [18-20] based assessment of fibrosis but not fibrosis assessment by shear wave elastography [21]. Liu H, et al., in a systematic review and meta-analysis evaluated the diagnostic efficacy of Acoustic Radiation Force Impulse (ARFI) elastography in detecting hepatic fibrosis in NAFLD patients found that majority of the Shear Wave Speed (SWV) increases with the degree of fibrosis observed by histopathology [22].

In the present study, the overall prevalence of significant, advanced fibrosis and cirrhosis as aby shear wave elastography was 56.6%,

32% and 20%, respectively. In a meta-analysis of 64 original articles (13,046 NAFLD patients) by Xiao G et al., the prevalence of significant, advanced fibrosis and cirrhosis in NAFLD patients were 45.0%, 24.0% and 9.4%, respectively [23].

On comparing the fibrosis staging by shear wave elastography and NAFLD fibrosis score, good agreement was obtained with a value of 0.71 (Kendall's Tau correlation coefficient). In a recent study by Alsowey AM and Shehata SM an excellent agreement was found between shear wave elastography and fibrotest in staging of liver fibrosis in 88% of their study population [24].

There are few studies that have compared the elastography with fibrosis score for assessment of liver fibrosis due to other aetiologies such as the Hepatitis B and C. Lee JE et al., and Lu Q et al., compared the utility of point shear wave elastography with serum fibrosis indices (APRI and FIB-4) and HPE findings [25,26]. Lee JE et al., reported a similar diagnostic accuracy of point SWE, ARFI and Transient Elastography (TE) with histopathological examination findings [25]. Lu Q et al., concluded that liver stiffness as measured by point SWE has a stronger correlation compared with histopathological fibrosis stages than APRI and Fibrosis-4 (FIB-4) [26].

Using NAFLD fibrosis score as a reference standard, a cut-off of 6.1 Kpas was obtained to differentiate no fibrosis from significant-advanced fibrosis with a good sensitivity and specificity. Based on the statistical analysis in this study, we found that point SWE had a high diagnostic accuracy with AUCs of 0.879 (cut-off value-6.1 Kpas). Studies by Dhyani M et al., Garcovich M et al., and Jamialahmadi T et al., reported a cut-off value of 6.83-10.8 KPas, 6.7 Kpas and 6.6 kpas for the diagnosis of significant-advanced fibrosis in NAFLD patients [27-29]. Furlan A et al., and Palmeri ML et al., reported slightly lower cut-off values of 5.7 kpas and 4.2 kpas for the diagnosis of significant-advanced fibrosis in NAFLD patients, respectively [30,31].

The clinical utility of fibrosis assessment in patients with NAFLD is less clearly defined than other types of liver disease. In this study, we focused on identifying the presence of significant-advanced liver fibrosis among the NAFLD patients as fibrosis has been well-established as a prognostic determinant among NAFLD patients. There is growing evidence that fibrosis has a great influence on the hepatic and extra-hepatic mortality as compared to simple steatosis or even NASH without fibrosis [2]. Hence, it is vital that fibrosis be diagnosed at the earliest for NAFLD patients. It also recognises candidates for surveillance, such as endoscopic screening for gastroesophageal varices and surveillance for hepatocellular carcinoma. In addition, the presence of fibrosis may encourage the physician and the patient to make efforts at sustainable weight reduction [32].

The second rational is that definitive diagnosis of fibrosis requires biopsy which is non invasive procedure and is associated with complications. This warrants a risk stratification of patients with NAFLD utilising the non invasive tests. Selective number of patients can be referred for a liver biopsy based on SWE and NAFLD fibrosis score values. NAFLD patients without evidence of fibrosis can be followed on USG instead of subjecting them to unnecessary biopsies. Further studies comparing the performance of other serum biomarkers {Enhanced Liver Fibrosis (ELF) panel, Fibrometer, FibroTest, and Hepascore} and imaging modalities such as MR elastography in staging of liver fibrosis in NAFLD patients is recommended.

Limitation(s)

The limitation of this study was that the 2D SWE values were not compared with histologic liver fibrosis stage.

CONCLUSION(S)

Two-dimensional shear wave elastography showed a good diagnostic performance for detection of liver fibrosis and had a good agreement with NAFLD fibrosis score in detecting the degree of liver fibrosis and hence can be used reliably for non invasive evaluation of fibrosis in NAFLD patients.

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