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ORIGINAL RESEARCH

Role of 2D-Shear Wave Elastography in the diagnosis and staging of fibrosis in patients of fatty liver disease with association with liver function tests

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INTRODUCTION

Fatty liver disease has emerged as a major global public health problem. The causes of fatty liver disease include multitude of factors. Fatty liver could be Alcoholic or Non-alcoholic fatty liver.[1] Alcoholic fatty liver develops as a result of excessive alcohol consumption. NAFLD is primarily caused by a high intake of calories and is associated with obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome, and other related conditions.[2] The accumulation and deposition of lipids, usually triglycerides, to greater than 5% of the weight of the liver in hepatocytes causes fatty liver disease, also known as hepatic steatosis.[3]

The prevalence of NAFLD in the world is estimated to be 25%,[4] with prevalence in India between 6.7% and 55.1%.[5] The prevalence of NAFLD increases with age. NAFLD includes a wide range of conditions, starting from the most prevalent form - hepatic steatosis or non-alcoholic fatty liver and progressing to non-alcoholic steatohepatitis (NASH) , advanced fibrosis and cirrhosis. Around 10-30% of individuals with simple steatosis progress to NASH, and within that group, approximately 5-10% develop liver cirrhosis within a span of five years. Furthermore, slightly more than 1 in 8 patients with liver cirrhosis develop hepatocellular carcinoma within three years.[6] In India, NAFLD has emerged as the primary factor contributing to cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation.[7]

Precise evaluation of liver fibrosis is essential for establishing prognosis, determining medication, monitoring disease progression, and assessing response to therapy in patients with chronic liver disease. The conventional method for identifying hepatic fibrosis, liver biopsy, is an invasive procedure that causes discomfort and entails potential consequences. Moreover, it is susceptible to sampling mistakes and variations in interpretation, rendering it inappropriate for repeated evaluations.[8,9] Consequently, there has been a rise in the need for non-invasive techniques that can precisely assess liver fibrosis.

NAFLD cannot be diagnosed or staged using a single biomarker. The main pattern observed in instances of NAFLD is a slight increase in blood amino-transferase levels. Liver enzyme elevation is not however sensitive to diagnose NAFLD. In patients with no or minimal fibrosis, the AST/ALT ratio is typically less than 1. However, when cirrhosis develops, this ratio may exceed 1.[10] Elevated levels of gamma-glutamyl transferase (GGT) in the blood are commonly observed in individuals with non-alcoholic fatty liver disease (NAFLD).[11] Many scholars have proposed evaluating other biomarkers to assist in identifying NAFLD. However, these studies have been constrained by their poor capacity to be replicated or effectively differentiate between mild fatty liver and more severe inflammation and fibrosis. Panel markers used for Non-alcoholic Steatohepatitis (NASH) include the APRI index, FIB-4 test,

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AST/ALT ratio, BARD score and NAFLD fibrosis score.

In some studies, the FIB-4 score has showed maximum accuracy in the diagnosisof advanced fibrosis, followed by AAR and other markers.[12] Some studies show that liver biopsy could have been avoided in 69% patients with AST/ALT ratio and 62% with FIB-4 in the diagnosis of advanced fibrosis.[13]

Among imaging techniques, ultrasonography is the primary and most used method for the purpose of screening cases of fatty liver due to its cost-effectiveness and widespread availability.

Ultrasound elastography techniques exhibit potential in assessing liver stiffness without necessitating invasive tools. These technologies have the benefit of offering real-time, quantitative evaluations of tissue stiffness, rendering them valuable instruments for assessing liver fibrosis in patients with chronic liver disorders.[6] Two-dimensional shear wave elastography (2D-SWE) is a technique that measures the stiffness of the liver in real time by using simultaneous ultrasound imaging and allows the user to choose the region of interest.[6]

The objective of this study is to utilise 2-D Shear wave Elastography to diagnose and determine the severity of fibrosis in individuals who have been identified with fatty liver during a routine abdominal ultrasound scan and associate the results with liver function test (LFT) data. The use of 2D-SWE could reduce the reliance on liver biopsy to diagnose and stage fibrosis.

METHODS

Study Design and Population

This hospital-based observational study was conducted at the Department of Radiodiagnosis, Mahatma Gandhi Medical College & Hospital, Jaipur, between July 2022 and December 2023. Ethical clearance was obtained before study initiation, and informed consent was collected from all participants.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients diagnosed with FLD on ultrasonography.
- Previously diagnosed FLD patients.

Exclusion Criteria:

- Patients unwilling to provide consent.

Elastography Technique

Liver stiffness was measured using General Electric LOGIQ P9 with 2D-SWE. The patient was positioned in a supine or slight left lateral decubitus position, with the right arm elevated for optimal imaging. Measurements were taken at a depth of 4-5 cm from the skin surface and within a minimum 1-2 cm of liver parenchyma avoiding vascular and biliary structures. Standardized protocols ensured accuracy by maintaining an IQR/median ratio below 30% for Young's modulus (E) and below 15% for shear wave velocity.

Cut off values provided by the manufacturer:

	Young's Modulus (kPa)	Shear Wave Velocity (m/s)	Fibrosis Grade
Normal	0-6.6	<1.48	F0-F1
	6.6-6.9	1.48-1.52	F1-F2
Mild Fibrosis	6.9-7.5	1.52-1.58	F2
	7.5-8.2	1.58-1.66	F2-F3
Severe Fibrosis	8.2-9.2	1.66-1.75	F3
	9.2-9.31	1.75-1.76	F3-F4
Cirrhosis	>9.31	>1.76	F4

Liver Function Tests

LFT parameter reports were collected, including:

- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Gamma-Glutamyl Transferase (GGT)
- Alkaline Phosphatase (ALP)
- Serum Bilirubin
- Serum Albumin

Platelet count report was also collected from the patients.

Fibrosis scores and biomarkers were ascertained:

- AST/ALT ratio (AAR)
- Aspartate-to-Platelet Ratio Index (APRI)
- Fibrosis-4 Index (FIB-4)

APRI = [(AST/upper limit of the normal AST range) X 100]/Platelet Count

FIB-4 = (Age (years) x AST Level (U/L)) / (Platelet Count (10/L) x √ALT (U/L))

Statistical Analysis

Data was entered into an Excel sheet and analyzed using statistical software. A p-value <0.05 was considered statistically significant.

RESULTS

In our study, more than one fourth of cases were of 49-58 years of age, followed by 22.0% of 39-48 years of age, and least four (3.1%) cases of 9-18 years of age. The mean age of cases was 45.76±15.11 years.

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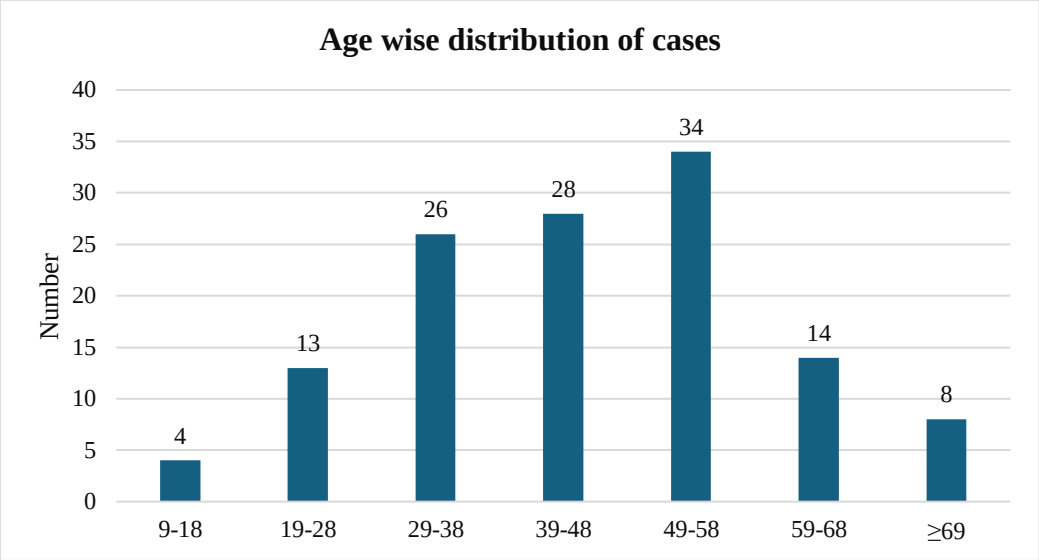
Table I. Age wise distribution of cases.

Age group (Years)	Number	Percentage
9-18	4	3.1
19-28	13	10.2
29-38	26	20.5
39-48	28	22.0
49-58	34	26.8
59-68	14	11.0
≥69	8	6.3
Total	127	100.0



Maximum cases (71.7%, 91/127) were male and rest 36(28.3%) were female.

In this study, 15(11.8%) had diabetes mellitus and a significant proportion of cases (41.7%, 53/127) cases had history of alcohol consumption. Almost one third (32.3%, 41/127) cases had history of smoking.

Table II- Fatty Liver Grade among cases based on B-Mode Ultrasonography

Fatty Liver Grade	Number	Percentage
Grade 1	43	33.9
Grade 2	55	43.3
Grade 3	29	22.8
Total	127	100.0

In current study, maximum cases 55(43.3%) were of Fatty Liver grade 2, followed by 43(33.9%) were of grade 1, and rest 29(22.8%) cases were of Fatty Liver grade 1.

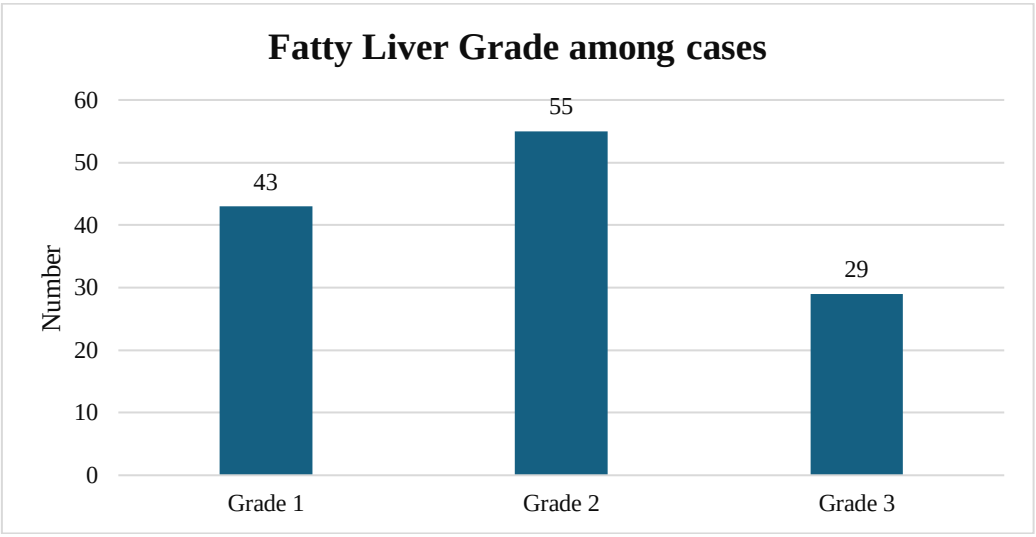


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Table III- Elasticity Grade among cases based on 2D-SWE.

Elasticity grade	Number	Percentage
F0-F1	65	51.2
F1-F2	3	2.4
F2	11	8.7
F2-3	7	5.5
F3	15	11.8
F3-F4	2	1.6
F4	24	18.8
Total	127	100.0

2D-SWE: Two Dimensional Shear Wave Elastography

According to the table provided by the manufacturer of the USG machine, we can group the cases into the following categories:

Table IV – Elasticity Grading - Categories

Elasticity Grade	Number	Percentage
Normal	68	53.6
Mild Fibrosis	18	14.2
Severe Fibrosis	17	13.4
Cirrhosis	24	18.8
Total	**127**	**100**

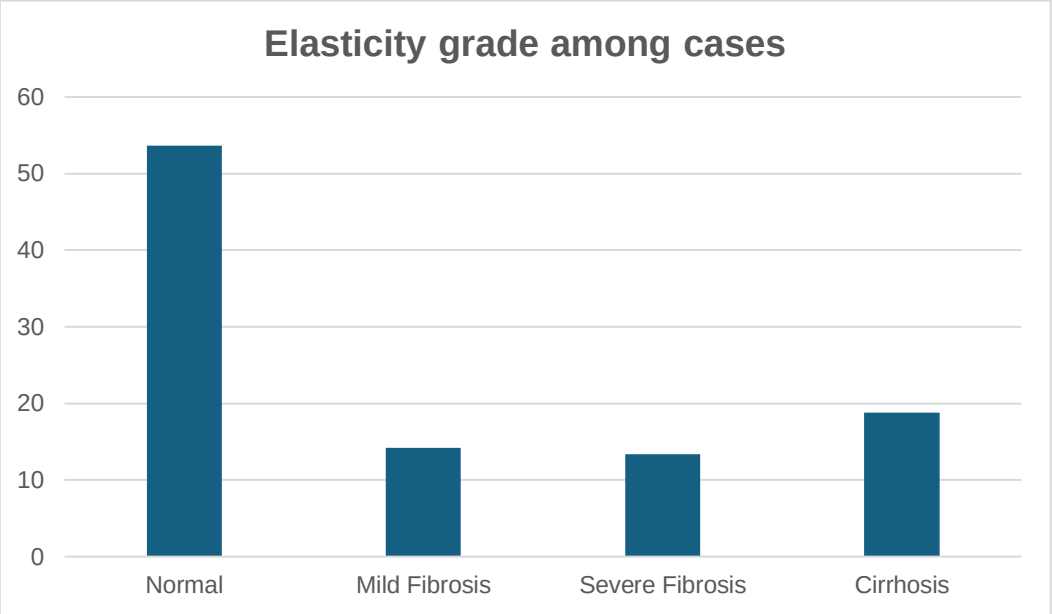

Table V. Correlation of Fatty Liver Grade with Elasticity Grade.

Fatty Liver Grade (USG)	Elasticity (Kpa) Grading (2D-SWE)			
	Normal	**Mild fibrosis**	**Severe fibrosis**	**Cirrhosis**
Grade 1	40(93%)	3(7%)	-	-
Grade 2	28(50.9%)	13(23.6%)	8(14.5%)	6(10.9%)
Grade 3	1(3.4%)	4(13.8%)	5(17.2%)	19(65.5%)

X^2=78.483, Df=6, p<0.001

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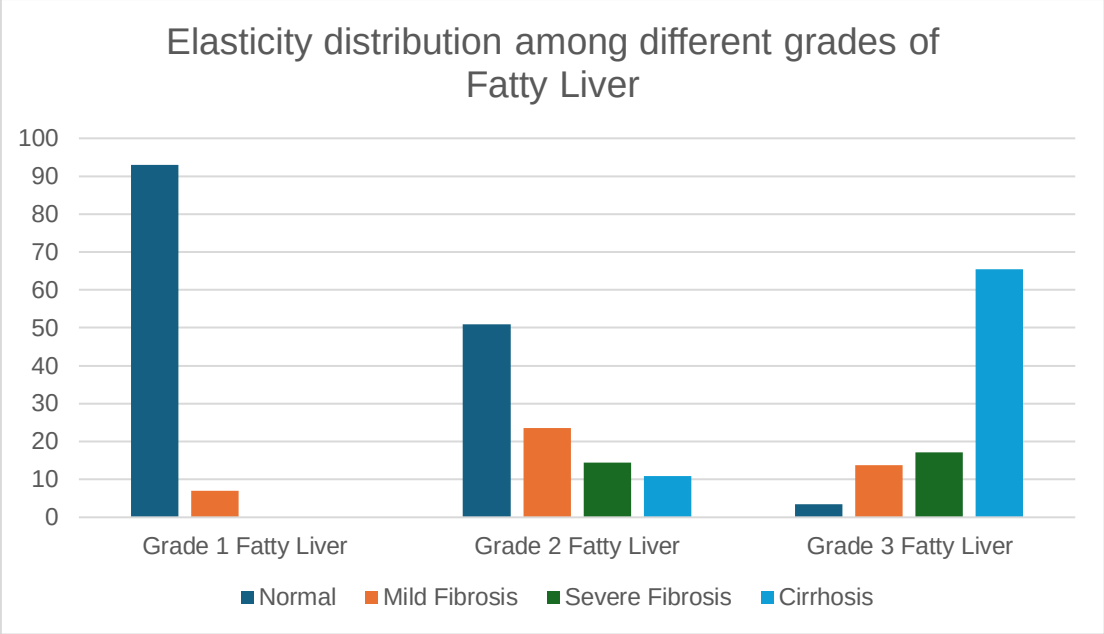
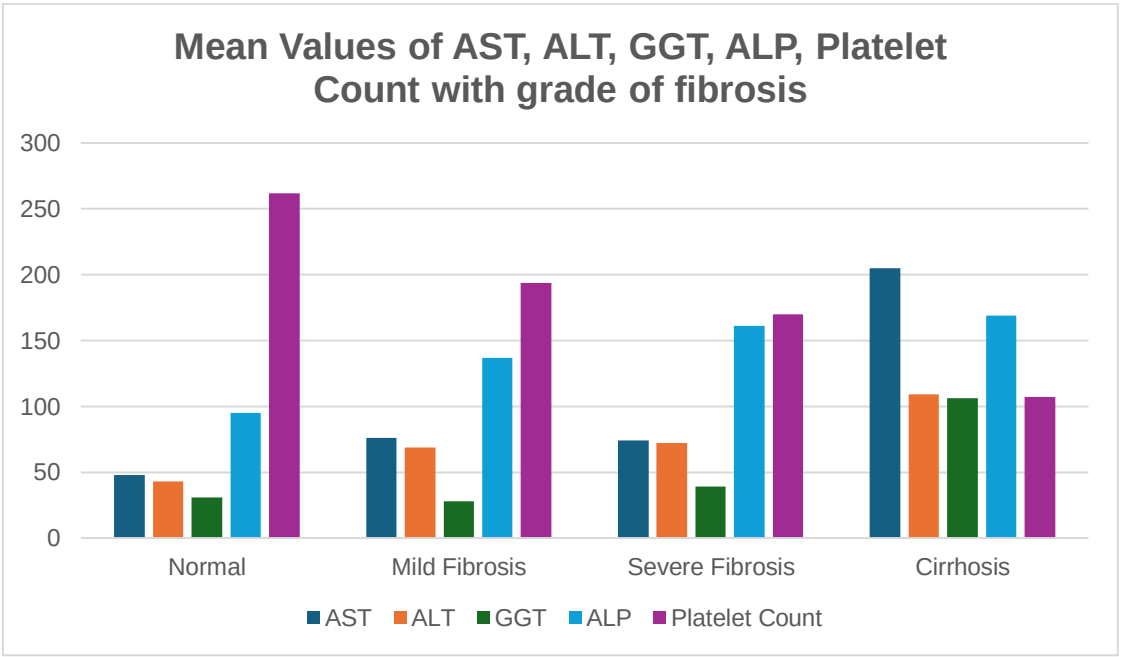


Majority of patients with fatty liver grade 1 had no evidence of fibrosis. On the other hand, majority of patients with grade 3 fatty liver had evidence of fibrosis ranging from mild to cirrhotic category.

Table VI. Differences in mean value of Liver Function Tests with grade of fibrosis.

Variable	Normal	Mild Fibrosis	Severe Fibrosis	Cirrhosis	p value
AST (U/L)	48.1±42.53	76.79±16.32	74.85±24.16	205.85±219.43	<0.001
ALT (U/L)	43.49±38.1	69±18.21	72.46±28.14	109.63±102.17	<0.001
GGT (U/L)	31.88±16.51	28.9±16.48	39.54±35.99	106.44±165.37	<0.001
ALP (U/L)	95.47±59.25	137.6±77.82	161.85±85.41	169.6±123.85	<0.001
Platelet count (x 10^3/µL)	262.09±109.24	194.35±65.47	170.77±22.99	107.84±46.67	<0.001
Total S. Bilirubin (mg/dL)	1.48±4.52	3.57±5.26	2.24±1.63	9.32±10.51	<0.001
Serum Albumin (g/dL)	4.24±0.5	3.75±0.54	3.51±0.53	3.07±0.64	<0.001

AST: Aspartate Transaminase
ALT: Alanine Transaminase
GGT: Gamma Glutamyl Transferase
ALP: Alkaline Phosphatase



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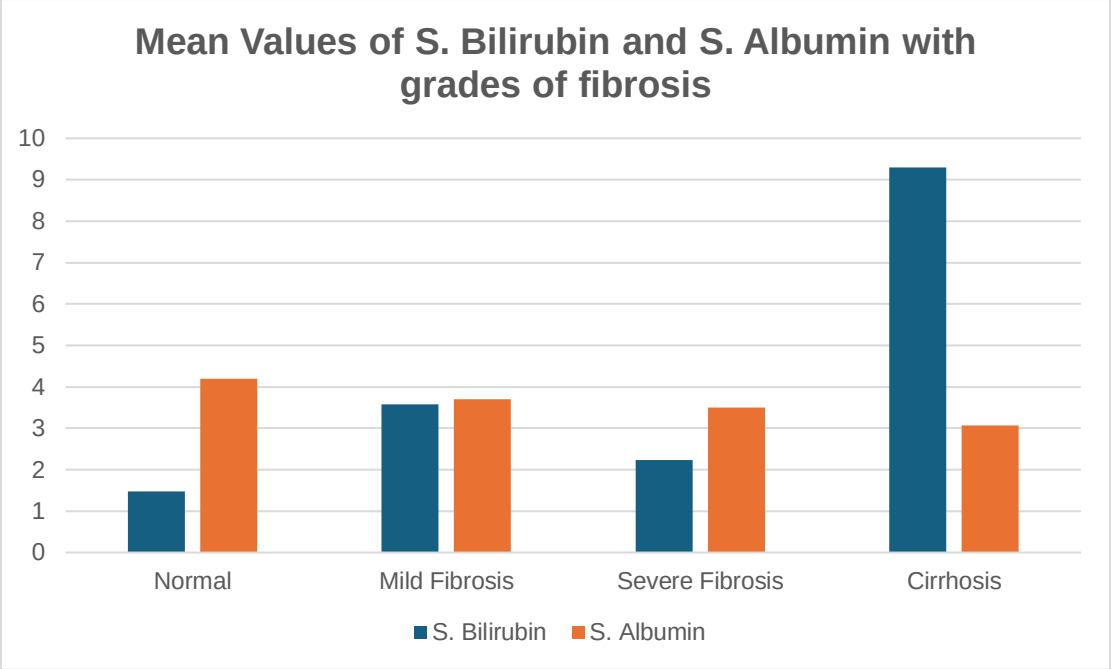

Table VII. Fibrosis markers with grade of fibrosis.

Variable	Normal	Mild Fibrosis	Severe Fibrosis	Cirrhosis	p value
AAR	1.25±0.57	1.19±0.42	1.07±0.15	1.93±0.84	<0.001
APRI	0.66±1.12	1.06±0.73	0.97±0.41	5.3±7.68	<0.001
FIB-4	1.71±1.74	2.81±1.79	2.89±0.89	8.8±6.59	<0.001

AAR: AST to ALT Ratio
APRI : AST to Platelet Ratio Index
FIB-4: Fibrosis – 4 score

In our study, mean value of AST, ALT, AAR, FIB-4, GGT, and ALP was lower in normal cases, and was increasing with increase in grade of cirrhosis, and this difference in mean value of above variables with grade of cirrhosis was found to be statistically significant ($p<0.05$)

In present study, with increase in grade of cirrhosis there was increase in mean value of total serum bilirubin, and decrease in platelet count and serum albumin, and this association was statistically significant ($p<0.05$).

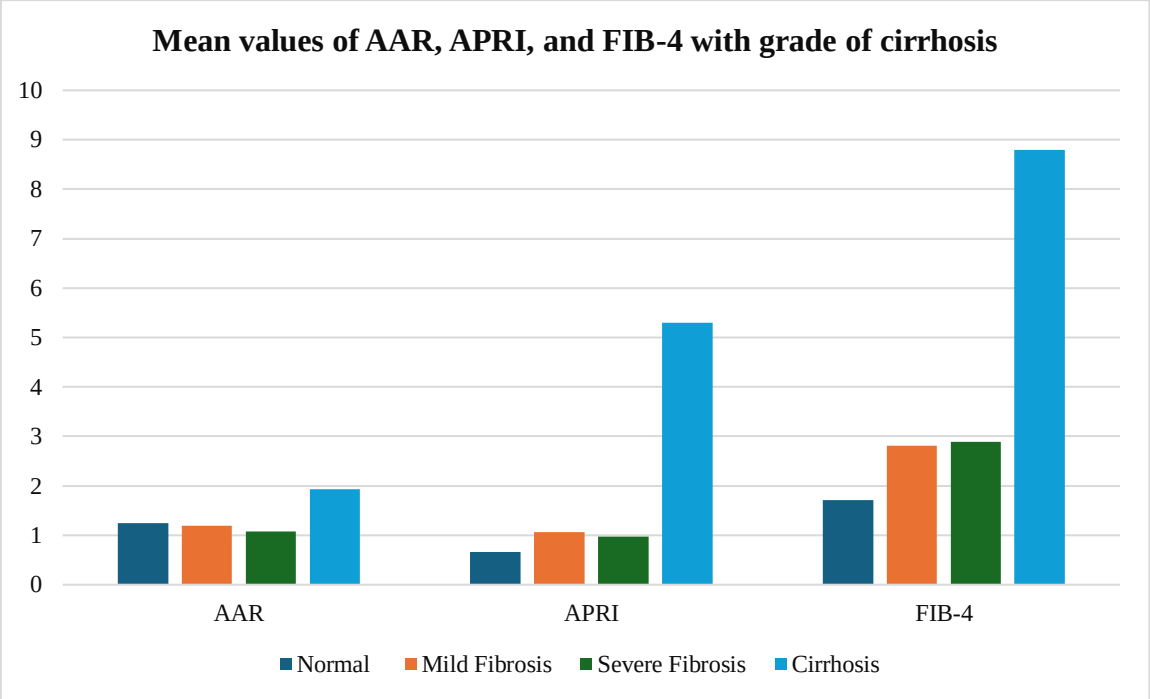

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Table VIII. Association of grade of fibrosis with diabetes, history of smoking and alcohol

Variable	Normal	Mild Fibrosis	Severe Fibrosis	Cirrhosis	p value
Diabetes					
Absent	60(53.6)	18(16.1)	11(9.8)	23(20.5)	
Present	9(60)	2(13.3)	2(13.3)	2(13.3)	1.000
History of alcohol consumption					
Absent	41(55.4)	12(16.2)	10(13.5)	11(14.9)	
Present	28(52.8)	8(15.1)	3(5.7)	14(26.4)	0.349
History of smoking					
Absent	46(53.5)	12(14)	12(14)	16(18.6)	
Present	23(56.1)	8(19.5)	1(2.4)	9(22)	0.305

Among cases without diabetes, 53.6% were normal and rest have some degree of fibrosis or cirrhosis, while in cases with diabetes 60% were normal and rest have some degree of fibrosis or cirrhosis. Similarly, among cases with history of alcohol and smoking, around half of them were normal and rest half have some degree of fibrosis or cirrhosis. This association of grade of cirrhosis with diabetes, history of smoking and alcohol was statistically insignificant ($p>0.05$)

DISCUSSION

This study, conducted at Mahatma Gandhi Hospital, Jaipur, included 127 participants diagnosed with fatty liver or chronic liver disease. The mean age was 45.76 ± 15.11 years, with most participants (71.7%) being male.

Liver fibrosis assessment showed 53.6% of cases in the normal category (F0-F1/F1-F2), 14.2% with mild fibrosis (F2/F2-F3), 13.4% with severe fibrosis (F3/F3-F4), and 18.9% with cirrhosis. Fibrosis staging distributions closely matched Herrmann et al. (2018), with similar proportions in F0-F1 (51.2% vs. 52.0%) and F4 (18.9% vs. 21.0%), while our F2 (8.7% vs. 11.0%) and F3 (11.8% vs. 16.0%) proportions were lower.[5]

A significant correlation ($p < 0.05$) was observed between fatty liver grade and fibrosis severity. Among FL Grade 1 cases, 93% were normal, while 65.5% of FL Grade 3 cases had cirrhosis. This aligns with Castera et al. (2008), who reported lower kPa values in early fibrosis (F0-F1) and increasing values in advanced fibrosis (F2-F4).[14] Similarly, Friedrich-Rust et al. (2009) confirmed kPa's efficacy in differentiating fibrosis stages,[15] and Mederacke et al. (2016) highlighted elastography's reliability, particularly in advanced fibrosis, consistent with our findings for FL Grade 3 cases.[16]

These findings reinforce elastography as a valuable tool in assessing fibrosis progression, with fatty liver severity correlating with increasing fibrosis stages.

Platelet Count

The study reveals a significant decline in platelet count with advancing fibrosis and cirrhosis, with values dropping from 262.09 ± 109.24 in normal individuals to 107.84 ± 46.67 in cirrhosis ($p < 0.001$). This trend aligns with findings from Valla et al. (2017), who noted that thrombocytopenia is a common feature in chronic liver disease.[17]

Total Serum Bilirubin

A marked increase in total serum bilirubin levels was observed with progression from normal to cirrhosis, with values rising from 1.48 ± 4.52 mg/dL in normal individuals to 9.32 ± 10.51 mg/dL in cirrhosis ($p < 0.001$). This finding is consistent with Kim et al. (2019), who demonstrated that elevated bilirubin levels reflect impaired hepatic function and bile excretion, which are characteristic of advanced liver disease.[18]

Serum Albumin

Serum albumin levels decreased progressively with disease severity, from 4.24 ± 0.5 g/dL in normal individuals to 3.07 ± 0.64 g/dL in cirrhosis ($p < 0.001$). This decrease mirrors findings by Tsochatzis et al. (2014), who reported reduced albumin levels in patients with cirrhosis. The decline in serum albumin is a result of the liver's diminished synthetic capacity and is a well-recognized marker of liver dysfunction.[19]

AST and ALT

The study reveals a significant increase in AST and ALT levels with advancing fibrosis and cirrhosis, with the highest values observed in cirrhosis. This aligns with findings from Kwo et al. (2017), which also noted elevated AST and ALT in more severe liver disease stages.[20]

AAR

An AAR above 1.0 often suggests advanced liver disease, particularly if elevated alongside other markers. In this study, the Aspartate Aminotransferase to Alanine Aminotransferase Ratio (AAR) varied significantly across fibrosis stages ($p < 0.001$), peaking in cirrhosis (1.95 ± 0.84) and reaching its lowest in severe fibrosis (1.11 ± 0.16). Notably, the normal group exhibited a slightly higher mean AAR (1.25 ± 0.58) compared to mild and severe fibrosis. This unexpected finding may stem from variability in ALT levels among normal subjects, leading to elevated AAR values. The broader standard deviation in the normal group suggests greater heterogeneity in AST/ALT ratios. Previous research indicates

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AST/ALT ratio had limited sensitivity in detecting early stages of fibrosis, suggesting it is less reliable as a standalone marker for early fibrosis detection.[21]

APRI and FIB-4

The AST to Platelet Ratio Index (APRI) is a commonly utilized non-invasive tool for evaluating liver fibrosis. In our study, APRI values showed a progressive increase with advancing stages of fibrosis ($p < 0.001$). These findings align with previous studies, which have reported mean APRI scores of approximately 0.5–0.7 for early fibrosis and above 1.5 as indicative of cirrhosis.[22,23] The markedly higher APRI value in cirrhosis observed in this study reinforces its diagnostic utility in advanced liver disease.

The FIB-4 index shows a marked increase in cirrhosis compared to other stages, reflecting the advanced fibrosis stage. Sterling et al. (2006) reported similar findings, demonstrating that FIB-4 is effective in distinguishing between varying degrees of fibrosis. [24]

GGT

Elevated GGT levels are commonly associated with cholestasis and liver dysfunction, suggesting the study population may have higher degrees of cholestatic liver disease. GGT levels are significantly higher in cirrhosis, which corresponds with the findings from Friedman (2008).[25]

ALP

Elevated ALP can be associated with hepatic or biliary obstruction, and the higher mean values in this study could indicate a cohort with biliary pathology or liver dysfunction.ALP levels increase with severity, with the highest levels seen in cirrhosis, as reported by Friedman (2008).[25]

The liver function test parameters demonstrate a clear pattern of increasing severity with advancing fibrosis and cirrhosis. These findings are consistent with the literature, highlighting the reliability of these tests in assessing liver disease progression.

Interestingly, AST, ALP, Serum Bilirubin, AAR, and APRI levels were slightly lower in severe fibrosis compared to mild fibrosis. This could be attributed to variations in disease activity, where mild fibrosis may have more active hepatocyte injury, leading to higher enzyme release. In severe fibrosis, hepatic inflammation may decrease as fibrosis advances, temporarily stabilizing or slightly lowering these markers. Additionally, differences in sample distribution, liver functional reserve, and the influence of APRI/AAR formulae may contribute to this trend. However, a significant increase in these markers in cirrhosis confirms progressive liver dysfunction.

Association with Diabetes mellitus, Alcohol consumption and Smoking

In this study, 11.8% of participants had diabetes mellitus, aligning with findings by Younossi et al., who reported a 22% prevalence among NAFLD patients.[26] However, no significant association was found between diabetes and cirrhosis severity ($p = 1.000$), with diabetes present in 60% of those with normal liver function and 13.3% of cirrhotic patients. This suggests that while diabetes is common in liver disease, it does not necessarily correlate with worsening fibrosis.

Alcohol consumption was reported in 41.7% of cases. Sugiyama et al. found that 85.8% of fatty liver patients in a Japanese cohort were non-drinkers.[27] In this study, alcohol consumption prevalence was 52.8% in those with normal liver function versus 26.4% in cirrhotic patients. While alcohol is a known risk factor for liver disease, no significant correlation with cirrhosis severity was observed.

Smoking history was noted in 32.3% of participants. While smoking contributes to oxidative stress and liver damage, its role in fibrosis progression remains unclear. El-Serag et al. reported smoking in 30-35% of liver disease patients,[28] comparable to this study's findings. However, no significant association with cirrhosis severity was observed ($p = 0.305$), with smoking more prevalent in those with normal liver function (56.1%) than in cirrhosis (22%).

Overall, diabetes, alcohol consumption, and smoking did not show significant correlations with cirrhosis severity in this cohort.

The study highlights that while 2-D shear wave elastography provides robust and reliable measurements of liver stiffness, its findings are well-supported by changes in liver function tests and fibrosis markers. The utility of elasticity measurements in assessing the severity of liver fibrosis is reinforced by their correlation with these laboratory parameters. Although risk factors such as diabetes mellitus, alcohol consumption, and smoking are prevalent among the study participants, their influence on liver fibrosis severity appears less pronounced, indicating the complexity of liver disease progression and the multifaceted role of these risk factors.

Overall, 2-D shear wave elastography proves to be a crucial diagnostic tool for evaluating liver fibrosis, providing valuable insights that complement traditional liver function tests and fibrosis markers.

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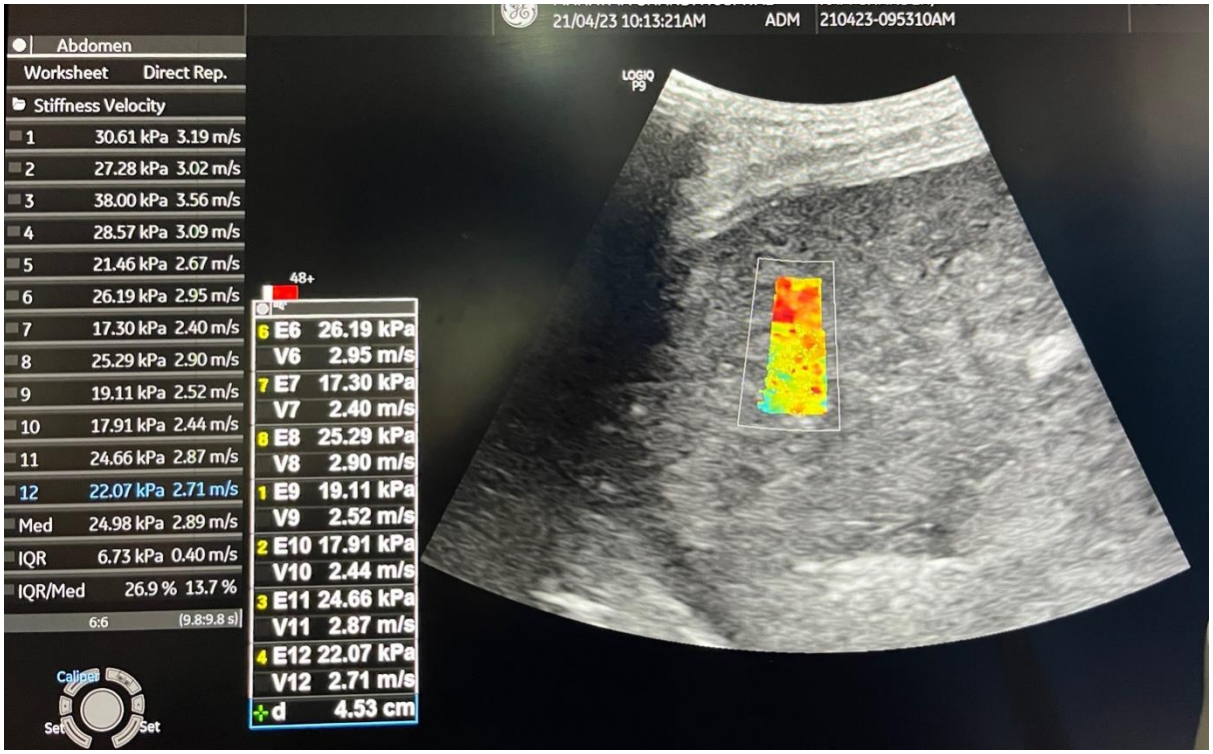

Figure 1. 2-D Shear Wave Elastography: Elasticity grade : 24.9 kPa corresponding to F4grade (Cirrhosis) in a 70 year old male patient with jaundice and swelling in both legswith history of excessive alcohol intake. Liver function tests and biochemical markers (AST : 469 U/L; ALT : 115 U/L; AAR: 4.07; APRI : 6.9; FIB-4 : 20.8; ALP: 432 U/L; GGT: 145 U/L; Platelet Count: 147 x 10^3 µL; Total Serum Bilirubin : 13mg/dL; Serum Albumin : 2.4 g/dL) were consistent with significant liver disease with fibrosis.

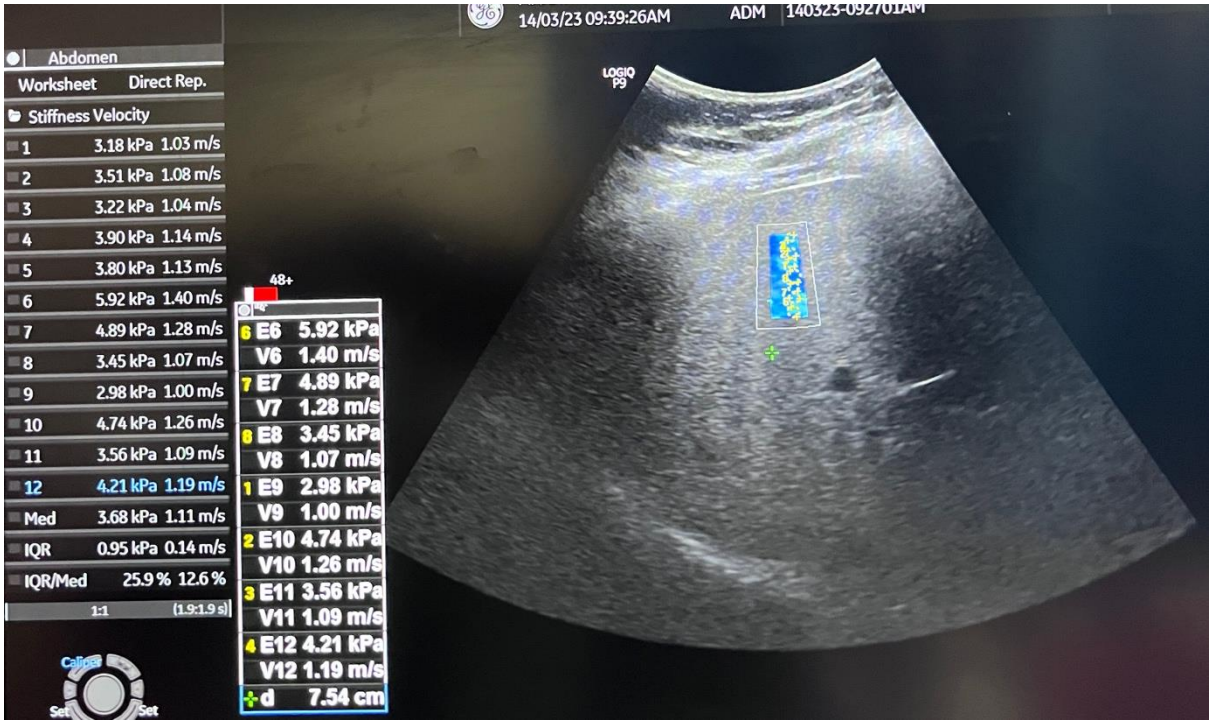

Figure 2. 2-D Shear Wave Elastography : Elasticity: 3.68 kPa, corresponding to F0-F1 grade (Normal) in a 51 year old female patient who came for a routine abdomen sonogram and was found to have fatty liver grade 2. Her Liver function tests and biochemical markers (AST : 44 U/L; ALT : 37 U/L; AAR: 1.1; APRI : 0.42; FIB-4 : 1.65; ALP: 63 U/L; GGT: 21 U/L; Platelet Count: 223 x 10^3 µL; Total Serum Bilirubin : 1.7 mg/dL; Serum Albumin : 4.8 g/dL) were within normal limits which corresponded with the elasticity measurements.

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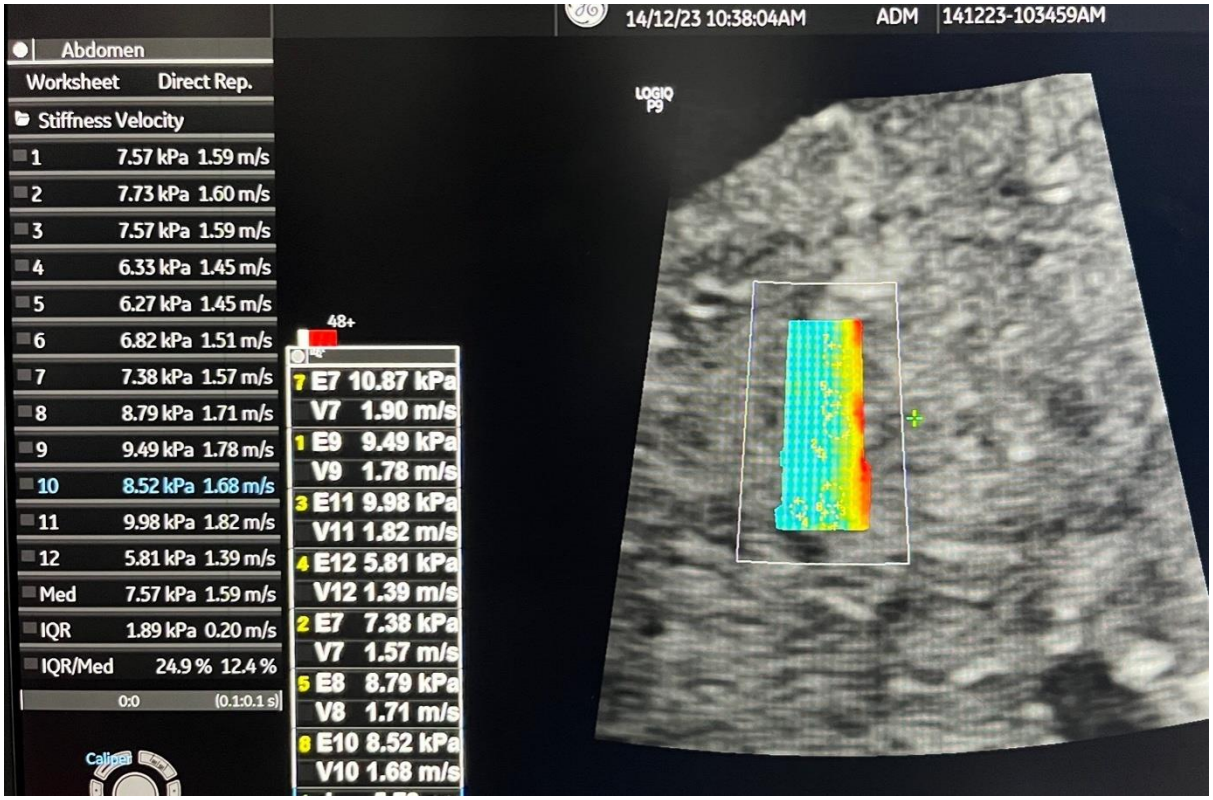

Figure 3. 2-D Shear Wave Elastography: Elasticity grade : 7.57 kPa (F2-3 : Mild fibrosis) in a 50 year old male patient who came with complaints of jaundice and distended abdomen. Patient had grade 2 fatty liver. Liver function tests and biomarkers (AAR: 1.27; APRI : 2.9; FIB-4 : 8.2; ALP: 283 U/L; Total Serum Bilirubin : 5.3mg/dL;) were mildly elevated consistent with Mild Fibrosis.

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