"ROLE OF SHEAR WAVE ELASTOGRAPHY IN ASSESSING LIVER FIBROSIS IN PATIENTS WITH HEPATIC DISEASES AND ITS CORRELATION WITH SEROLOGICAL INDICES"

By

Dr. GURU YOGENDRA. M

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

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IN
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Under the Guidance of

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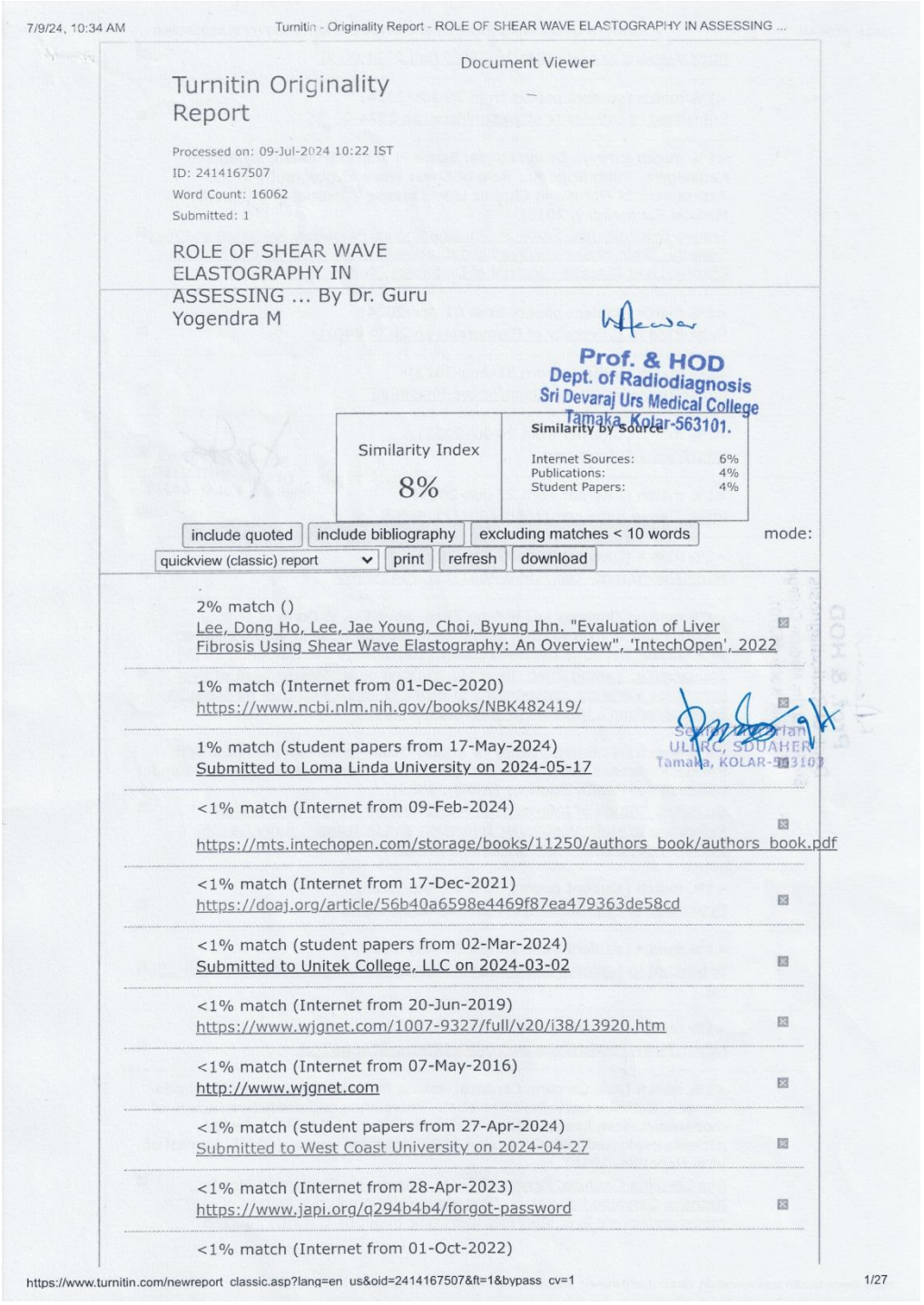

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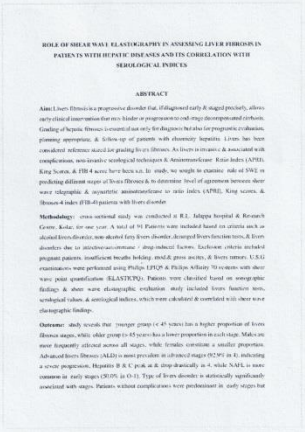

ROLE OF SHEAR WAVE ELASTOGRAPHY IN ASSESSING LIVER FIBROSIS IN PATIENTS WITH HEPATIC DISEASES AND ITS CORRELATION WITH SEROLOGICAL INDICES

ABSTRACT

Aim: Liver fibrosis is a progressive disorder that, if diagnosed early & staged precisely, allows early clinical intervention that may hinder or progression to end-stage decompensated cirrhosis. Grading of hepatic fibrosis is essential not only for diagnosis but also for prognostic evaluation, planning appropriate, & follow-up of patients with chronicity hepatitis. Livers has been considered reference stated for grading livers fibroses. As livers is invasive & associated with complications, non-invasive serological techniques & Aminotransferase Ratio Index (APRI), King Scotes, & FIB-4 scores have been set. In study, we sought to examine role of SWE in predicting different stages of livers fibroses & to determine level of agreement between sheer wave telegraphic & aspartate aminotransferase to ratio index (APRI), King scores, & fibrosis-4 index (FIB-4) patients with livers disorder.

Methodology: cross sectional study was conducted in R.L. Jalappa hospital & Research Centre, Kolar, for one year. A total of 91 Patients were included based on criteria such as alcohol livers disorder, non-alcohol fatty livers disorder, decreased livers function tests, & livers disorders due to infective/auto-immune / drug-induced factors. Exclusion criteria included pregnant patients, insufficient breaths holding, medical gross ascites, & livers tumors. U.S.G examinations were performed using Philips EPUP & Philips Affinity 70 systems with sheer wave point quantification (ELASTPQ). Patients were classified based on sonographic findings & sheer wave elastographic evaluation study included livers function tests, serological values, & serological indices, which were calculated & correlated with sheer wave elastographic findings.

Outcome: study reveals that younger group (< 45 years) has a higher proportion of livers fibrosis stages, while older group (> 45 years) has a lower proportion in each stage. Males are more frequently affected across all stages, while females constitute a smaller proportion. Advanced livers fibrosis (ALD) is most prevalent in advanced stages (92.9% in F), indicating a severe progression. Hepatitis B & C, p.vk, & drug drastically in 4, while NAFL is more common in early stages (50.0% in O-1). Type of livers disorder is statistically significantly associated with stages. Patients without complications were predominant in early stages but

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GLOSSARY	ABBREVIATIONS
ECM	Extracellular Matrix Proteins.
CLD	Chronic Liver Disease
HBV	Hepatitis B
HBC	Hepatitis C
US	Ultrasonography
LS	Liver Stiffness
TE	Transient Elastography
ARFI	Acoustic Radiation Force Impulse
MRE	Magnetic Resonance Elastography
SWE	Shear Wave Elastography
AST	Aspartate Transaminase
APRI	Aspartate Transaminase To Platelet Ratio
HA	Hyaluronic Acid
NASH	Nonalcoholic Steatohepatitis
HSC	Hepatic Stellate Cells
KC	Kupffer Cells
SEC	Sinusoidal Endothelial Cells
NO	Nitric Oxide
ET-1	Endothelin -1
RAAS	Renin-Angiotensin Aldosterone System
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
GGT	Gamma-Glutamyl Transferase
PT	Prothrombin Time
PCR	Polymerase Chain Reaction
ANA	Anti-Nuclear Antibodies
ASMA	Anti-Smooth Muscle Antibodies
ALKM-1	Anti-Liver-Kidney Microsomal Antibody
HCC	Hepatocellular Carcinoma

MRC	Magnetic Resonance Cholangiography
EGD	Esophagogastroduodenoscopy
HVPG	Hepatic Venous Pressure Gradient
pSWE	Point Shear Wave Elastography
2D SWE	Two-Dimensional Shear Wave Elastography
MMP	Matrix Metalloproteinases
TIMP	Tissue Matrix Metalloproteinase Inhibitor
QIBA	Quantitative Image Biomarker Alliance
ALD	Alcoholic Liver Disease
NAFLD	Non-Alcoholic Fatty Liver Disease
FIB-4	Fibrosis 4
BMI	Body Mass Index
CHB	Chronic Hepatitis B
CHC	Chronic Hepatitis C

ABSTRACT

Aim: To evaluate patients with liver diseases using ultrasonography. To perform shear wave elastography and derive cut-off for patients with liver diseases. To correlate ultrasound and shear wave elastography findings with serological indices in patients with liver disease.

Introduction: Liver fibrosis is a progressive disorder that, if diagnosed early and staged precisely, allows early clinical intervention that may hinder or slow down the progression to end-stage decompensated cirrhosis. Grading of hepatic fibrosis is essential not only for diagnosis but also for prognostic evaluation, planning appropriate therapy, and follow-up of patients with chronic hepatitis. Liver biopsy has been considered the gold standard for grading liver fibrosis. As liver biopsy is invasive and associated with complications, non-invasive serological techniques and Aminotransferase Platelet Ratio Index (APRI), King's Score, and FIB 4 scores have been spotlighted. In this study, we sought to examine the role of SWE in predicting different stages of liver fibrosis and to determine the level of agreement between shear wave elastography and aspartate aminotransferase to platelet ratio index (APRI), King's score, and fibrosis-4 index (FIB-4) scores in patients with liver disease.

Methodology: This cross-sectional study was conducted at R.L. Jalappa Hospital and Research Center, Kolar, for one year. A total of 91 Patients were included based on criteria such as alcoholic liver disease, non-alcoholic fatty liver disease, deranged liver function tests, and liver diseases due to infective/autoimmune/drug-induced factors. Exclusion criteria included pregnant patients, insufficient breath holding, moderate and gross ascites, and liver tumours. Ultrasound examinations were performed using Philips EPIQ5 and Philips Affinity 70 systems with shear wave point quantification (ELASTPQ). Patients were classified based on sonographic findings and shear wave elastographic evaluation. The study included liver function tests, serological values, and serological indices, which were calculated and

correlated with shear wave elastographic findings.

Results: The study reveals that the younger group (< 45 years) has a higher proportion of liver fibrosis stages, while the older group (> 45 years) has a lower proportion in each stage. Males are more frequently affected across all stages, while females constitute a smaller proportion. Advanced liver fibrosis (ALD) is most prevalent in advanced stages (92.9% in F4), indicating a severe progression. Hepatitis B and C peak at F3 and drop drastically in F4, while NAFLD is more common in the early stages (50.0% in F0-F1). Type of liver disease is statistically significantly associated with stages. Patients without complications were predominant in the early stages but decreased substantially in F4. Patients with complications show a substantial increase in advanced fibrosis stages, comprising 78.6% of F4 cases. Hematemesis is the most common complication, especially in advanced stages (30.0% in F3, 39.3% in F4). Increased echogenicity is more common in advanced stages, rising from 65.0% in F0-F1 to 96.4% in F4. Significant changes in liver size and stiffness with advancing fibrosis are less pronounced. All APRI, FIB 4 and King's scores demonstrate strong correlations with fibrosis progression, making them valuable for assessing liver fibrosis severity and monitoring disease advancement. The SWE test has high AUC values, indicating strong discriminatory power when comparing stages (F0-F1) against F2, F3, and F4. It also demonstrates high accuracy in differentiating between minimal or no fibrosis (F0-F1) and advanced fibrosis (F3), with a sensitivity of 95% and a specificity of 90% at a cut-off value of ≥ 6.60. It also exhibits outstanding discriminatory ability in distinguishing between minimal or no fibrosis (F0-F1) and severe fibrosis/cirrhosis (F4), with a sensitivity of 96.4% and a specificity of 91.4% at a cut-off value of ≥7.50.

SWE also shows good discriminatory performance in differentiating between moderate (F2) and advanced fibrosis (F3), with a sensitivity of 95% and a specificity of 77.6% at a cut-off value of ≥ 8.0. It also shows excellent accuracy in distinguishing between moderate fibrosis (F2) and severe fibrosis/cirrhosis (F4), with a sensitivity of 92.9% and a specificity of 79.8% at a cut-off value of ≥ 9.0. However, the diagnostic accuracy decreases when distinguishing between adjacent stages, such as F2 vs. F3 and F3 vs. F4, as indicated by lower AUC values and slightly lower sensitivity and specificity values. The test also has strong positive correlations with APRI and KING, suggesting that as liver size increases, all APRI, FIB 4, and King's scores tend to increase significantly.

Conclusion: The study found significant associations between liver disease type, stages, complications, echogenicity, liver texture, liver size, stiffness, portal vein diameter, and spleen size. It also found strong correlations between liver elastography and size, APRI, King's and FIB 4 scores, and SWE, making them valuable tools for assessing liver fibrosis severity and monitoring disease advancement.

Keywords: Chronic liver fibrosis, APRI, King's score & FIB-4, Serological markers, SWE.

TABLE OF CONTENTS

INTRODUCTION

INTRODUCTION

Liver disease is one of the most common diseases in the world. Viral liver diseases are affecting about 500 million people in the world, and up to one million deaths occur annually from cirrhosis and hepatocellular carcinoma[1] The prognosis and treatment outcome for these patients are related to the liver fibrosis stage, especially in patients with hepatitis C.[1] Advanced stages of liver disease often result in fibrosis, which is characterised by the excessive accumulation of extracellular matrix proteins (ECM).[2,3] The normal hepatic structure was disorganised by fibrous scar, and more fibrosis developed, resulting in more hepatocyte damage, portal hypertension, impaired liver function, and ultimately, liver failure and hepatocellular carcinoma.[4,5]

Chronic liver disease (CLD) is a major public health problem, causing significant morbidity and mortality around the world. The timely diagnosis and determination of the fibrosis stage is necessary for the management and treatment of patients with chronic liver disease.[6,7,8] In patients with chronic hepatitis, the progression of inflammatory reactions and necrosis of hepatocytes causes hepatic fibrosis and leads to cirrhosis, which presents various clinical complications, including ascites, jaundice, or hepatocellular carcinoma[1].

The fibrosis stage is important for treating and managing chronic liver disease.[9] Particularly in cases of chronic viral hepatitis B (HBV) and hepatitis C (HCV), it is important to detect significant and advanced fibrosis because these stages are the critical points for anti-viral treatment.[10,11] Traditionally, liver biopsy has been the gold standard for liver fibrosis staging.[10] The drawbacks of liver biopsy are that it is invasive, is associated with morbidity and sampling errors [12] and has many contraindications, such as abnormal clotting parameters and decreased platelet count, which are common in chronic liver disease.

In addition, hepatic fibrosis affects the liver homogeneously, and biopsy specimens may be inadequate samples that do not represent the histology of the whole hepatic parenchyma; this can lead to an inter-observer variation of 10%-20% in histologic measurements.[12,13] Non-invasive complementary tools, including traditional imaging using ultrasonography (US) or computerised tomography and blood tests using several serum markers, have been developed, but there is limited clinical evidence that these techniques are effective, particularly for predicting and diagnosing earlier stages of hepatic fibrosis.[14-17]

Recently, non-invasive methods for measuring liver stiffness (LS), including transient elastography (TE), acoustic radiation force impulse imaging (ARFI), and magnetic resonance elastography (MRE), have been developed, and several studies report good results in their ability to predict the degree of hepatic fibrosis.[18,19] Real-time shear wave elastography (SWE), another method for measuring LS, has been developed.[20]

Elastography is an imaging technique that images or quantifies the elasticity (mechanical properties) of the biological tissues.[21,22] In these techniques, a force is applied, and the tissue response is observed. The SWE techniques are divided into three different groups: ElastPQ, (TE), and two-dimensional (2D) SWE, depending on the type of force applied and the method used for measuring or displaying the tissue response.[23,24] ElastPQ provides tissue stiffness information.[25] ElastPQ is an elastography mode on ultrasound equipment in which a burst of push pulses is transmitted, creating shear waves in the soft tissues. The tissue stiffness is estimated by determining the speed at which these shear waves travel.

Multidimensional SWE (e.g., 2D SWE and 3D SWE) is an adynamic elastographic technique in which focused ultrasound beams are transmitted continuously to tissue at different depths. As in TE and ElastPQ, the property is measured in shear wave speed.

However, the region of interest (ROI) is fan-shaped and larger than the ROI with other modalities. The shear wave speed measurements are displayed as a 2D map.

Ultrasound and MR are used for elasticity imaging.[26] These methods can evaluate the differences in soft tissue elastic properties during mechanical stress.[1] Elastography is one of the latest technological advances in ultrasound that measures resilience and tissue consistency, especially in soft tissues.[26] Unlike TE, SWE measures tissue elasticity simultaneously during B-mode ultrasound examination, and elasticity values can be measured on the basis of anatomical information. In addition, SWE provides elastography color maps according to the degree of stiffness, allowing an assessment of homogeneity. As a result, SWE provides more accurate information about hepatic fibrosis staging than TE.[26] However, there are few studies comparing SWE results with histologic diagnosis using liver biopsy, and to our knowledge, there are no reports comparing SWE results with indirect serologic markers of hepatic fibrosis such as aspartate aminotransferase (AST) to platelet (PLT) ratio index (APRI), hyaluronic acid (HA), and type IV collagen.[27]

Since very few structured studies have been conducted to date on the correlation of ultrasound and SWE with serum markers, this comparison needs to be explored further to establish facts. Hence, we conducted this study to evaluate the correlation between ultrasonography, shear wave elastography, and serological indices in patients with liver diseases.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

1. To evaluate patients with liver diseases using ultrasonography.
2. To perform shear wave elastography and derive cut-off for patients with liver diseases.
3. To correlate ultrasound and shear wave elastography findings with serological indices in patients with liver disease.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Liver Fibrosis

Cirrhosis is characterised by fibrosis and nodule formation of the liver, secondary to a chronic injury, which leads to alteration of the normal lobular organisation of the liver. Various insults can injure the liver, including viral infections, toxins, hereditary conditions, or autoimmune processes.

With each injury, the liver initially forms scar tissue (fibrosis) without losing its function. After a long-standing injury, most of the liver tissue gets fibrosed, leading to loss of function and the development of cirrhosis.

Aetiology & Classification

Chronic liver diseases usually progress to cirrhosis. In the developed world, the most common causes of cirrhosis are HCV, alcoholic liver disease, and non-alcoholic steatohepatitis (NASH), while HBV and HCV are the most common causes in the developing world.[28]

Based on the cause of cirrhosis which is sub-classified as follows:

- Viral - hepatitis B, C, and D
- Toxins - alcohol, drugs
- Autoimmune - autoimmune hepatitis
- Cholestatic - primary biliary cholangitis, primary sclerosing cholangitis
- Vascular - Budd-Chiari syndrome, sinusoidal obstruction syndrome, cardiac cirrhosis

- Metabolic - hemochromatosis, NASH, Wilson disease, alpha-1 antitrypsin deficiency, cryptogenic cirrhosis.

Epidemiology

The worldwide prevalence of cirrhosis is unknown; however, it has been estimated to be between 0.15% and 0.27% in the United States.[29,30]

Pathophysiology

Multiple cells play a role in liver cirrhosis, including hepatocytes and sinusoidal lining cells such as hepatic stellate cells (HSCs), sinusoidal endothelial cells (SECs), and Kupffer cells (KCs). HSCs form a part of the wall of the liver sinusoids, and their function is to store vitamin A. When these cells are exposed to inflammatory cytokines, they get activated, transform into myofibroblasts, and start depositing collagen, which results in fibrosis. SECs form the endothelial lining and are characterised by the fenestrations they make in the wall that allow the exchange of fluid and nutrients between the sinusoids and the hepatocytes.[31]

Defenestration of the sinusoidal wall can happen secondary to chronic alcohol use and promote perisinusoidal fibrosis.[32] KCs are satellite macrophages that line the wall of the sinusoids as well. Studies mainly from animal models have shown that they play a role in liver fibrosis by releasing harmful mediators when exposed to injurious agents and acting as antigen-presenting cells for viruses.[33] Hepatocytes are also involved in cirrhosis's pathogenesis, as damaged hepatocytes release reactive oxygen species and inflammatory mediators that can promote activating HSCs and liver fibrosis.[34]

The major cause of morbidity and mortality in cirrhotic patients is the development of portal hypertension and hyperdynamic circulation. Portal hypertension develops secondary to

fibrosis and vasoregulatory changes intra-hepatically and systematically, leading to collateral circulation formation and hyperdynamic circulation.[35]

Intrahepatically, SECs synthesise nitric oxide (NO) and endothelin-1 (ET-1), which act on HSCs, causing relaxation or contraction of the sinusoids, respectively, and controlling sinusoidal blood flow. In patients with cirrhosis, there is an increase in ET-1 production and an increase in the sensitivity of its receptors with a decrease in NO production. This leads to increased intrahepatic vasoconstriction and resistance, initiating portal hypertension. Vascular remodelling mediated by the contractile effects of HSCs in the sinusoids augments the increase in vascular resistance. To compensate for this increase in intrahepatic pressure, collateral circulation is formed.[35]

In systemic and splanchnic circulation, the opposite effect happens, with an increase in NO production, leading to systemic and splanchnic vasodilation and decreased systemic vascular resistance. This promotes activating the renin-angiotensin-aldosterone system (RAAS), leading to sodium and water retention and hyperdynamic circulation. Thus, in cirrhosis with portal hypertension, there is a depletion of vasodilators (predominantly NO) intra-hepatically but an excess of NO extrahepatically in the splanchnic and systemic circulation, leading to sinusoidal vasoconstriction and splanchnic (systemic) vasodilation. The collaterals also contribute to the hyperdynamic circulation by increasing the venous return to the heart.[35,36]

Pathogenesis of liver fibrosis

Hepatic fibrosis results from the liver's wound-healing response to repeated injury. [37] (Figure 1) After an acute liver injury (e.g., viral hepatitis), parenchymal cells regenerate and replace the necrotic or apoptotic cells. This process is associated with an inflammatory response and a limited deposition of ECM. If the hepatic injury persists, the liver

regeneration eventually fails, and hepatocytes are substituted with abundant ECM, including fibrillar collagen. The distribution of this fibrous material depends on the origin of the liver injury. In chronic viral hepatitis and chronic cholestatic disorders, the fibrotic tissue is initially located around portal tracts, while in alcohol-induced liver disease, it is located in pericentral and perisinusoidal areas.[38]

As fibrotic liver diseases advance, disease progression from collagen bands to bridging fibrosis to frank cirrhosis occurs.

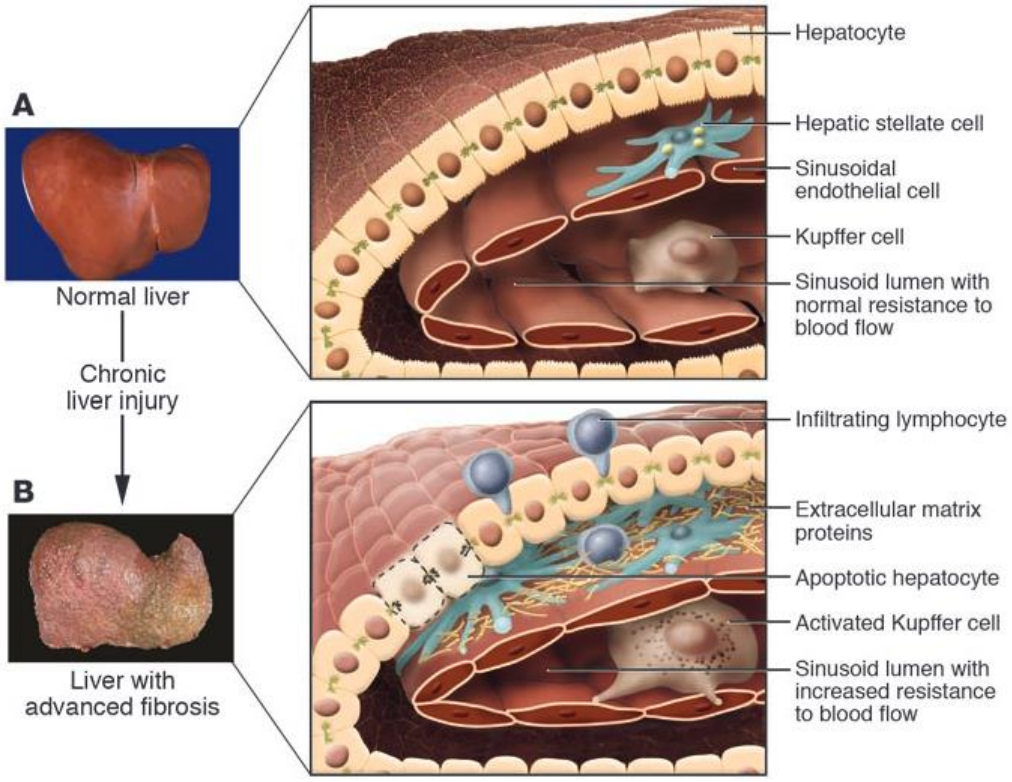


Figure 1: Changes in the hepatic architecture (A) associated with advanced hepatic fibrosis (B). Following chronic liver injury, inflammatory lymphocytes infiltrate the hepatic parenchyma. Some hepatocytes undergo apoptosis, and Kupffer cells activate, releasing fibrogenic mediators. HSCs proliferate and undergo a dramatic phenotypical activation, secreting large amounts of extracellular matrix proteins. Sinusoidal endothelial cells lose their fenestrations, and the tonic contraction of HSCs causes increased resistance to blood flow in the hepatic sinusoid.

Histopathology

Cirrhosis is classified based on morphology or aetiology.

Morphology Classification

Morphologically, cirrhosis is [28] micronodular, [29] macronodular, or [30] mixed. This classification is not as clinically useful as etiologic classification.

- Micronodular cirrhosis (uniform nodules less than 3 mm in diameter): Cirrhosis due to alcohol, hemochromatosis, hepatic venous outflow obstruction, chronic biliary obstruction, jejunoileal bypass, and Indian childhood cirrhosis.
- Macronodular cirrhosis (irregular nodules with a variation greater than 3 mm in diameter): Cirrhosis due to HBV & HCV, alpha-1 antitrypsin deficiency, and primary biliary cholangitis.
- Mixed cirrhosis (when micronodular and macronodular cirrhosis features are present): Usually, micronodular cirrhosis progresses into macronodular cirrhosis over time.

History and Physical

Patients with cirrhosis can be asymptomatic or symptomatic, depending on whether their cirrhosis is clinically compensated or decompensated. In compensated cirrhosis, patients are usually asymptomatic, and their disease is detected incidentally by labs, physical exams, or imaging. One of the common findings is mild to moderate elevation in aminotransferases or gamma-glutamyl transpeptidase with possible enlarged liver or spleen on the exam. On the other hand, patients with decompensated cirrhosis usually present with a wide range of signs and symptoms arising from a combination of liver dysfunction and portal hypertension.

The diagnosis of ascites, jaundice, hepatic encephalopathy, variceal bleeding, or hepatocellular carcinoma in a patient with cirrhosis signifies the transition from a compensated to a decompensated phase of cirrhosis. Other cirrhosis complications include spontaneous bacterial peritonitis and hepatorenal syndrome, which occur in patients who have ascites.

Is liver fibrosis reversible?

In contrast with the traditional view that cirrhosis is an irreversible disease, recent evidence indicates that even advanced fibrosis is reversible.[39] In experimentally induced fibrosis, cessation of liver injury results in fibrosis regression.[40] In humans, spontaneous resolution of liver fibrosis can occur after successful treatment of the underlying disease. This observation has been described in patients with iron and copper overload, alcohol-induced liver injury, chronic hepatitis C, B, and D, hemochromatosis, secondary biliary cirrhosis, NASH, and autoimmune hepatitis.[39,41] .

It may take years for significant regression to be achieved; the time varies depending on the underlying cause of the liver disease and its severity. Chronic HCV infection is the most extensively studied condition, and therapy (IFN-α plus ribavirin) with viral clearance improves fibrosis. Importantly, nearly half of patients with cirrhosis exhibit reversal to a significant degree (90^0). Whether this beneficial effect is associated with improvements in long-term clinical outcomes, including decreased portal hypertension, is unknown.

Complications

Complications of hepatic cirrhosis can include: [42]

- Portal hypertension
- Edema in the abdomen and lower extremities

- Ascites
- Splenomegaly
- Infections
- Hemorrhage
- Hepatic encephalopathy

Evaluation

Lab Findings

Aminotransferases are usually mildly to moderately elevated with AST greater than alanine aminotransferase (ALT); however, normal levels do not exclude cirrhosis.[43] In most forms of chronic hepatitis (except alcoholic hepatitis), the AST/ALT ratio is less than one. As chronic hepatitis progresses to cirrhosis, there is a reversal of this AST/ALT ratio. Alkaline phosphatase (ALP), 5'- nucleotidase, and gamma-glutamyl transferase (GGT) are elevated in cholestatic disorders. Prothrombin time (PT) is elevated due to coagulation factor defects and bilirubin, while albumin is low as it is synthesised by the liver, and the liver's functional capacity decreases. Thus, serum albumin and PT are true indicators of synthetic hepatic function.

Normochromic anaemia is seen; however, macrocytic anaemia can be seen in alcoholic liver cirrhosis. Leukopenia and thrombocytopenia are also seen secondary to sequestration by the enlarged spleen and alcohol suppression effect on the bone marrow.[44] Immunoglobulins, especially the gamma fraction, are usually elevated due to impaired clearance by the liver.[45]

Specific tests to Investigate newly Diagnosed fibrosis

Serology and PCR techniques for viral hepatitis and autoimmune antibodies (anti-nuclear antibodies [ANA], anti-smooth muscle antibodies (ASMA), anti-liver-kidney microsomal antibodies type 1 (ALKM-1) and serum IgG immunoglobulins) for autoimmune hepatitis and anti-mitochondrial antibody for primary biliary cholangitis may be ordered. Ferritin and transferrin saturation for hemochromatosis, ceruloplasmin, and urinary copper for Wilson disease, Alpha 1-antitrypsin level, and protease inhibitor phenotype for alpha 1-antitrypsin deficiency, and serum alpha-fetoprotein for hepatocellular carcinoma (HCC) are other useful tests.

Imaging and Liver Biopsy

Several imaging modalities are used alongside labs to help diagnose cirrhosis. These include ultrasound, CT, MRI, and TE (fibroscan).

Ultrasonography is a cheap, non-invasive, and available modality for evaluating cirrhosis. It can detect nodularity and increased echogenicity of the liver, which are seen in cirrhosis; however, it is nonspecific as these findings can also be seen in fatty liver.[46] It can also determine the ratio of the caudate lobe width to the right lobe width, which usually increases in cirrhosis.[47] Moreover, it is a useful screening tool for HCC in cirrhotic patients. Duplex Doppler ultrasonography helps to assess the patency of hepatic, portal, and mesenteric veins.

CT and MRI, in contrast, can detect HCC and vascular lesions, with MRI being superior to CT.[48] MRI can also detect the level of iron and fat deposition in the liver for hemochromatosis, steatosis, and biliary obstruction if an MRC (magnetic resonance cholangiography) is obtained.[49] MRI, however, is expensive and not readily available.

In cirrhosis, a colloid liver spleen scan using technetium-99m sulfur colloid may show increased colloid uptake in the bone marrow and spleen compared to the liver. The presence of varices in the oesophagus or stomach on esophagogastroduodenoscopy (EGD) suggests portal hypertension.

Liver biopsy is the gold standard for diagnosing cirrhosis and assessing the degree of inflammation (grade) and fibrosis (stage) of the disease. Nevertheless, it can miss the diagnosis at times due to sampling errors.[50] The diagnosis of cirrhosis by biopsy requires the presence of fibrosis and nodules. The nodular pattern can be micronodular, macronodular, or mixed with the micronodular pattern, representing an independent risk factor for elevated hepatic venous pressure gradient (HVPG) and more severe disease.[51] Non-invasive tests using direct and indirect serum markers are used to detect patients with significant fibrosis/cirrhosis from patients with no/mild fibrosis.[52-54]

There has been a continuous need for reliable and non-invasive methods for evaluating liver fibrosis in clinical practice, and tremendous effort has been made to develop non-invasive diagnostic methods for assessing liver fibrosis.[55] In this regard, shear wave-based ultrasound elastography has been developed and introduced as an accurate, non-invasive diagnostic method for evaluating liver fibrosis. After the introduction of TE, which was the first commercially available liver elastography technique, various ultrasound-based SWE methods, including point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE), have been introduced in clinical practice and reported a good diagnostic performance in assessing liver fibrosis.[56,57]

Principle of shear wave elastography

Elastography is an imaging technique measuring a tissue's mechanical characteristics, such as elasticity, first described by Ophir et al. [58]. Tissue elasticity is defined as the

resistance to the deformation of a certain tissue against applied stress [59], and stiff tissue is more resistant to deformation than soft tissue under a given applied stress. For the superficial organs such as the breast and thyroid, tissue elasticity can be measured by using strain elastography. In strain elastography, tissue stress is directly applied by manual compression of an ultrasound transducer, and then the degree of tissue deformation after compression is measured by ultrasound imaging.[58] Manual compression works fairly well for superficial organs; therefore, strain elastography is a useful technique for evaluating breast or thyroid lesions, providing information regarding tissue stiffness. [60] However, it is very challenging to induce stress to deeper located organs by manual compression, such as the liver, limiting the application of strain elastography to the liver.[61]

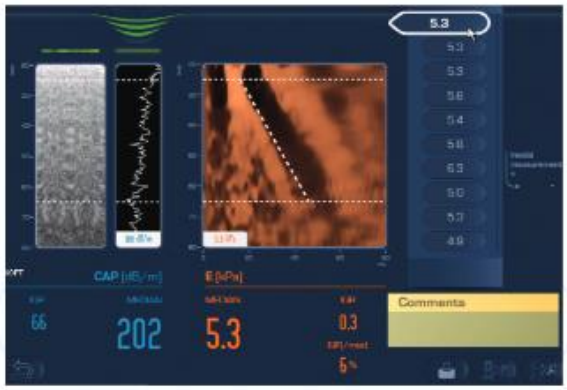
For deeper-located organs such as the liver, the stress can be employed by ARFI or mechanical push pulse to generate a shear wave within the target tissue.[59] Since shear wave propagation velocity is related to tissue elasticity and the shear wave velocity is faster in stiff tissue than in soft tissue, measurement of shear wave velocity generated by either ARFI or mechanical push pulse leads to the quantitative assessment of tissue elasticity.[60] Given that, the type of ultrasound-based shear wave elastography for the liver can be determined by two factors:

1) how to generate a shear wave within the liver tissue? & 2) How can the velocity of the generated shear wave within the liver tissue be measured? Based on these two factors, currently, there are three available ultrasound-based shear wave elastography techniques for the liver: 1) one-dimensional transient elastography (TE), 2) point shear wave elastography (pSWE), and 3) two-dimensional shear wave elastography (2D-SWE).[60] The characteristics of these three elastography techniques are summarised in Table 1.

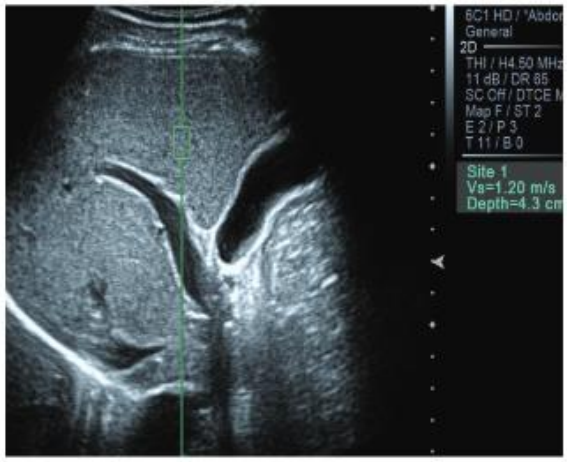
	Excitation method	Frequency of generated shear wave	Shear wave velocity measurement direction	Measurement area	Placement of region of interest	Reported parameter
TE	Mechanical push pulse	50 Hz	Parallel to excitation	Small	Restricted, no guidance	Young modulus (kPa)
pSWE	ARFI, single focal location	Wideband (100–500 Hz)	Perpendicular to ARFI application	Small	Flexible under B-mode guidance	Young modulus (kPa) or shear wave velocity (m/s)
2D-SWE	ARFI, multiple focal zones	Wideband (100–500 Hz)	Perpendicular to ARFI application	Medium	Flexible under B-mode guidance	Young modulus (kPa) or shear wave velocity (m/s)

Note: TE, transient elastography; pSWE, point shear wave elastography; 2D-SWE, two-dimensional shear wave elastography; ARFI, acoustic radiation force impulse; kPa, kilopascal.

Table 1. Characteristics of currently available ultrasound-based shear wave elastography techniques for the liver.



(a)



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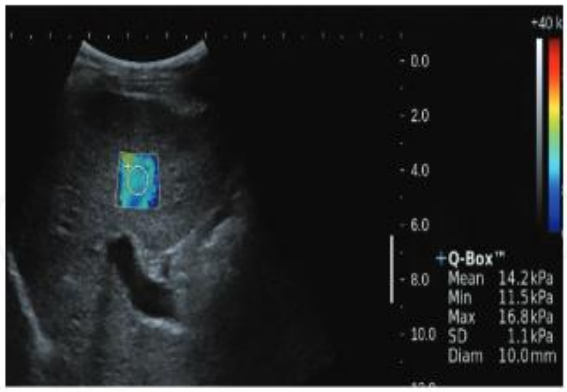


(c)

Figure 2: Currently available ultrasound-based shear wave elastography methods for the liver. (a) Transient elastography (TE) (b) Point shear wave elastography (pSWE) (c) Two-dimensional shear wave elastography (2D-SWE)

Measurement protocol and reliability criteria

Regarding patient preparation, ultrasound-based shear wave elastography techniques, including TE, pSWE, and 2D-SWE, share the same recommended protocol.[56] Since the amount of portal flow can affect the result of liver stiffness measurement obtained by shear wave elastography, fasting for at least 4 hours before the examination is recommended for patients who undergo shear wave elastography examination to minimise the effect of portal flow. The liver stiffness measurement using shear wave elastography is usually performed in either a supine or slightly left lateral decubitus position (not more than 30 degrees) with the right arm extended above the head to obtain the optimal sonic window via the stretching of the intercostal muscles.[55]

It has been known that both deep inspiration and deep expiration can influence the result of liver stiffness measurement using shear wave elastography, and therefore, the neutral breath-hold is recommended for shear wave elastography examination to minimise the effect of breath-hold status. In addition to the aforementioned protocols for patient preparation, current guidelines for both pSWE and 2D-SWE have several recommendations for imaging acquisitions since pSWE as well as 2D-SWE provide B-mode images of the liver simultaneously, and the measurement area of pSWE and 2D-SWE can be selected under the real-time B-mode imaging guidance.[56] The transducer should be placed perpendicular to the liver capsule to ensure proper generation and propagation of the shear wave. The measurement box for both pSWE and 2D-SWE is placed parallel to the liver capsule, and the upper edge of the measurement box should be placed 1.5 to 2.0 cm apart from the liver capsule to minimise the effect of reverberation artefact, which is generally seen in the area adjacent to the liver capsule. In most currently available ultrasound systems, the ARFI pulse reaches the maximum intensity at 4.0 to 4.5 cm apart from the transducer and is attenuated by 6.0 to 7.0 cm.[62]

Given that, the 4.0 to 4.5 cm area apart from the transducer would be optimal for liver stiffness measurement. Since the B-mode image is utilised to trace the shear wave in both pSWE and 2D-SWE, high-quality B-mode images without artefacts should be acquired for accurate and reliable liver stiffness measurement. The recommended protocols for both patient preparation and imaging acquisition are summarised in table 2.

	Recommendation	Aim
Patient preparation	Fasting for at least 4 hours before examination	To minimize effect of portal flow
	Position: supine or slight left lateral decubitus (not more than 30°) with right arm extended above the head	To obtain optimal sonic window via stretching of the intercostal muscles
	Neutral breath hold, neither deep inspiration nor expiration	To minimize effect of breath-hold status
Imaging acquisition for pSWE and 2D-SWE	Transducer placed perpendicular to the liver capsule	To ensure proper shear wave generation
	Upper portion of measurement box placed at least 1.5–2.0 cm apart from liver capsule	To minimize effect of reverberation artifact
	Ideal location of measurement box: 4–4.5 cm apart from the transducer	To maximize intensity of ARFI pulse

Note: pSWE, point shear wave elastography; 2D-SWE, two-dimensional shear wave elastography; ARFI, acoustic radiation force impulse.

Table 2: Recommendation for patient preparation and imaging acquisition

Diagnostic performance for staging liver fibrosis

Liver fibrosis results from chronic liver injury and is defined as an abnormal and excessive deposition of collagen and other extracellular matrix components in the liver.[63] Essentially, any kind of chronic liver disease caused by HBV or HCV infection, alcohol abuse, and NAFLD leads to steatosis, inflammation with necrosis in response to an injury.[63] Without appropriate management, these liver cell injury continuously progresses, eventually developing liver cirrhosis. Information regarding the liver fibrosis stage is beneficial for predicting prognosis, personalised follow-up, and treatment decisions. For example, the information regarding the liver fibrosis stage might guide antiviral therapy for HBV or HCV infection.[64,65]

Therefore, an accurate assessment of the liver fibrosis stage is an important step for chronic liver disease management. For this purpose, liver biopsy with histopathologic examinations using various staging systems, including Ishak, METAVIR, and Batts-Ludwig systems, has been traditionally used as the standard reference method.[66,67]

However, liver biopsy is limited for widespread application in clinical practice, mainly due to its invasive nature. To overcome the limitation of liver biopsy, ultrasound-based shear wave elastography techniques, including TE, pSWE, and 2D-SWE, have emerged as non-invasive methods for evaluating liver fibrosis and reported good diagnostic performance.

Limitation of ultrasound-based shear wave elastography for the liver

Although currently available ultrasound-based shear wave elastography systems, including TE, pSWE, and 2D-SWE, provide an excellent diagnostic capability in assessing the liver fibrosis stage and are widely used in clinical practice, ultrasound-based shear wave elastography systems have some limitations. Operators should be aware of the limitations of current ultrasound-based shear wave elastography techniques for accurate measurement of liver stiffness value and for the appropriate interpretation of the results. Many manufacturers have provided SWE systems for liver stiffness measurement after introducing pSWE and 2D-SWE, which can be incorporated into commercial ultrasound systems for routine B-mode imaging. Therefore, inter-platform variability among the different SWE systems from the various vendors may be an issue.[59]

In physics, the liver stiffness measurement values obtained by different SWE systems from different vendors cannot be interchangeable. Thus, vendor-specific cut-off values for the assessment of the liver fibrosis stage are needed since the frequencies of shear wave generated within the liver tissue are different among the various SWE systems from different

vendors: 50 Hz for TE and wideband ranging from 100 to 500 Hz for pSWE and 2D-SWE.[69,70] However, the application of vendor-specific cut-off might be infeasible in clinical practice, and it is impossible to follow up with patients using the same SWE system during the disease course. According to the result of the study evaluating inter-observer variability of liver stiffness measurements among seven different SWE systems, including TE, four pSWE methods, and two 2D-SWE methods, the overall agreement among the liver stiffness measurements performed with different SWE systems was good to excellent having ICCs ranging from 0.74 to 0.97 [93]. There would be an approximately 10% variability of the liver stiffness measurements among the different vendor SWE systems.[71] Therefore, these inter-platform variabilities should be considered when applying various SWE systems from different vendors to assess liver fibrosis staging.

To calculate the liver stiffness value from the measured shear wave propagation velocity, the current SWE systems assume that the tissue in which stress is applied is purely elastic and neglects the tissue viscosity. However, in some clinical situations, the assumption of pure tissue elasticity does not work well, leading to errors in the liver stiffness measurements. These conditions include acute hepatitis, liver inflammation with necrosis, obstructive cholangitis, hepatic congestion, and infiltrative diseases such as amyloidosis or lymphoma, and have been known to increase tissue viscosity. When the tissue viscosity is increased by various causes, the liver stiffness values measured by SWE systems are usually higher than without those conditions, leading to overestimating the liver fibrosis stage. [73]

Therefore, current guidelines for liver elastography examination do not recommend the liver stiffness measurement for assessing liver fibrosis stage when the serum level of AST and/or ALT is elevated greater than five times the upper normal limits.[59] The assessment of the liver fibrosis stage by using liver SWE can be performed after the normalisation of AST and/or ALT level to minimise the effect of liver inflammation on the results of liver stiffness

measurement. In addition, tissue viscosity introduces a dependency of shear wave propagation velocity on excitation frequencies [23]. Given that, more complex modelling considering tissue viscoelasticity is warranted to overcome the limitation of ultrasound-based shear wave elastography for the liver.

Serum markers of liver fibrosis

Serum markers of liver fibrosis are divided into direct and indirect markers. Indirect markers reflect the liver damage and include routine laboratory parameters such as AST, ALT, platelet count, gamma globulin, albumin, cholinesterase, and INR. Direct markers reflect the changes in the extracellular matrix and enzymes. This category includes glycoproteins, such as hyaluronic acid and laminin; collagens, such as procollagen III and collagen type IV; and matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). The advantage of serum markers is that they are universally available and reproducible.

However, they can be influenced by comorbidities and medications that must be considered when interpreting results. The table shows the different serum markers that are available.

Cut off values

There is a known variability between technologies and SWE measurements from different vendors. QIBA (Quantitative Image Biomarker Alliance, an RSNA organisation with vendors, scientists, US Food and Drug Administration members, and clinicians) developed a standardised phantom that the vendors use to standardise their measurements. The difference in cut-off value between various systems increases as liver stiffness increases. [71]

Association between fibroscan and serum markers

Several algorithms have been proposed in which a combination of FibroscanTM and serum markers must be used to evaluate liver fibrosis. An algorithm considering FibroscanTM and FibroTestTM (Castera/Bordeaux algorithm) was evaluated to optimise non-invasive diagnosis in patients with chronic hepatitis C. According to a prospective study with 302 patients with chronic hepatitis C, the Castera algorithm showed a higher number of biopsies avoided. According to this algorithm, if both non-invasive methods agree, hepatic biopsy is unnecessary; if there is discordance between the two methods, liver biopsy should be performed.

The combination of other elastographic methods and serum markers could be equally useful. Using such algorithms, biopsies could be reduced by 50-70%.

Clinical studies

Liver fibrosis is a chronic progressive condition that occurs due to the accumulation of extracellular matrix proteins, including the formation of collagenous matrix leading to fibrosis and, ultimately, cirrhosis, liver failure, portal hypertension, variceal bleeding, encephalopathy and various other complications. Nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), cardiac hepatopathy, chronic HCV or HBV–related hepatitis is still widespread in the world with very high morbidity and mortality rates.[1]

Liaqat et al. [2021] examined the optimal cut-off values for predicting different stages of liver fibrosis and to determine the level of agreement between shear wave elastography and APR) and fibrosis-4 index (FIB-4) scores in patients with chronic liver disease. A descriptive, cross-sectional study was performed at the Radiology Department of Shaukat Khanum Memorial Hospital Lahore from 1 Jun 2019 until 1 June 2020. FIB-4 and APRI scores were determined by the following formula: FIB-4 = (age × AST) ÷ (platelet

count × (√ (ALT)) and APRI = (AST÷AST upper limit of normal) ÷ platelet × 100. Data was analysed with the help of SPSS version 24.0 and Microsoft Excel 2013. The results showed that 80 individuals were conveniently selected, of which 62.5% were men and 37.5% were women. The mean age of the subjects was 43.47 SD ± 13.85 years. APRI and FIB-4 scores predicted F4 patients using the cutoff values of 0.47 (Sn. 72%, Sp. 70%) and 1.27 (Sn. 78%, Sp. 73%), respectively. The cutoff values of 0.46 for APRI and 1.27 for FIB-4 predicted F3–F4 patients (Sn. 74% and 77%; Sp. 76% and 76%), respectively. To predict F1–F4 compared to F0, the cutoff value was 0.34 (Sn. 68%, Sp. 75%) for APRI, while the cutoff value for FIB was 0.87 (Sn. 72%, Sp. 75%). The findings suggest that FIB-4 shows better diagnostic accuracy than APRI. This study provides optimal cut-off values for both serum markers for different groups of fibrosis patients. Also, the diagnostic accuracy of FIB-4 for predicting liver fibrosis was found to be superior to APRI in all disease stages.[73]

The severity of the liver disease is represented by its capacity for fibrotic evolution. Ultrasound is used in the evaluation of cirrhosis. It may show increased areas of echogenicity, shrunken liver, enlarged caudate lobe, splenomegaly, and increased portal vein pulsatility index. [74] Elastography is an imaging technique that images or quantifies the elasticity (mechanical properties) of the biological tissues. In these techniques, a force is applied, and the tissue response is observed.[75]

Bellamkonda et al. [2018] evaluated the diagnostic performance of shear wave elastography in estimating fibrosis in patients with chronic liver disease by using biopsy and/or serum markers as reference standards. 100 patients underwent point quantification-shear wave elastography, for whom noninvasive serum fibrosis indices like APRI, FIB-4, and King's score were calculated. The receiver-operator characteristic (ROC) curve analysis was performed. The study results showed that the shear wave elastography measurements showed moderate agreement with APRI and FIB-4 and fair agreement with King's score. The

AUROC for differentiating F0-F1, F2-F3, F2-F3, and F4 are 0.873 and 0.504, respectively, using APRI as reference standard. The cutoff values derived for differentiating F0-F1 and F2-F3 was 7.07, and for differentiating F2-F3 and F4 was 11.94. The authors concluded that the diagnostic performance of shear wave elastography is comparable with that of serum fibrosis indices APRI and FIB-4. [76]

Ayonrinde et al. [2022] conducted a cross-sectional study to compare SWE, TE and clinical markers of chronic liver disease in patients with various liver disorders. Liver ultrasound with SWE was performed on 421 adult patients, 227 of whom also had TE. Patient age, gender, body mass index (BMI), liver disease aetiology and laboratory results were recorded. Associations between SWE, TE and other tests for liver fibrosis and chronic liver disease severity were sought. Advanced liver fibrosis was defined as liver stiffness measurement (LSM) equivalent to ≥ F3 using METAVIR staging. The results showed that patients were predominantly male (68%), with a mean (standard deviation) age of 54 years, BMI 28 kg/m^2 and serum ALT 39 U/L. Liver disorders were predominantly NAFLD, chronic hepatitis B (CHB), chronic hepatitis C (CHC) and alcohol-related liver disease. The median (interquartile range) LSM was 10 kPa with SWE and 9.2 kPa with TE. Advanced liver fibrosis was associated with older age, higher BMI, a model for end-stage liver disease score, AST, AST/ALT ratio, APRI, FIB-4 and Hepascore. SWE and TE LSM were positively correlated, particularly for NAFLD and CHC. SWE LSM predicted ultrasound and endoscopy-diagnosed portal hypertension and oesophageal varices. The study concluded that across various liver diseases, SWE is at least comparable with TE and other non-invasive tests of liver fibrosis. SWE is accurate for predicting liver-related portal hypertension. [77]

According to a study done in Karachi, Pakistan, by Zaki, M. et al. [2019], ultrasound liver changes were seen in 100% of the included patients. Colour Doppler revealed portosystemic collaterals in 20% of patients. Shear wave elastography could differentiate cases from control with a cut-off value of 13.1 kPa. There was a significant correlation between shear wave elastography and ultrasound changes in cirrhotic patients. Shear wave elastography could predict the presence of gastro-oesophageal varices in cirrhotic patients with a cutoff value of 26.5 kPa sensitivity of 88% and specificity of 85%.[78]

The consensus of the Society of the radiologist in ultrasound panel proposed a vendor-neutral "rule of four" (5, 9, 13, 17 kPa) for the shear wave elastography for viral aetiologies and non-alcoholic fatty liver disease: Liver stiffness of 5 kPa (1.3 m/sec) or less has high probability of being normal; liver stiffness less than 9 kPa (1.7 m/sec), in the absence of other known clinical signs, rules out cACLD; values between 9 kPa (1.7 m/sec) and 13 kPa (2.1 m/sec) are suggestive of cACLD but may need further test for confirmation; and values greater than 13 kPa (2.1 m/sec) are highly suggestive of cACLD. There is a probability of CSPH with a liver stiffness value greater than 17 kPa (2.4 m/sec) [79]

Yoo et al. [2022] conducted a prospective study to determine whether the newly developed 2D-SWE, RS85, and Samsung-SWE were more valid and reliable than TE for predicting the stage of liver fibrosis. The study enrolled a total of 116 patients with chronic liver disease who underwent 2D-SWE, TE, laboratory testing, and liver biopsy on the same day from two tertiary care hospitals. One patient with unreliable measurement was excluded. The measurement of 2D-SWE was considered acceptable when a homogenous colour pattern in a region of interest of at least 10 mm was detected at 10 different sites. Diagnostic performance was calculated using the area under the receiver operating

characteristic curve (AUROC). The study results showed that liver fibrosis stages included F0 (18%), F1 (19%), F2 (24%), F3 (22%), and F4 (17%). The interclass correlation coefficient for inter-observer agreement in 2D-SWE was 0.994 (95% confidence interval [CI], 0.988 to 0.997). Overall, the results of 2D-SWE and stages of histological fibrosis were significantly correlated ($r = 0.601$, $p < 0.001$). The 2D-SWE showed good diagnostic ability (AUROC, 0.851; 95% CI, 0.773 to 0.911) comparable to TE (AUROC, 0.859; 95% CI, 0.781 to 0.916) for the diagnosis of significant fibrosis (≥ F2), and the cut-off value was 5.8 kPa. AUROC and optimal cut-off of 2D-SWE for diagnosing liver cirrhosis were 0.889 (95% CI, 0.817 to 0.940) and 9.6 kPa, respectively. TE showed similar diagnostic performance in distinguishing cirrhosis (AUROC, 0.938; 95% CI, 0.877 to 0.974; $p = 0.08$). The study concludes that 2D-SWE is comparable to TE in diagnosing significant fibrosis and liver cirrhosis with high reliability.[80]

MATERIALS & METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

Patients are referred for ultrasound examination to the Department of Radio-Diagnosis at R.L. Jalappa Hospital and Research Center, attached to Sri Devaraj Urs Medical College, Kolar.

STUDY DESIGN: A cross-sectional analytical study.

METHODOLOGY:

This cross-sectional study was conducted in the Department of Radio-Diagnosis at R.L. Jalappa Hospital and Research Center attached to Sri Devraj Urs Medical College, Kolar, following approval from the institutional ethical committee. The study was conducted for a period of 18 months year, from September 2022 to February 2024.

SAMPLE SIZE CALCULATION

Bellamkonda S et al. reported the correlation coefficient (r) as 0.39. Assuming alpha error = 0.05 (95% Confidence Limit) and a power of 80%. The final required sample size was calculated to be 91.

$$n = \frac{\left(Z_{1-\beta} + Z_{1-\frac{\alpha}{2}}\right)^2}{\left(\frac{r^2}{1-r^2}\right)}$$

Where,

r : Correlation coefficient.

$Z_{1-\alpha/2}$: Desired confidence level

1-β : Power

INCLUSION CRITERIA:

1. Patients diagnosed with alcoholic liver disease.
2. Patients with non-alcoholic fatty liver disease
3. Patients with deranged liver function tests.
4. Patients clinically and serologically diagnosed with liver diseases due to infective/ autoimmune/ drug-induced.

EXCLUSION CRITERIA:

1. Pregnant patients.
2. Patients with insufficient breath holding or uncooperative.
3. Patients with moderate and gross ascites.
4. Patients diagnosed with liver tumours.

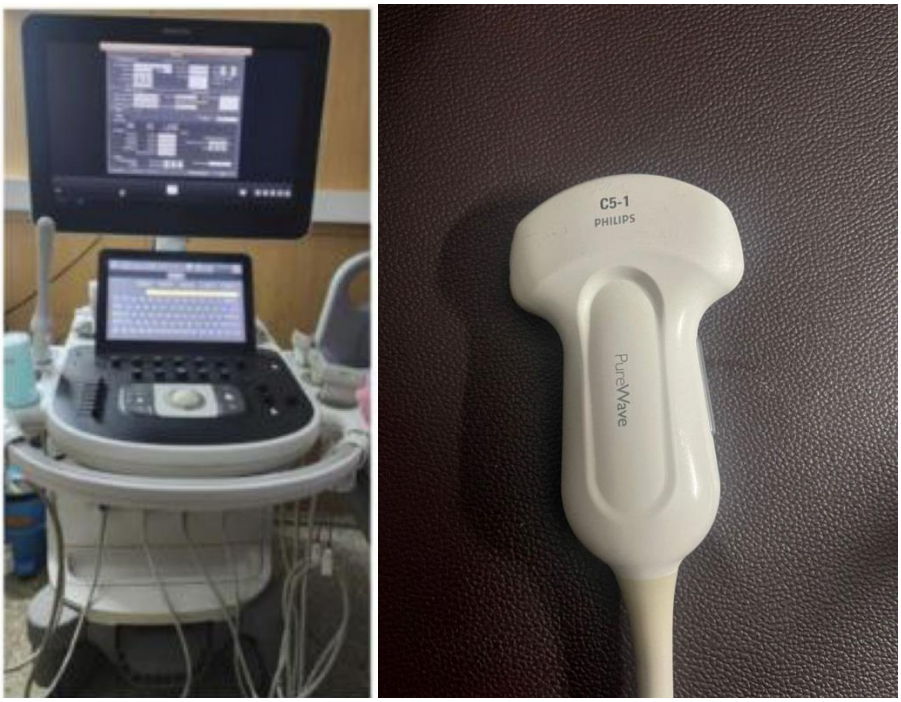
PROTOCOL FOR EXAMINATION

All ultrasound examinations were performed using a Philips EPIQ5 system equipped with shear wave point quantification, ELASTPQ, using a curvilinear broadband transducer (C5-1). The elastography technique employed by the EPIQ5 US system is ElastPQ, which was approved by the US Food and Drug Administration for liver stiffness measurement. Patients who satisfied the inclusion criteria for this study have undergone an ultrasound and shear wave elastographic evaluation of the liver after giving consent.

The patients were placed in the supine position, or the left lateral position with the right arm abducted. Conventional gray-scale sonography was performed initially. Depending on those sonographic findings of the liver, the patients were classified as having coarse echotexture fatty infiltration or normal echotexture. SWE measurements were obtained through an intercostal approach. After placing the probe over the abdomen, the patients were asked to hold his or her breath, and a grayscale sonographic image was used to place the ROI

in an area of the liver devoid of visible ducts and vessels. The ROI size is predetermined on the ultrasound equipment at 0.5 cm × 1.5 cm. The ROI was placed at a distance < 8 cm from the liver capsule.

Stiffness is expressed in terms of kilopascals (kPa). For each patient, 10 SWE measurements were taken from different areas of the right lobe of the liver. The ultrasound equipment displays an average liver stiffness based on the 10 SWE measurements taken. We are considering Yoo et al. study cut-off as a reference standard to compare the various fibrosis stages. The cut-off from this study was 6.4 - 6.6 kPa for F1 stage, 6.6 – 8.07 kPa for F2 stage, 8.07 – 9.3 kPa as F3 stage and > 9.3 kPa as F4 stage.[72] This indicates the liver stiffness for that particular patient. Liver function tests were done, serological values were recorded, and serological indices were calculated and correlated with shear wave elastographic findings.



3a **3b**

Figures 3a and 3b Ultrasound scanner Philips Epic 5 (3a) and C1-5 MHz convex transducer (equipped with shear wave point quantification, ELAST PQ)

STATISTICAL ANALYSIS:

The study encompassed both qualitative and quantitative variables. Qualitative variables were expressed as numbers (%), while quantitative variables were denoted by mean ± SD and Median (QR). The normality of the data was assessed via the Kolmogorov-Smirnov test. The Chi-square and Fisher exact test were utilised to explore associations between two independent qualitative variables. The significance of differences among ultrasound, clinical, and serological variables across SWE scores was assessed using the Nonparametric Kruskal Wallis test. Receiving Operating Characteristic (ROC) analysis was employed to ascertain the optimal SWE (Shear Wave Elastography) cut-off values for discriminating between various liver fibrosis stages based on SWE scores. Kendall's tau b correlation technique was applied to assess relationships between ultrasound and serological variables. A confidence level of 95% was maintained for all statistical tests. SPSS 20 was employed for data analysis.

RESULTS

RESULTS

Table 3 Distribution of age based on shear wave elastography stages

	Distribution of age on basis of shear wave elastography stages				Total
Age	F0-F1	F2	F3	F4	
	N (%)	N (%)	N (%)	N (%)	
<45 years	14 (70.0%)	16 (69.6%)	12 (60.0%)	16 (57.1%)	58
>45 years	6 (30.0%)	7 (30.4%)	8 (40.0%)	12 (42.9%)	33
Total	20 (100.0%)	23 (100.0%)	20 (100.0%)	28 (100.0%)	91

The table categorises shear wave elastography stages, segmented by age groups (< 45 years and > 45 years) and fibrosis stages (F0-F1, F2, F3, F4). Fisher Exact applied was applied (P value > 0.05). In the younger group (< 45 years), a higher proportion is seen across all stages (70.0% in F0-F1, 69.6% in F2, 60.0% in F3, 57.1% in F4). Conversely, the older group (> 45 years) has a lower proportion in each stage, increasing from 30.0% in F0-F1 to 42.9% in F4. The age group is not significantly associated with the shear wave elastography stages.

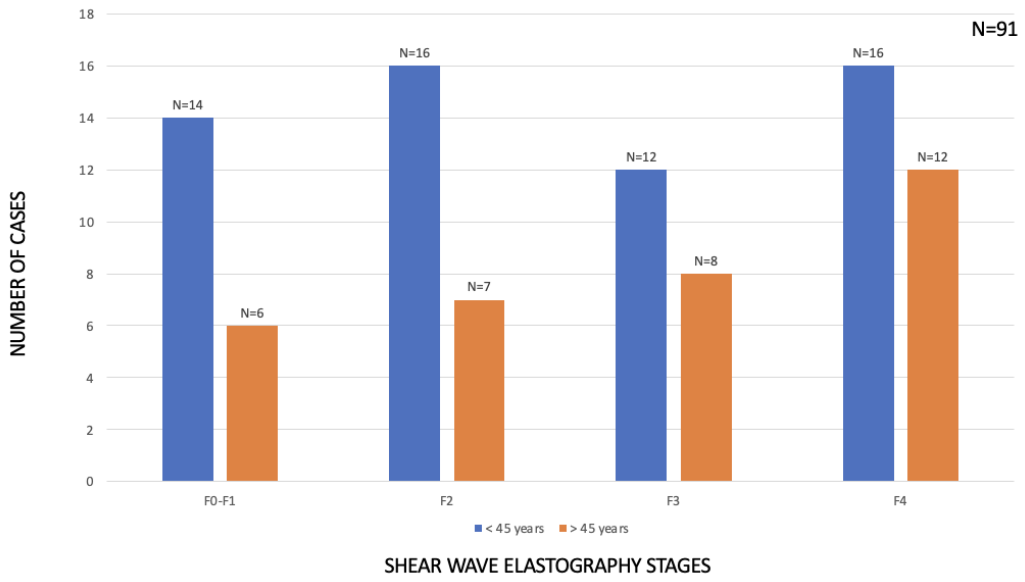


Figure 4 Age distribution of fibrosis based on shear wave elastography stages.

Table 4 Distribution of fibrosis stages based on gender distribution

	Stages on the basis of shear wave elastography stages				Total
Gender	F0-F1	F2	F3	F4	
	N (%)	N (%)	N (%)	N (%)	
Female	5 (25.0%)	4 (17.4%)	3 (15.0%)	4 (14.3%)	16
Male	15 (75.0%)	19 (82.6%)	17 (85.0%)	24 (85.7%)	75
Total	20 (100.0%)	23 (100.0%)	20 (100.0%)	28 (100.0%)	91

The table shows the distribution of complications by gender across different fibrosis stages (F0-F1, F2, F3, F4) based on the shear wave elastography stages. A chi-square test was applied (P- value 0.723). Males consistently represent a higher percentage in each stage (75.0% in F0-F1, 82.6% in F2, 85.0% in F3, and 85.7% in F4), indicating that males are more frequently affected across all stages. Females constitute a smaller proportion in each stage, highlighting a gender disparity in fibrosis severity. Gender is not significantly associated with the stages based on shear wave elastography.

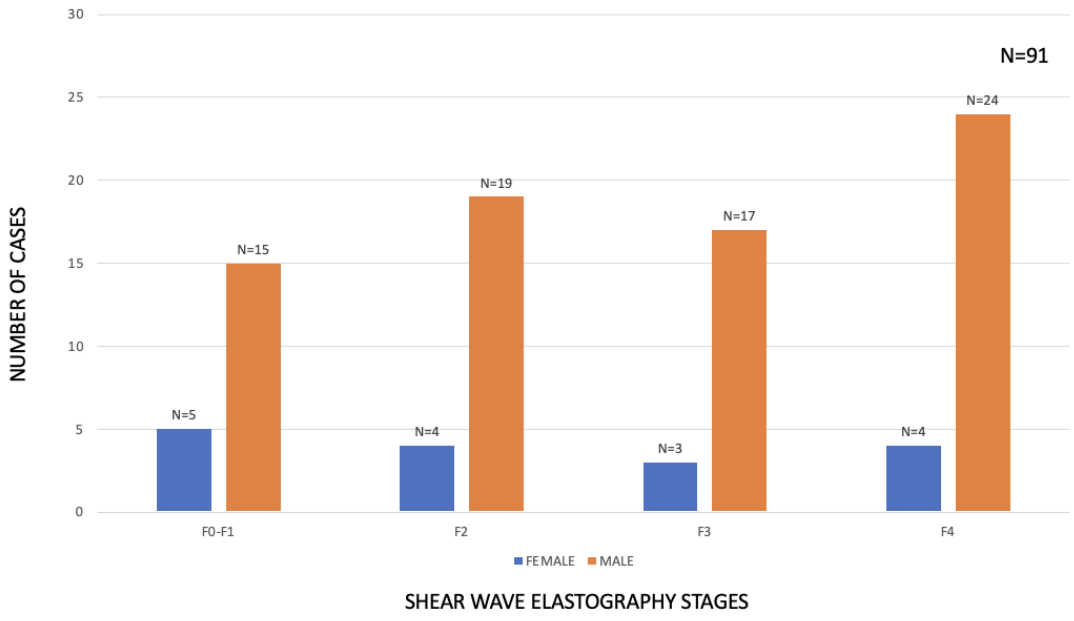


Figure 5 Distribution of fibrosis stages based on gender distribution.

Table 5 Categorises fibrosis stages (F0-F1, F2, F3, F4) according to underlying conditions

	Stages based on shear wave elastography stages				Total
Liver Disease	F0-F1	F2	F3	F4	
	N (%)	N (%)	N (%)	N (%)	
ALD	7 (35.0%)	12 (52.2%)	7 (35.0%)	26 (92.9%)	52
HEPATITIS B	2 (10.0%)	4 (17.4%)	6 (30.0%)	0 (0.0%)	12
HEPATITIS C	1 (5.0%)	0 (0.0%)	4 (20.0%)	1(3.6%)	6
NAFLD	10 (50.0%)	7 (30.4%)	3 (15.0%)	1 (3.6%)	21
Total	20 (100.0%)	23 (100.0%)	20 (100.0%)	28 (100.0%)	91

Table categorises fibrosis stages (F0-F1, F2, F3, F4) according to underlying conditions: Fisher Exact test (P Values < 0.05). ALD (Alcoholic Liver Disease), Hepatitis B, Hepatitis C, and NAFLD (Non-Alcoholic Fatty Liver Disease). ALD is most prevalent in advanced stages (92.9% in F4), indicating a severe progression. Hepatitis B shows significant presence in early and intermediate stages but none in F4. Hepatitis C peaks at F3 (20.0%) and drops drastically in F4 (3.6%). NAFLD is expected in early stages (50.0% in F0-F1), decreasing prevalence with advanced fibrosis. Type of liver disease is statistically significantly associated with stages based on shear wave elastography.

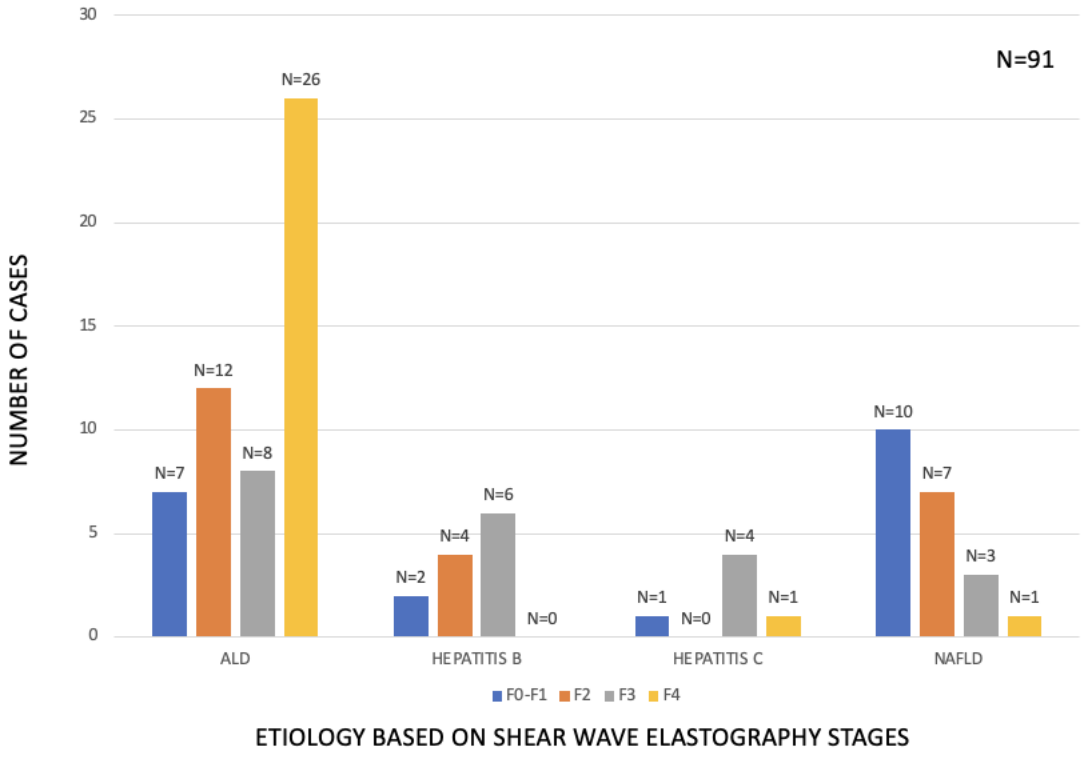


Figure 6 categorises fibrosis stages (F0-F1, F2, F3, F4) according to underlying etiology

Table 6 Shear wave elastography stages and presence of complications

	Stages on the basis on Shear wave elastography				Total
Complications	F0-F1	F2	F3	F4	
	N (%)	N (%)	N (%)	N (%)	N
NO	13 (65.0%)	15 (65.2%)	10 (50.0%)	6 (21.5%)	44
YES	7 (35.0%)	8 (34.8%)	10 (50.0%)	22 (78.5%)	47
Total	20 (100.0%)	23 (100.0%)	20 (100.0%)	28 (100%)	91

Table 6 illustrates the distribution of fibrosis stages (F0-F1, F2, F3, F4) based on the presence of complications. Chi-square P - 0.016 was applied. Patients without complications were predominant in the early stages (65.0 % in F0-F1, 65.2 % in F2) but decreased significantly in F4 (21.5%). Patients with complications show a substantial increase in advanced fibrosis stages, comprising 78.5% of F4 cases. The complications were significantly associated with Stages based on shear wave elastography stages.

Table 7 Distribution of complications based on shear wave elastography

Complications	Stage of fibrosis based on shear wave elastography				Total
	F0-F1	F2	F3	F4	
Mild	2 (28.5%)	2 (25.0 %)	1 (10.0%)	2 (9.0 %)	7
Moderate	1 (14.2 %)	2 (25.0 %)	3 (30.0%)	5 (22.7%)	11
Severe	4 (57.1 %)	4 (50.0 %)	6 (60.0%)	15 (68.1%)	29
Total	7 (100.0%)	8 (100.0%)	10 (100.0%)	22 (100%)	47

Table 7 illustrates the distribution of fibrosis stages (F0-F1, F2, F3, F4) based on the presence of complications and the severity of complications in each stage, as described below**.**

1. Mild complications – icterus and mild ascites
2. Moderate complications – moderate to gross ascites and hepatorenal syndrome
3. Severe complications – hematemesis and hepatic encephalopathy

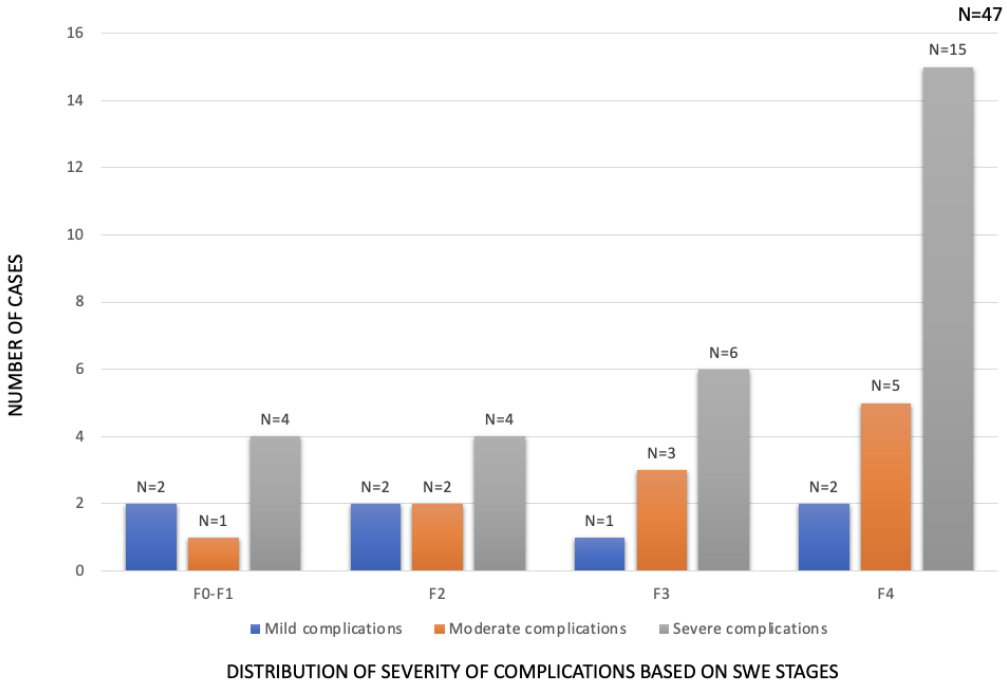


Figure 7 presents the distribution of various complications (Ascites, Encephalopathy, Hematemesis, Hepatic Encephalopathy, Hepatorenal Syndrome, Jaundice, Mild Ascites) across fibrosis stages (F0-F1, F2, F3, F4). Hematemesis is the most common complication, especially in advanced stages (30.0% in F3, 39.3% in F4). Early stages have no complications predominantly. (65.0% in F0-F1, 65.2% in F2) but decrease significantly in F4 (21.4%). This indicates that the likelihood of complications increases as fibrosis progresses, highlighting the severity of advanced fibrosis.

Table. 8 show the distribution of liver echotexture

	Stages on the shear wave elastography fibrosis				Total
Echotexture	F0-F1	F2	F3	F4	
	N (%)	N (%)	N (%)	N (%)	
Coarse	0 (0.0%)	1 (4.3%)	16 (80.0%)	28 (100.0%)	45
Increased	20 (100.0%)	22 (95.7%)	4 (20.0%)	0 (0.0%)	46
Total	20 (100.0%)	23 (100.0%)	20 (100.0%)	28 (100.0%)	91

Table 8 shows the distribution of liver echotexture (Coarse vs. increased) across SWE fibrosis stages (F0-F1, F2, F3, F4). Chi-square (P- value <0.001) was applied. The liver texture predominantly increases in the early stages (F0-F1, F2) (100.0% and 95.7%, respectively). However, coarse liver texture becomes more prevalent as fibrosis advances, dramatically increasing to 80.0% in F3 and 100.0% in F4. This indicates a strong correlation between advanced fibrosis stages and coarse liver texture, suggesting that liver texture coarseness can significantly indicate severe fibrosis (P- value < 0.001). Out of 45 patients with coarse echotexture of the liver, 38 % i.e.17 of these also had nodularity and surface irregularities belonging to stage F4 of liver fibrosis.

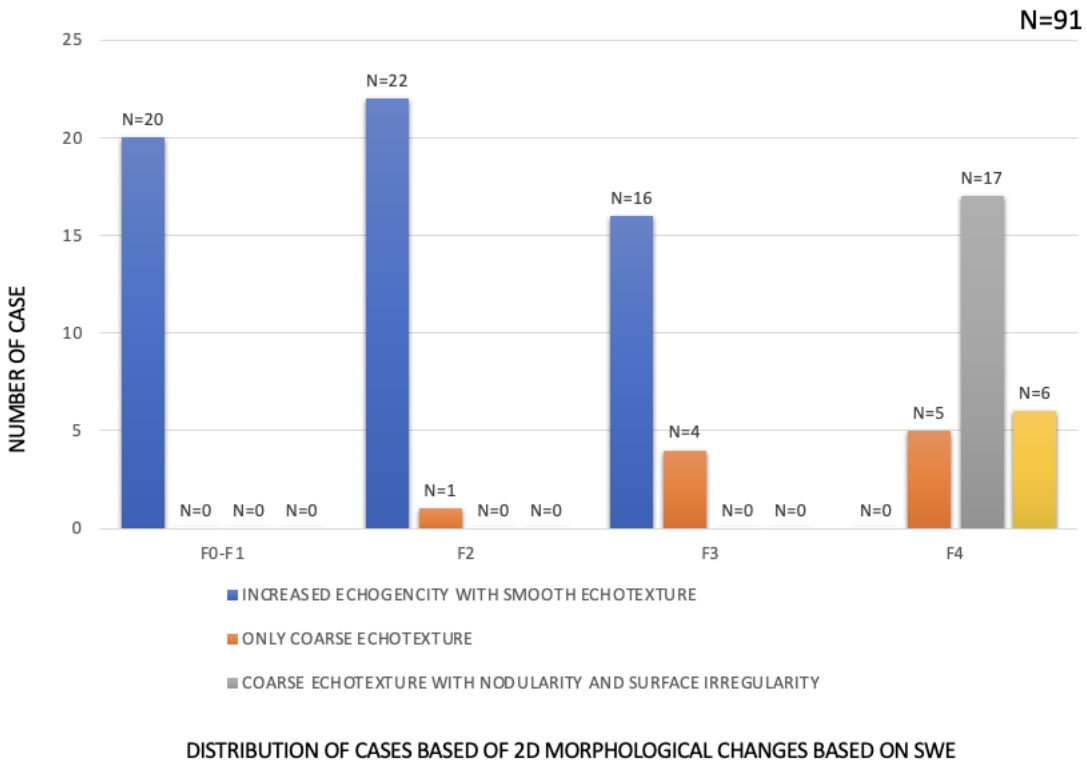


Figure 8 shows the distribution of liver echotexture across SWE fibrosis stages

Table 9 Details of ultrasound findings and shear wave elastography fibrosis stages

SWE Stages	Liver size	PV Diameter	SWE (Kpa)	Spleen (cm)
F0-F1	18.6 (12.5-18.9)	12.6 (12.1-14.3)	6.1 (5.5-6.2)	12.1 (9.7-12.5)
F2	14.8 (12.1-15.9)	12.4 (12.1-14.1)	7.6 (6.9-7.9)	11.1(9.9-12.8)
F3	14 (12.2-15.2)	13.2 (12.1-16.1)	8.75 (8.3-8.9)	11.8 (10.1-13.1)
F4	12.3 (11.6-14.2)	14.6 (12.4-15.5)	11.7 (9.8-12.7)	12.5 (11.8-12.8)
P- value	0.004	0.15	P < 0.001	0.162

The table presents liver size, portal vein diameter (PV), liver elastography (Kpa), and spleen size across fibrosis stages (F0-F1, F2, F3, F4). The Kruskal-Wails test was applied.

Liver Size: Liver size decreases significantly with advancing fibrosis, from 15.6 cm (F0-F1) to 12.35 cm (F4), with a P-value of 0.004, indicating a statistically significant reduction as fibrosis progresses.

Portal Vein Diameter: The portal vein diameter shows an increasing trend from 12.6 mm (F0-F1) to 14.6 mm (F4), but with a P-value of 0.15, this change is not statistically significant.

Liver Elastography (Kpa): Liver stiffness, measured by elastography, increases markedly from 6.1 Kpa (F0-F1) to 11.7 Kpa (F4), with a P-value of < 0.001, signifying a highly significant increase in stiffness with advanced fibrosis.

Spleen Size: Spleen size shows a slight increase from 12.1 cm (F0-F1) to 12.5 cm (F4), but this change is not statistically significant (P-value 0.162).

Table 10 shows significant increases in APRI, KING's and FIB 4 scores across fibrosis stages (F0-F1, F2, F3, F4), with P-values < 0.001 for both measures.

SWE Stages	APRI	KING Score	FIB 4
F0-F1	0.45 (0.375-0.8)	7.1 (5.4-9.6)	0.70 (0.425-0.775)
F2	0.8 (0.7-1.1)	12.9 (12.1-14.1)	1.10 (0.90-1.30)
F3	0.95 (0.725-1.2)	13.5 (12.3-16.05)	1.56 (1.50-1.60)
F4	1.7 (1.425-1.875)	18 (16.825-18.85)	1.78 (1.67-1.90)
P - Value	P < 0.001	P < 0.001	P < 0.001

APRI Score: Raised from 0.45 (F0-F1) to 1.7 (F4), indicating increasing liver damage.

KING Score: Increased from 7.1 (F0-F1) to 18 (F4), reflecting worsening liver function.

FIB 4: Increased from 0.70 (F0-F1) to 1.78 (F4), reflecting worsening liver function

All three scores demonstrate strong correlations with fibrosis progression based on shear wave elastography values, making them valuable for assessing liver fibrosis severity and monitoring disease advancement.

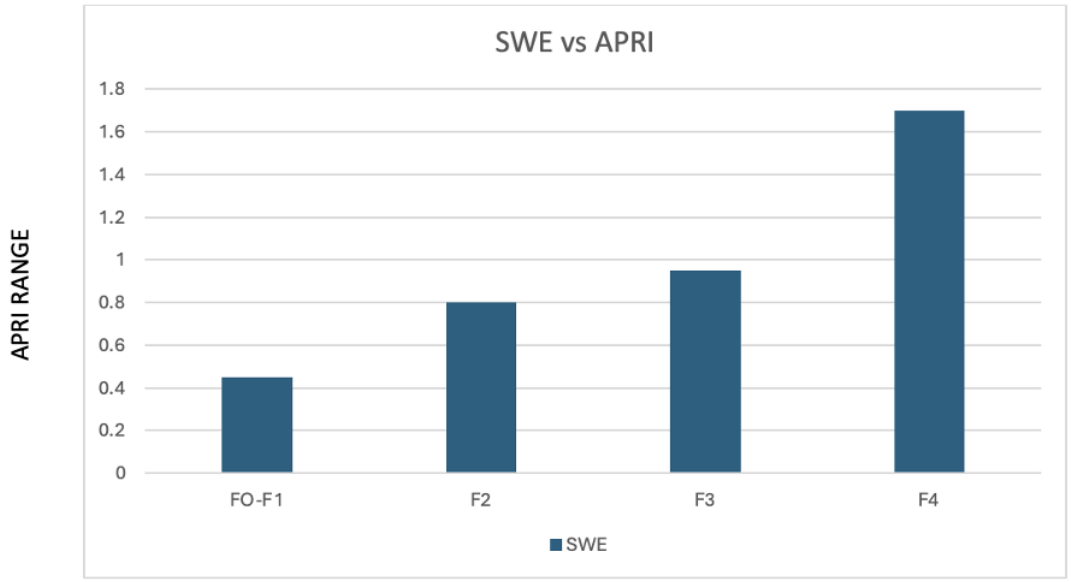


Figure 9 shows the SWE correlation with APRI values.

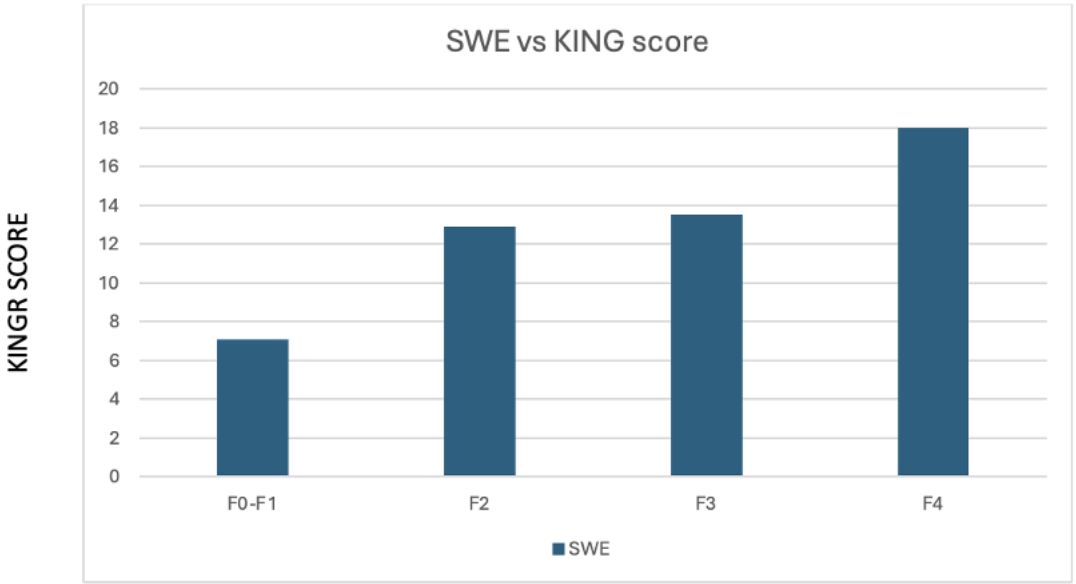


Figure 10 shows the SWE correlation with KING score values.

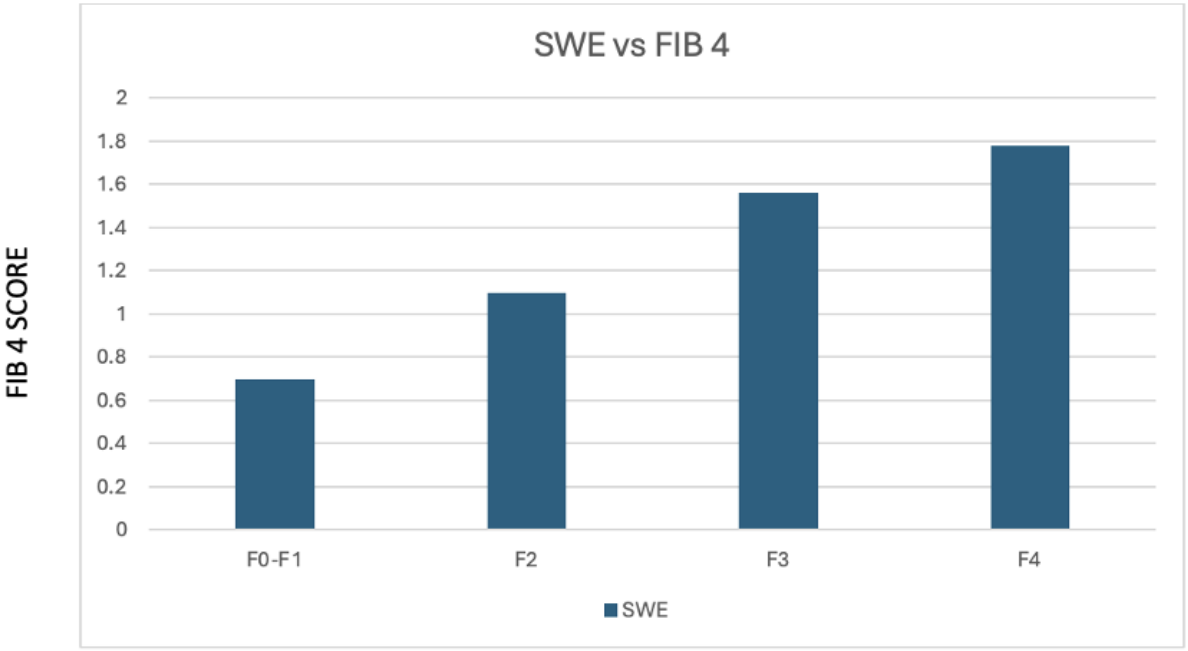


Figure 11 shows the SWE correlation with FIB 4 values.

Table 11 Correlation of the parameters and interpretation

Study variables correlation with SWE	Correlation coefficient	P value
APRI	0.541	P<0.001
KING	0.576	P<0.001
FIB 4	0.597	P<0.001

1. **STAGE (F)**:

    - Strong positive correlations with APRI ($r=0.659$, $p<0.01$) and KING ($r=0.740$, $p<0.01$) indicate that as the fibrosis stage increases, both APRI and KING scores tend to increase significantly.
    - A moderate positive correlation with liver size ($r=0.150$, $p<0.01$) suggests a modest association between fibrosis stage and liver size.
    - There is no significant correlation with portal vein diameter ($p=0.065$).
    - Weak positive correlation with liver elastography in kPa ($r=0.181$, $p<0.01$) and spleen size ($r=0.745$, $p<0.01$).

2. **LIVER ELASTOGRAPHY IN KPA**:

    - Moderate positive correlations with APRI ($r=0.541$, $p<0.01$) and KING ($r=0.576$, $p<0.01$) suggest that as liver elastography values increase, both APRI and KING scores tend to increase significantly.

3. **PORTAL VEIN DIAMETER**:

    - There is a weak positive correlation with spleen size ($r=0.256$, $p<0.01$), indicating a slight association between portal vein diameter and spleen size.

4. **LIVER SIZE**:

    - Strong negative correlations with APRI ($r=-0.224$, $p=0.001$) and KING ($r=-0.242$, $p<0.01$) indicate that as liver size decreases, both APRI and KING scores tend to increase significantly.

- Moderate negative correlations with portal vein diameter ($r=-0.467$, $p<0.01$) and spleen size ($r=-0.215$, $p<0.01$), suggesting a moderate inverse relationship with these parameters.

5. **SPLEEN IN CM**:

   - A weak positive correlation with liver size ($r=0.222$, $p=0.003$) indicates a slight association between spleen size and liver size.

6. **APRI and KING**:

   - There is a strong positive correlation between APRI and KING ($r=0.524$, $p<0.01$), indicating a significant association between these two scoring systems for liver fibrosis assessment

7. **FIB 4**

   - Strong Positive correlation between FIB 4 and SWE and APRI and KING Score.

Overall, the data highlight significant changes in liver size and stiffness with advancing fibrosis, while changes in portal vein diameter and spleen size are less pronounced. The findings suggest that liver elastography and size are crucial to assessing fibrosis progression.

Table 12 Shows P values, sensitivity and specificity of cut-offs derived across various fibrosis stages based on shear wave elastography.

Test Result Variable(s)	AUC	P- Value	Asymptotic 95% Confidence Interval		Cut-off Value of SWE	Sensitivity	Specificity
			Lower Bound	Upper Bound			
(F0-F1) Vs F2	0.957	P<0.001	0.873	1.00	≥ 6.55	97%	95.5%
(F0-F1) Vs F 3	0.953	P<0.001	0.862	1.00	≥ 6.60	95%	90%
(F0-F1) Vs F4	0.993	P<0.001	0.976	1.00	≥ 7.50	96.4%	91.4%
F2 Vs F3	0.803	P<0.001	0.651	0.980	≥ 8.0	95%	77.6%
F2Vs F4	0.938	P<0.001	0.873	1.00	≥ 9.0	92.9%	79.8%
F3 Vs F4	0.898	P<0.001	0.790	1.00	≥ 9.15	89.3%	84.3%

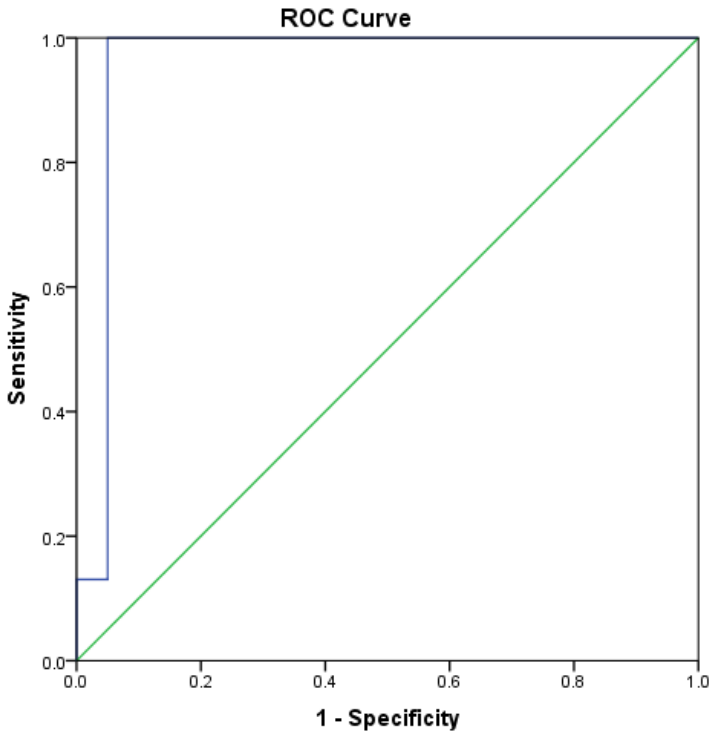


Figure 12 The receiver-operator characteristic curve for prediction of (F2) over (F0-F1) using shear wave elastography measurement

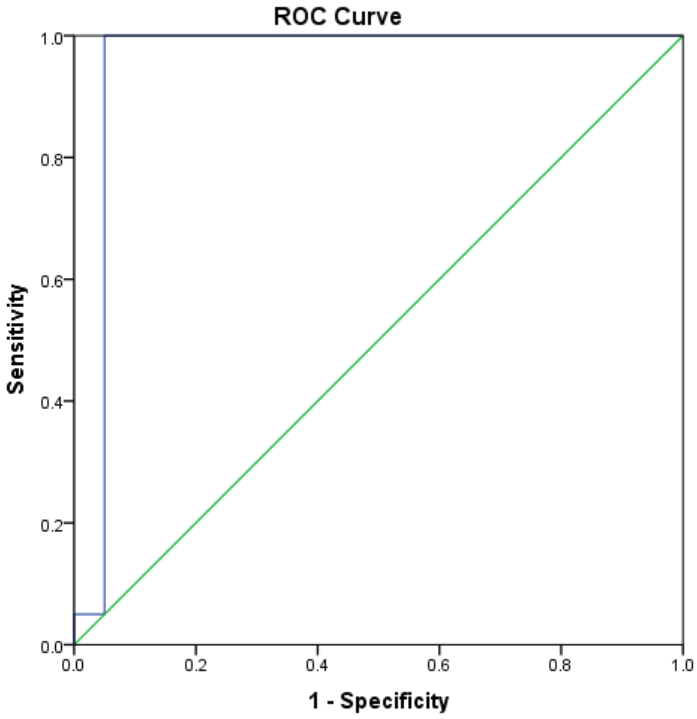


Figure 13 The receiver-operator characteristic curve for prediction of (F3) over (F0-F1) using shear wave elastography measurement

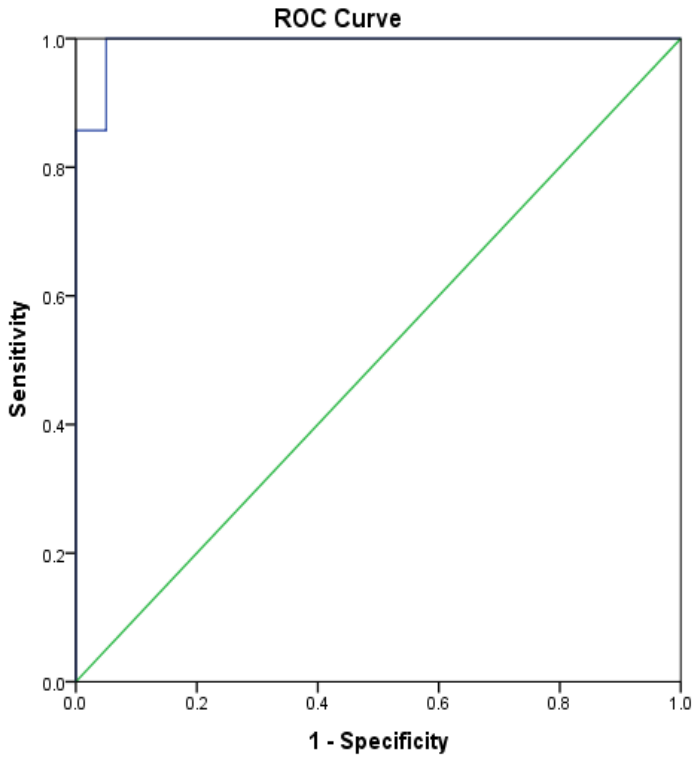


Figure 14 The receiver-operator characteristic curve for prediction of (F4) over (F0-F1) using shear wave elastography measurement.

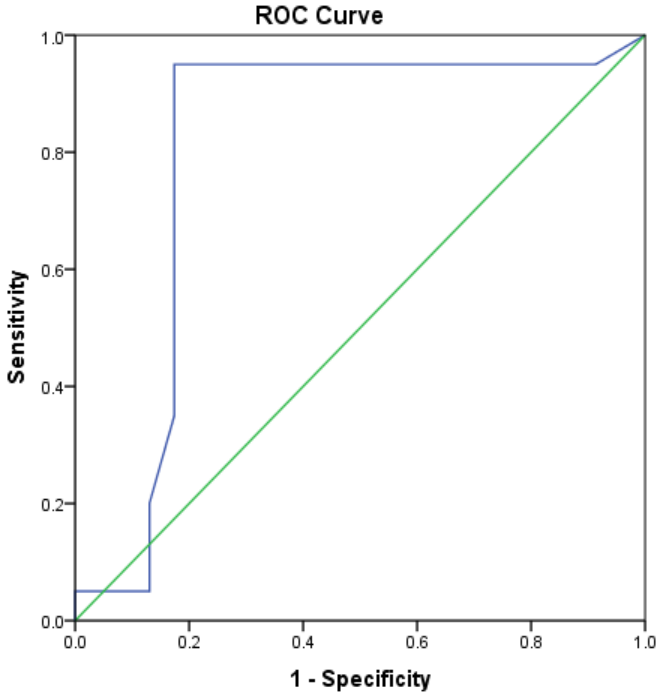


Figure 15 The receiver-operator characteristic curve for prediction of (F2) over (F3) using shear wave elastography measurement

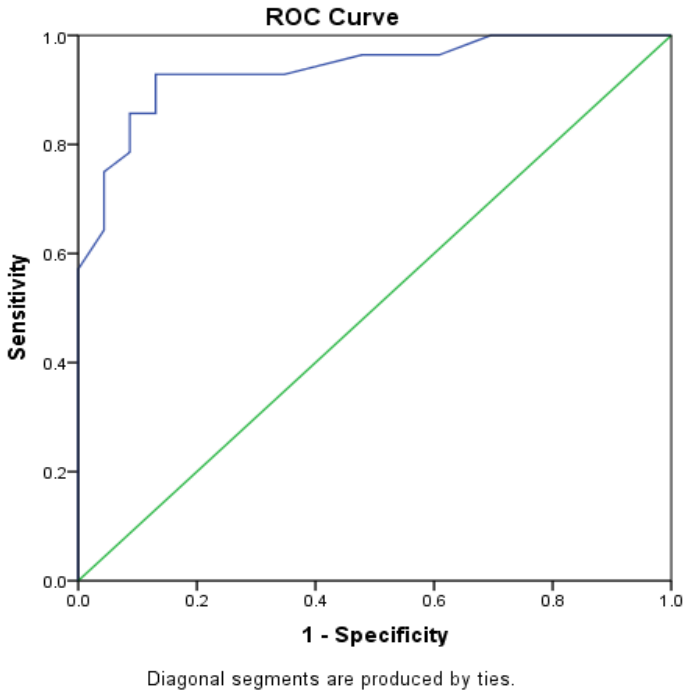


Figure 16 The receiver-operator characteristic curve for prediction of (F2) over (F4) using shear wave elastography measurement

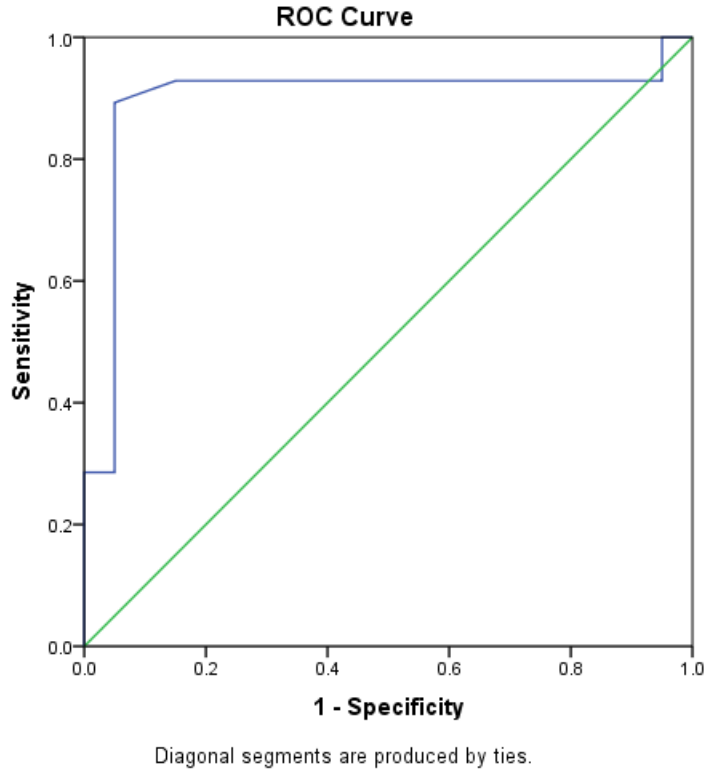


Figure 17 The receiver-operator characteristic curve for prediction of (F3) over (F4) using shear wave elastography measurement

Based on the above results, the proposed cut-off for different stages of liver fibrosis

1. F0-F1 – **below 6.5 kPa**. – Suggestive of ordinary to mild disease/fibrosis
2. F2 – **> 6.5 kPa – 8 kPa** – Suggestive of moderate disease/fibrosis
3. F3 - **> 8 kPa – 9.15 kPa** – Suggestive of significant disease / advanced fibrosis
4. F4 - **> 9.15 kPa** – Suggestive of cirrhosis.

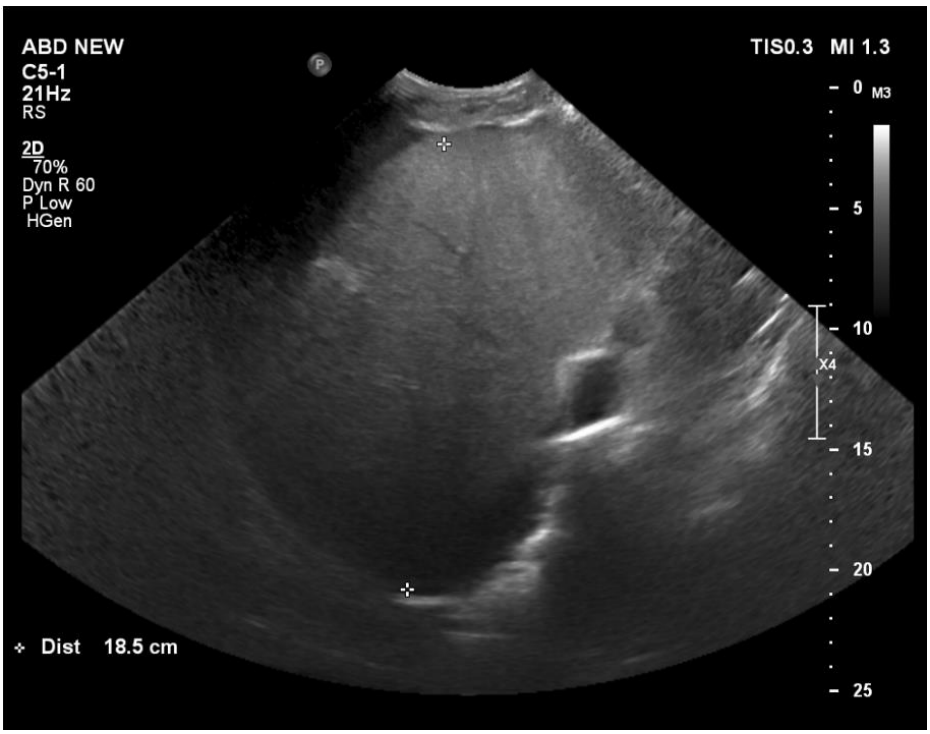


Figure 18 shows 2D greyscale ultrasound image of the liver, demonstrating increased echogenicity with smooth echotexture with increased liver size – suggestive of hepatomegaly with fatty liver.

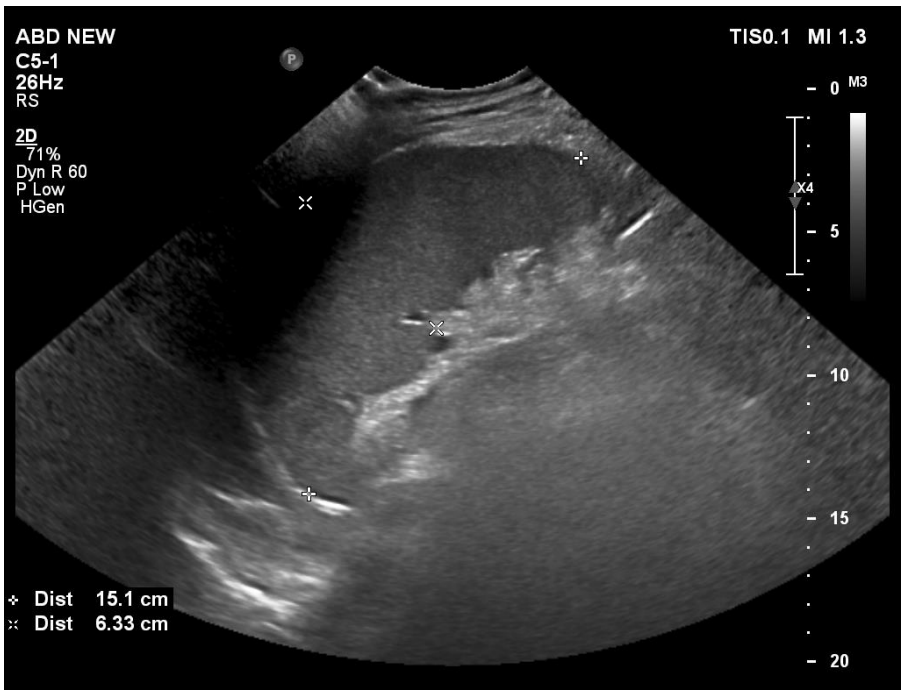


Figure 19 2D grey scale ultrasound image shows an enlarged spleen measuring – 15.1 cm on the long axis – suggestive of splenomegaly.

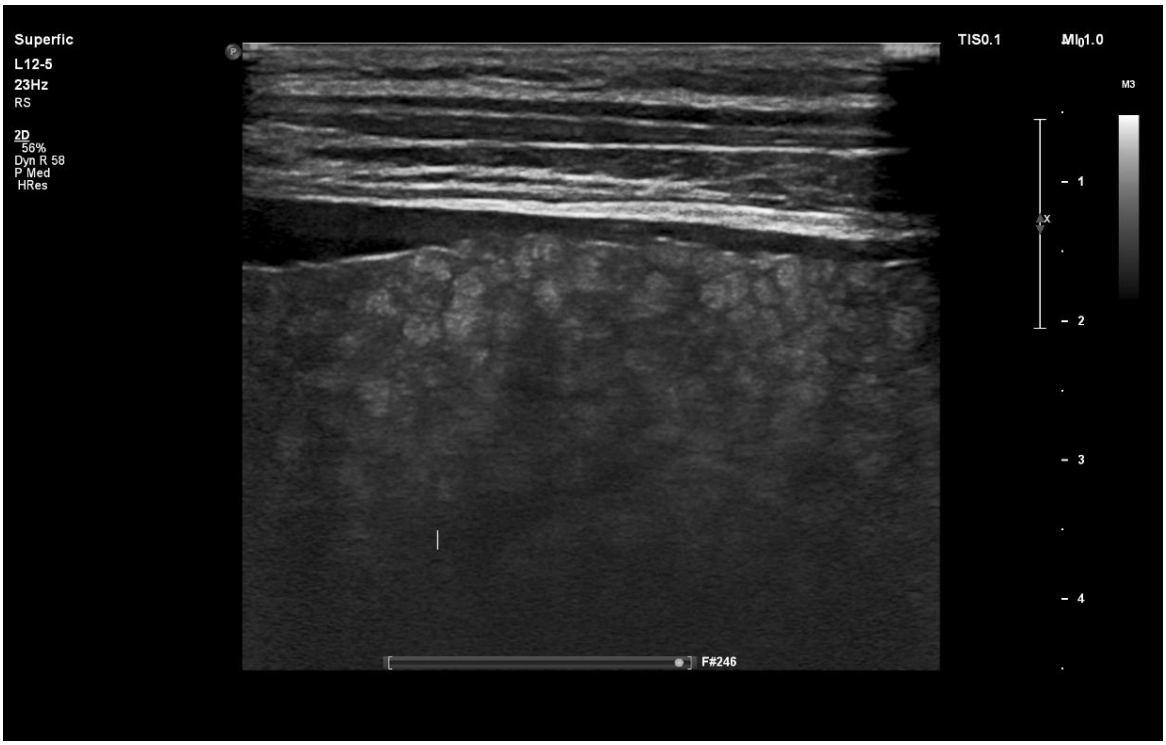


Figure 20 2D grey scale zoomed in image of liver demonstrating hepatic parenchymal nodules and surface irregularity − suggestive of cirrhosis.

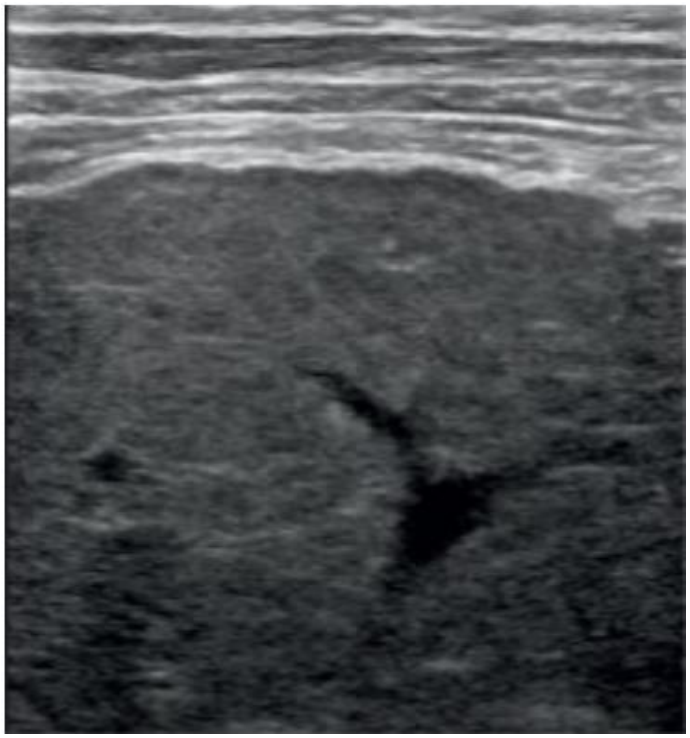


Figure 21 2D grey scale zoomed-in image of liver demonstrating hepatic parenchymal nodules and surface irregularity – suggestive of cirrhosis.

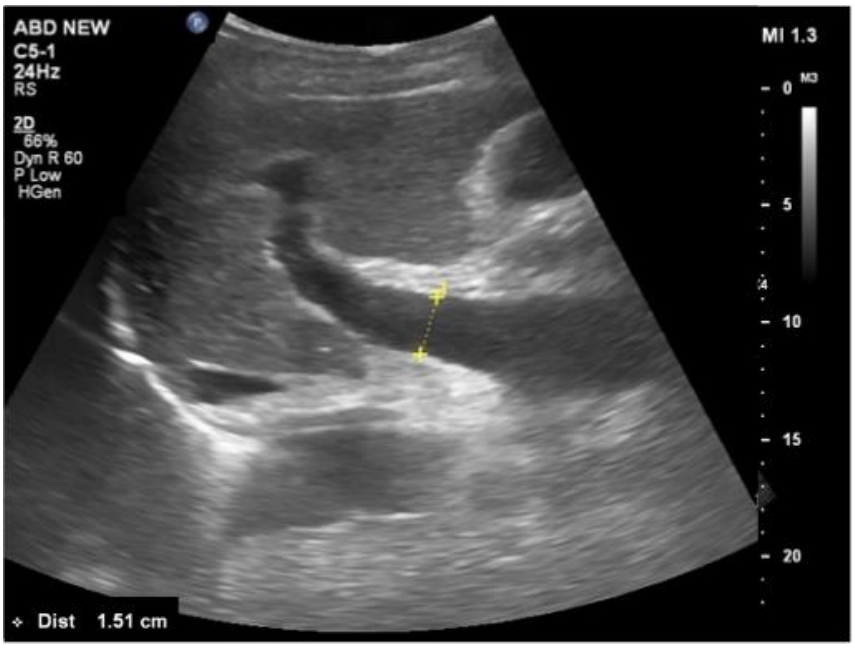


Figure 22 shows a 2D grey scale image of an increased portal vein diameter of 15.1 mm – suggestive of portal hypertension.

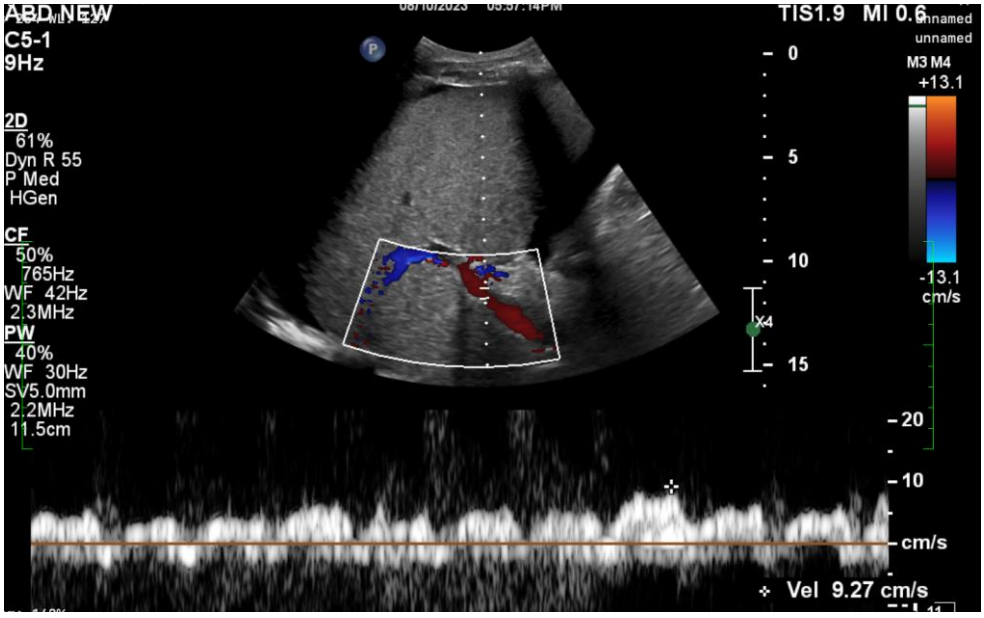
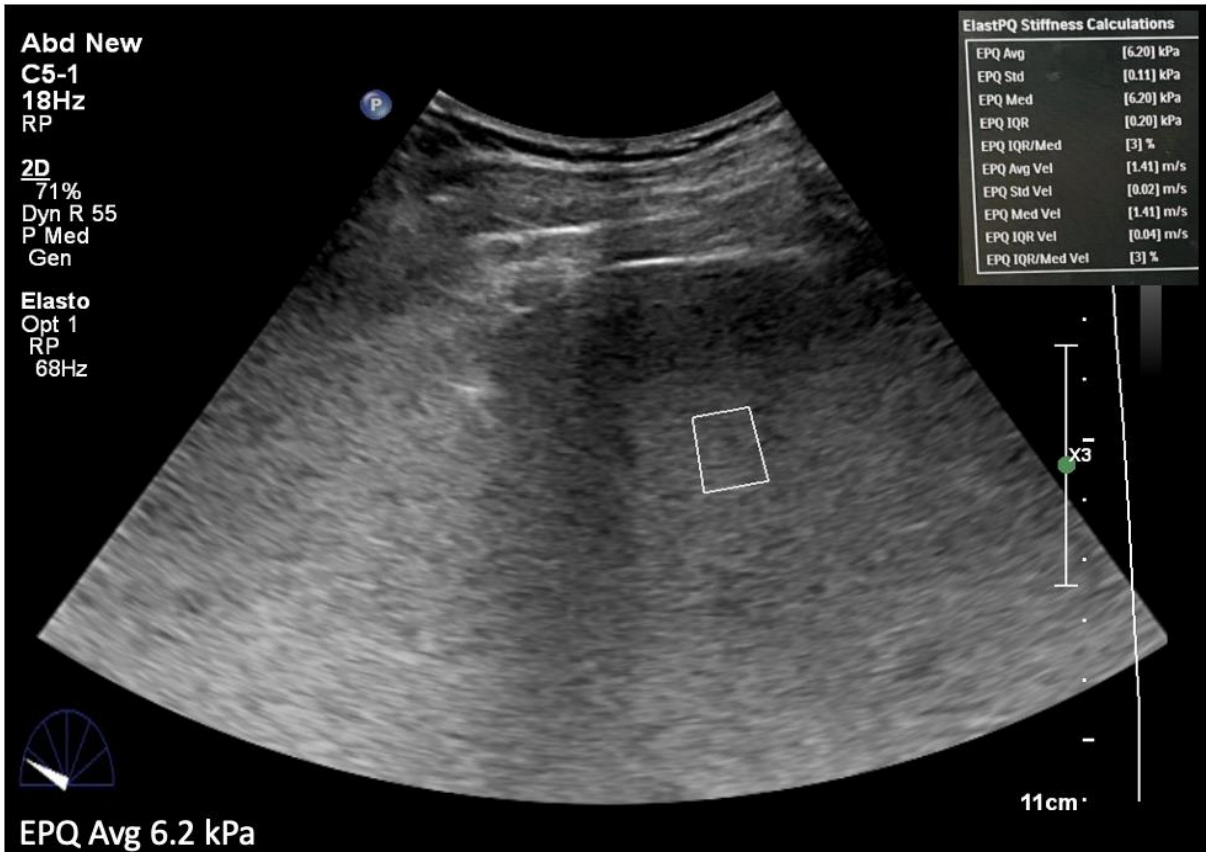


Figure 23 shows an ultrasound color Doppler image of the liver with portal vein spectral Doppler image demonstrating reduced peak systolic velocity of – 9.2 cm/s (normal > 16 cm/s) – consistent with portal hypertension.



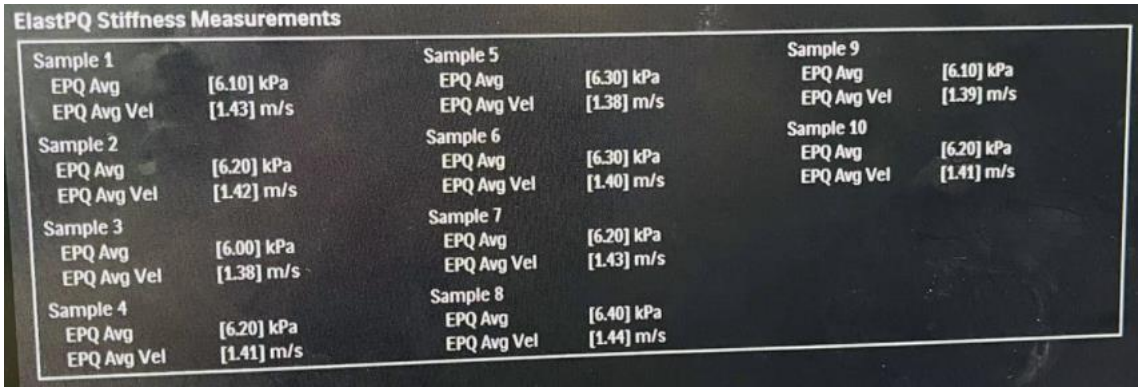
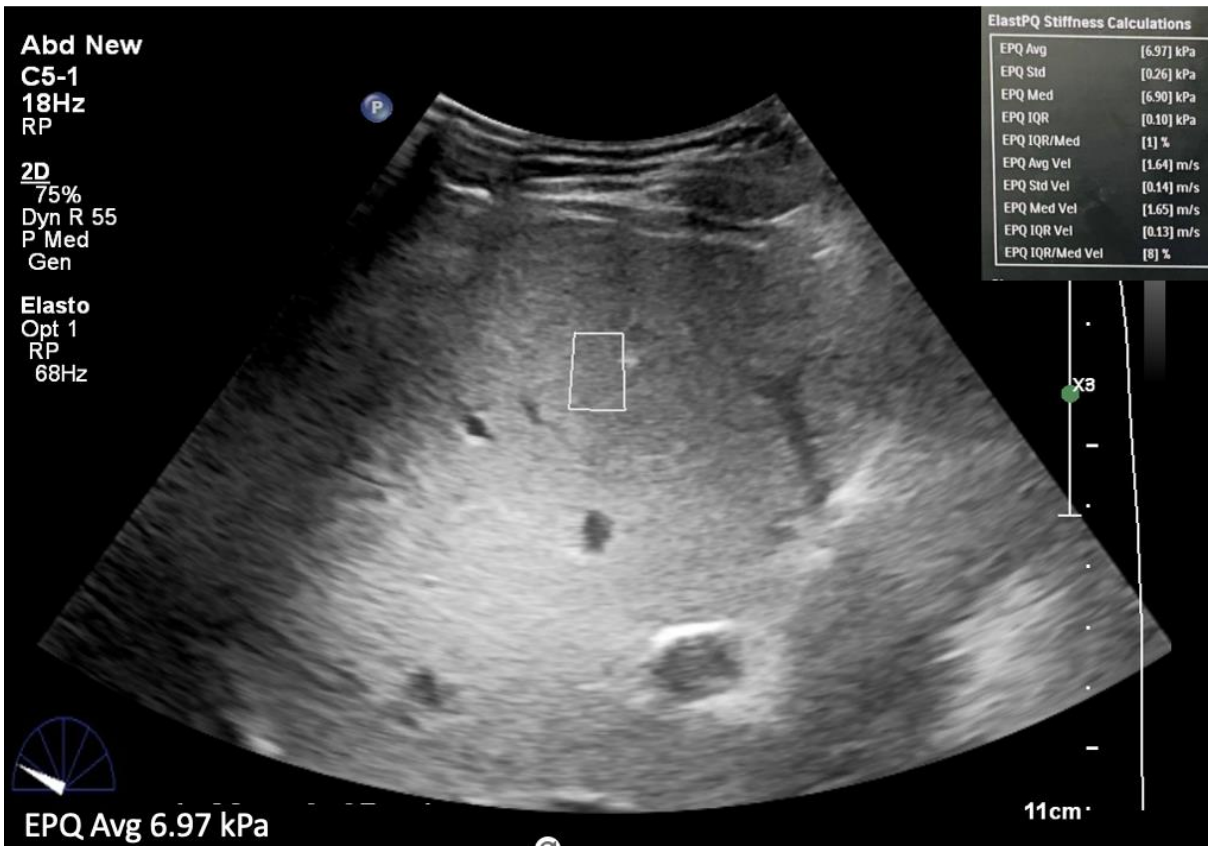


Figure 24. The case for routine check-up. On ultrasound, the liver showed grade I fatty liver.Median elastography values were 6.2 kPa, corresponding to the normal value with APRI-0.45, FIB 4 - 0.91 – Suggestive of normal/mild fibrosis, i.e., stage FI disease.



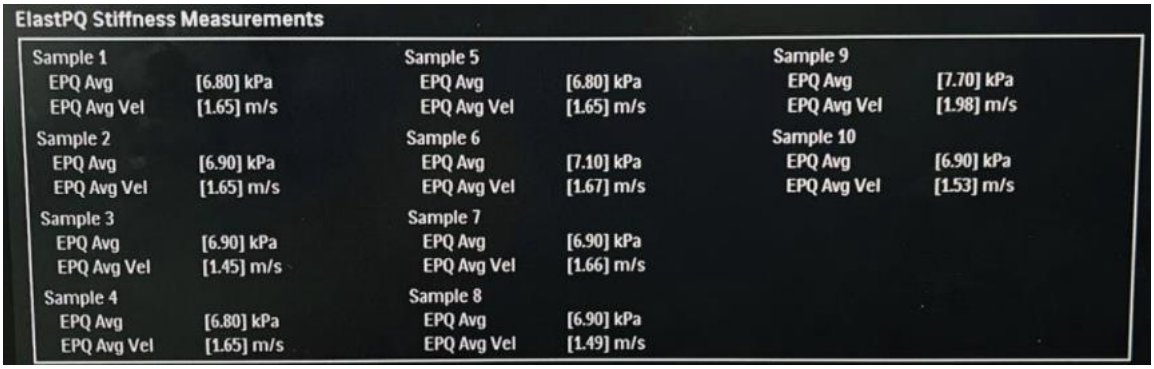
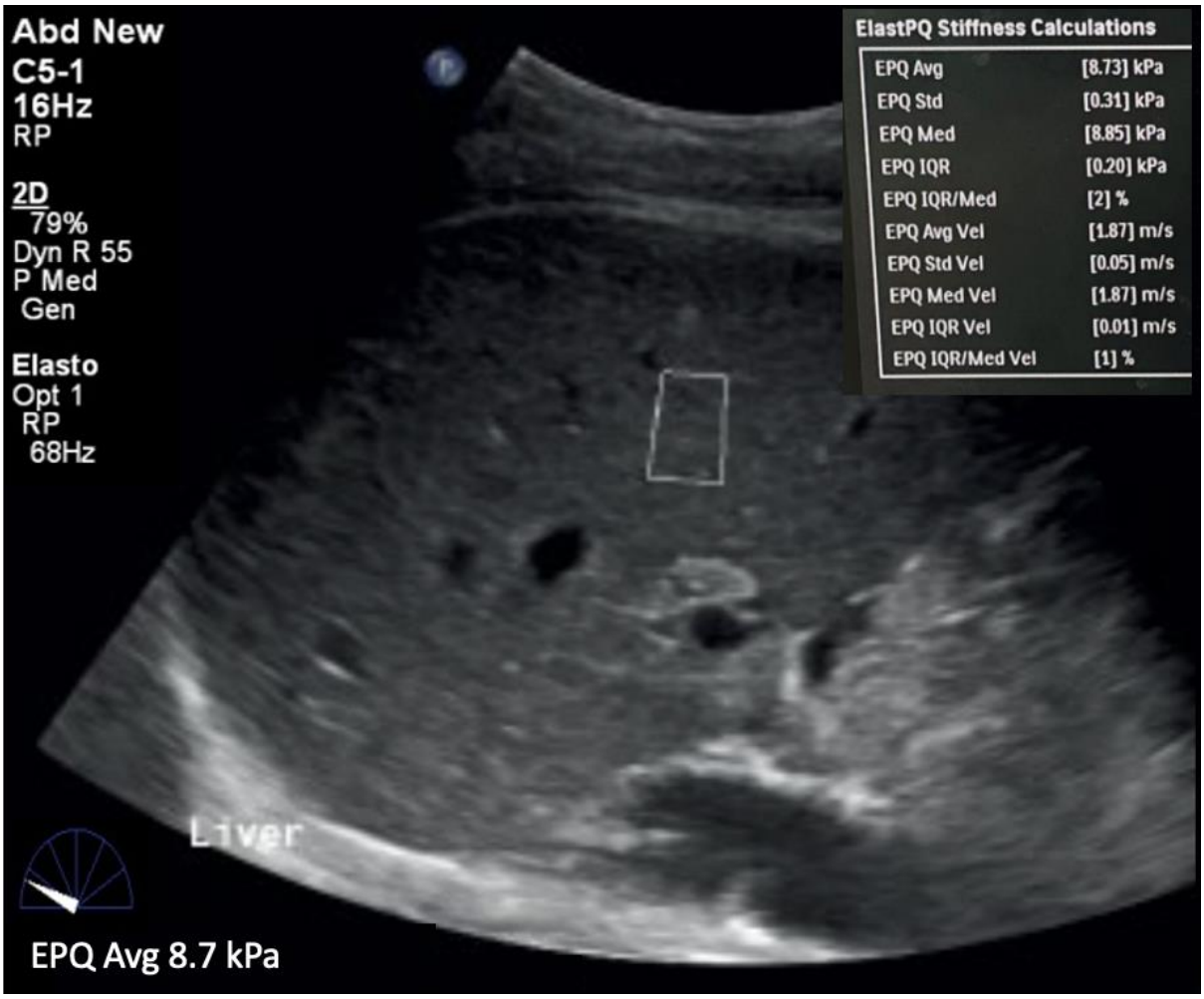


Figure 25 Case with the history of DM (non-alcoholic). Ultrasound showed grade II fatty liver. Median elastography values were elevated (6.90 kPa) with APRI-0.62, FIB4- 1.32, KING's score – 7 - corresponding to moderate fibrosis i.e. stage F2 disease



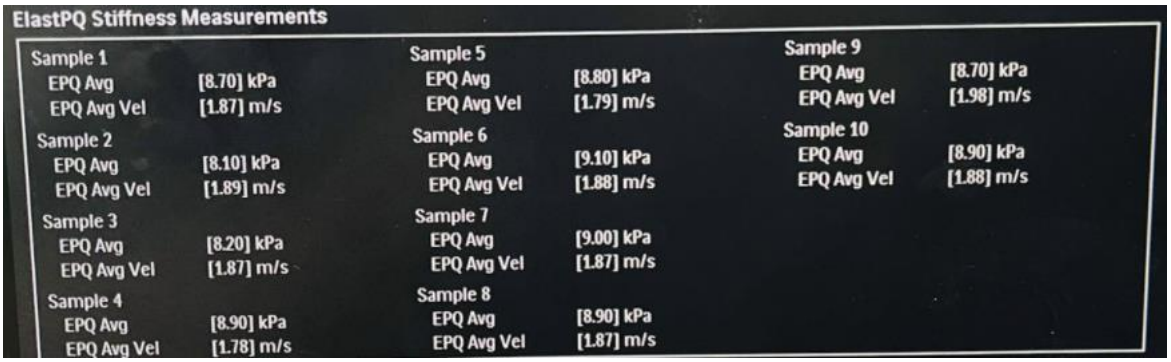
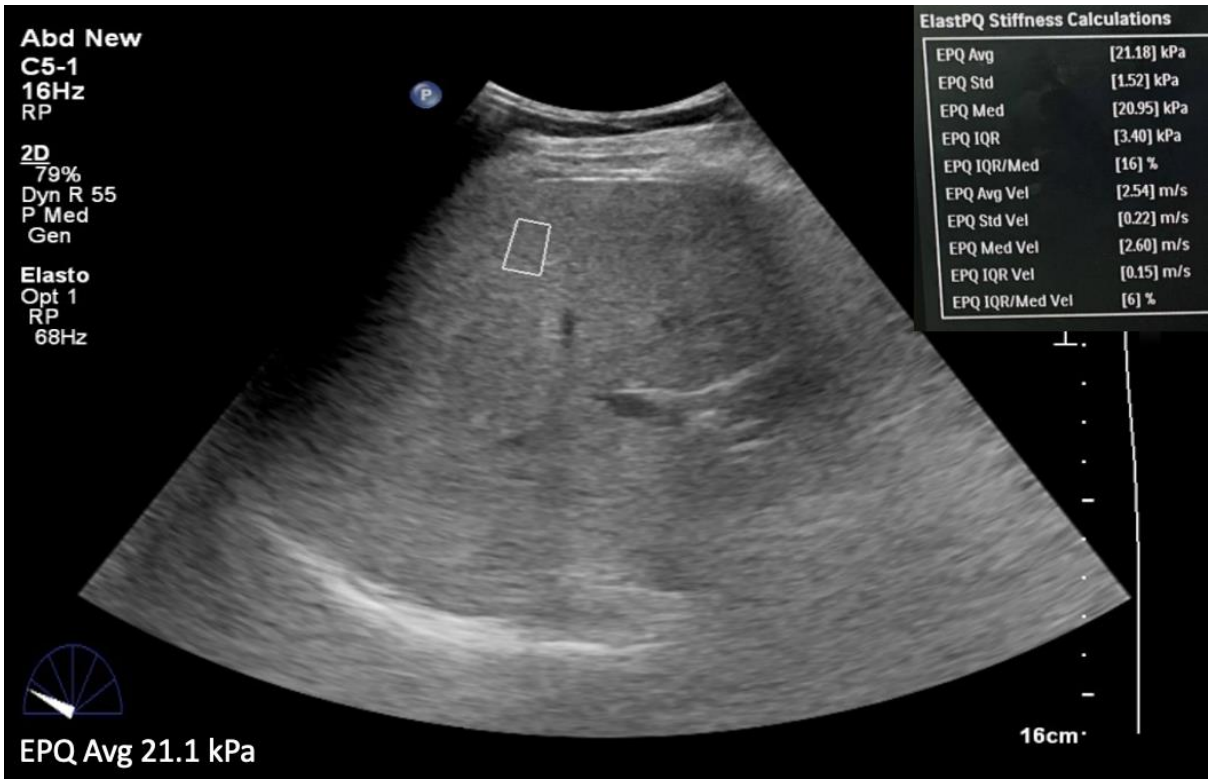


Figure 26 Case of hepatitis C infection. Ultrasound shows coarse echotexture of the liver. median elastography values were elevated (8.85 kPa), corresponding to the F3 stage. APRI- 1.1 FIB4 – 1.6, KING's score – 12.1 – suggestive of advanced fibrosis i.e., stage F3 disease



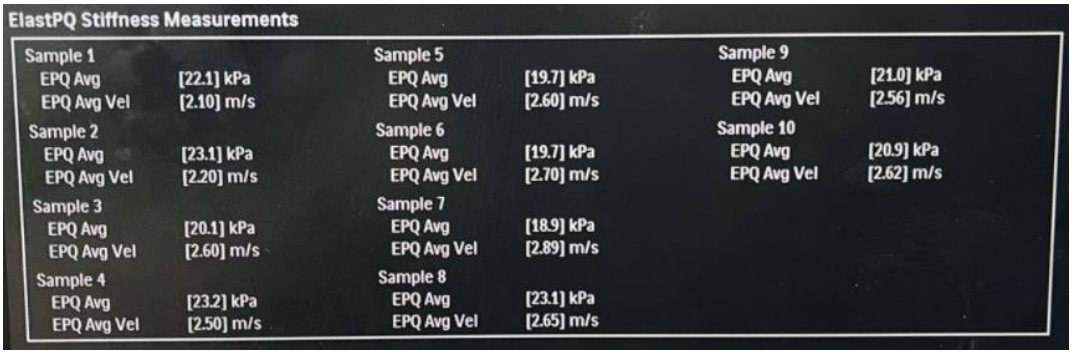


Figure 27 Ultrasound in a patient showed coarse altered echotexture, median elastography values were elevated (20.95 kPa) with APRI- 1.7 FIB4 – 1,9, KING's score – 16.7 – suggestive of severe fibrosis / cirrhosis i.e. stage F4 disease.

DISCUSSION

DISCUSSION

The management of chronic liver disease and its prognosis depends on the stage of fibrosis.[81]Although liver biopsies are commonly used for investigative purposes, the method also has several limitations, such as being invasive and costly. Also, it may bring about sampling errors and inter-and intra-observer variations when considering hepatic fibrosis. SWE is an innovative, non-invasive practice that evaluates liver fibrosis by assessing liver stiffness. Hence, these limitations of liver biopsy have encouraged research for non-invasive approaches for assessing liver fibrosis. SWE is an innovative practice grounded on shear waves and implemented using an investigative ultrasound method. Using B-mode ultrasound and shear wave elastography, this technique helps in more precise fibrosis staging.[82]

We evaluated the diagnostic performance of the APRI, King score and FIB-4 scores accompanying SWE in determining the stages of fibrosis (F0–F4). The main benefit of biochemical non-invasive scores (APRI, King score and FIB-4) in considering liver fibrosis is that they are generally available at a low cost and are very easy to perform. Though SWE measurement is not far and wide owing to the technical and practical field together with its unusual cost, on the other hand, its use is not widespread in low mid-income nations,[83,84.] In contrast, APRI and FIB-4 scores are reliable for evaluating liver fibrosis. [85]

In the past few years, the number of liver biopsies has decreased because of the availability of non-invasive methods such as SWE and serum fibrosis indices for estimating liver fibrosis. Serum fibrosis indices such as APRI, FIB-4, and King's score are used for the non-invasive assessment of liver fibrosis.[86-9] A meta-analysis completed by Xiao et al.[90] indicated that serum fibrosis indices such as APRI, FIB-4, and King's score have moderate sensitivity and accuracy in identifying fibrosis.

Liver biopsy has been extensively regarded as the gold standard for assessing liver fibrosis. However, it has been nearly entirely replaced by non-invasive approaches that measure liver stiffness (LS), such as transient elastography (TE),[91,92] or biochemical markers and scoring systems.[93,94]. In the present study, two non-invasive techniques, SWE and serological findings, were evaluated for fibrosis grading in liver disease, and an agreement between SWE and serological findings (APRI, King's and FIB-4 scores) for the estimation of fibrosis grading in liver disease. A total of 91 patients were evaluated. The associations of the patient's characteristics at different stages of fibrosis were assessed using the chi-square test.

Nikolaos Papadopoulos *et al*. evaluated APRI/FIB-4 scores compared with TE-liver stiffness in detecting significant fibrosis or cirrhosis (F3 or F4). In that study, the authors retrospectively enrolled 575 patients with CHC who underwent TE-LS and found that both scores projected F4 patients adequately. This also shows that FIB-4 is a suitable evaluation for ruling out noncirrhotic patients.[95]

Another study was done by **Lun-Gen Lu *et al***. in 2003 on the grading and staging of hepatic fibrosis and its correlation with non-invasive investigative considerations. That study aimed to examine the grades and stages of pathology and their relationship with hepatic fibrosis and non-invasive indicative factors. It was concluded that the categorising and staging of liver fibrosis are interconnected with serum markers, Doppler ultrasound, computed tomography (CT) scan and magnetic resonance imaging (MRI). The combinations of the above-stated non-invasive factors were recognised to be relatively sensitive and specific in determining liver fibrosis. The sensitivity, specificity and accuracy values were 80.36%, 86.67%, and 81.10%, respectively.[96]

Comparison of Liver Stiffness Measured by SWE and Serum Fibrosis Indices

The results of the present study demonstrated moderate agreement, based on the correlation coefficient, between the SWE measurements and APRI, which was 0.541. The correlation coefficient between the SWE measurements and FIB-4 was 0.597, and between SWE and King's score was 0.576. All three serological indices, i.e. APRI, King's score and FIB4, strongly correlated with SWE.

Bellamkonda et al.'s study demonstrated moderate agreement, based on the Kendall Tau C correlation coefficient, between the SWE measurements and APRI, which was 0.46. In addition, there was moderate agreement based on the Kendall Tau C correlation coefficient between SWE measurements and FIB-4, which was 0.44. The SWE measurements and King's score showed a fair deal based on the Kendall Tau C correlation coefficient between SWE and FIB-4, which was 0.39.

Lee et al. and Lu et al. evaluated the correlation of SWE measurements and serum fibrosis indices (APRI and FIB-4) with HPE findings.[97,98] **Lee et al.** reported a significant positive correlation of ElastPQ, TE, and APRI with HPE findings.[97] **Lu et al.** concluded that liver stiffness (based on ElastPQ) demonstrated a significantly stronger correlation compared with fibrosis stages than APRI and FIB-4.[98]

Performance of SWE in the Estimation of Fibrosis

In the present study, the diagnostic ability of SWE to differentiate the fibrosis stage was evaluated using AUC curve analysis. Patients were divided into a lack of significant fibrosis (F0–F1), significant-advanced fibrosis (F2–F3), and cirrhosis (F4). The ROC curves were plotted using stages (F0-F1) against F2, F3 and F4. The AUC was 0.957 for predicting a lack of significant fibrosis (F0-F1) over F2 using SWE measurements with optimum sensitivity and specificity of 100% and 95.5%. The AUC was 0.953 for predicting lack of

significant fibrosis (F0-F1) over F3 using SWE measurements with optimum sensitivity and specificity of 95% and 90%.

The AUC was 0.993 for predicting a lack of significant fibrosis (F0-F1) over F4 using SWE measurements with optimum sensitivity and specificity of 96.4 % and 91.4%. The study demonstrates that SWE is effective in distinguishing between moderate (F2) and advanced fibrosis (F3), with a sensitivity of 95% and a specificity of 77.6% at a cut-off value of ≥8.0. It also shows excellent accuracy in distinguishing between moderate (F2) fibrosis and severe fibrosis/cirrhosis (F4), with a sensitivity of 92.9% and a specificity of 79.8% at a cut-off value of ≥9.0. SWE effectively differentiated advanced fibrosis (F3) from severe fibrosis/cirrhosis (F4), with a sensitivity of 89.3% and specificity of 84.3% at a cut-off value of ≥ 9.15.

Bellamkonda et al. demonstrated that the AUROC was 0.873 for the prediction of significant and advanced fibrosis (F2–F3) over a lack of significant fibrosis (F0–F1) using SWE measurements, and the cutoff value of the SWE measurements with optimum sensitivity and specificity was 7.07. The AUROC was 0.504 for the prediction of cirrhosis (F4) over significant-advanced fibrosis (F2–F3) using SWE measurements, and the cutoff value of SWE measurements with optimum sensitivity and specificity was 11.94. The present study showed better sensitivity and specificity than Bellamkonda et al.'s.[99]

Ferraioli et al. used the Fibro-Scan (TE) as the reference standard to evaluate the diagnostic performance of ElastPQ using the AUROC curve analysis. The cut-off values derived from the present study (e.g., 7.25 (mean) and 9.15, respectively, for significant fibrosis [⩾F2] and cirrhosis [F4]) were comparable to those derived by **Ferraioli et al.**[82]

Ma et al. evaluated the reproducibility of ElastPQ technology in determining liver stiffness and also investigated the value of ElastPQ in liver fibrosis staging among chronic hepatitis B

patients.[20] The cut-off value in the present study for the differentiation of cirrhosis (F4) and significantly advanced fibrosis F2 and F3 was ≥ 9.0 and ≥ 9.15. This was similar to the results obtained by **Ma et al.** (e.g., 9.0), and also, the sensitivity and specificity were high in the present study compared with that of **Ma et al**. [21]

In the present study, the liver texture is generally expected in the early stages of fibrosis (F0-F1, F2). Still, as fibrosis progresses, the coarse texture becomes more prevalent, reaching 80.0% in F3 and 100.0% in F4, indicating a strong correlation between advanced fibrosis stages and coarse liver texture. There is a significant correlation between coarse echotexture, nodularity, surface irregularity and advanced fibrosis stages—normal echotexture declines from 35.0% in F0-F1 to 3.6% in F4.

Performance of ultrasound on liver size, spleen size, portal vein diameter and liver elastography across fibrosis stage

Our study reveals that liver size decreases significantly with fibrosis progression, from 18.6 cm to 12.35 cm. Portal vein diameter increases from 12.6 mm to 14.6 mm, but this is not statistically significant. Liver stiffness increases from 6.1 Kpa to 21.1 Kpa, indicating a considerable increase. Spleen size slightly increases from 11.1 cm to 12.5 cm, but this is not statistically significant. The data suggests that liver elastography and size are crucial parameters in assessing fibrosis progression, while portal vein diameter and spleen size changes are less pronounced.

Performance of SWE in the Estimation of liver disease staging.

The study found significant increases in APRI, KING and FIB 4 scores across fibrosis stages, indicating increased liver damage. The APRI score rose from 0.45 to 1.7, indicating liver damage, while the KING score increased from 7.1 to 18 and the FIB 4 score from 0.70

to 1.78, indicating worsening liver function. These scores are valuable for assessing liver fibrosis severity and monitoring disease progression.

Performance of SWE in the Estimation of liver size, portal vein (diameter), spleen (cm), evaluating APRI FIB 4 and King's score and estimation of fibrosis using shear wave elastography staging.

Our study found strong positive correlations between APRI, FIB4, and King's scores as the fibrosis stage increased. A moderate positive correlation was found with liver size, suggesting a modest association. No significant correlation was found with portal vein diameter. A weak positive correlation was found with liver elastography in kPa and spleen size.

The present study found strong negative correlations between APRI, King's, and FIB 4 scores as liver size decreases and moderate positive correlations with portal vein diameter and spleen size. These findings suggest a moderate direct relationship between these parameters.

Our study found a weak positive correlation ($r=0.256$, $p<0.01$) between portal vein diameter and spleen size, suggesting a slight association. A moderate positive correlation between liver elastography values and APRI and KING scores was seen, and it increased both as liver elastography values increased. The study found a weak positive correlation between liver size and spleen size but a strong positive correlation between APRI and KING, indicating a significant association between these scoring systems for liver fibrosis assessment, and a strong positive correlation between FIB 4, and SWE, APRI, and KING Score.

A moderate positive correlation was seen between liver SWE values and APRI and King's scores. A weak positive correlation with liver size ($r=0.222$, $p=0.003$) indicates a

slight association between spleen size and liver size. On significant and advanced fibrosis (F2–F3) over a lack of significant fibrosis (F0–F1) using SWE measurements, the cut-off value of the SWE measurements with optimum sensitivity and specificity was 7.07.

In the present study, we found different cut-off values for different fibrosis stages in different groups of fibrosis to distinguish their optimal cut-off values according to AUC and the diagnostic accuracies (sensitivity and specificity) of the Fibrosis index for predicting the performance of fibrosis accompanying ultrasound SWE elastography. The SWE has high AUC values for comparing stages (F0-F1) against F2, F3, and F4. For distinguishing between F0-F1 and F2, a cut-off value of ≥ 6.55 yields 97 % sensitivity and 95.5% specificity. SWE also demonstrates high accuracy in differentiating between minimal or no fibrosis (F0-F1) and advanced fibrosis (F3), with a sensitivity of 95% and a specificity of 90% at a cut-off value of ≥6.60. It also showed an outstanding discriminatory ability in differentiating between minimal or no fibrosis and severe fibrosis/cirrhosis (F4), with a sensitivity of 96.4% and a specificity of 91.4% at a cut-off value of ≥7.50. However, diagnostic accuracy decreased when distinguishing between adjacent stages, such as F2 vs. F3 and F3 vs. F4.

In a similar type of study, **Liaqat et al**. found different cutoff values for APRI and FIB-4 in different groups of fibrosis to distinguish their optimal cutoff values according to AUROC and the diagnostic accuracies (sensitivity and specificity) of APRI and FIB-4 (average AST level up-to 40 IU/L) for predicting the performance of APRI and FIB-4 accompanying ultrasound SW elastography.[101]

Yi-Hao Yen *et al.* examined the optimum cut-off values of the two compound surrogates for envisaging cirrhosis by the AST level according to the AUROC analysis results differentiating cirrhotic (F4) from noncirrhotic (F0–F3).[22] They concluded that the ideal cut-off values of both APRI and FIB-4 to predict cirrhosis graded by AST levels could

be more practicable compared to the single cut-off values offered in the preceding research paper.[102]

Conferring to former findings, APRI and FIB-4 were associated with the international normalised ratio, albumin level, and neuroinflammatory score.[23,24] Additionally, the positive correlations of APRI and FIB-4 with neuroinflammatory score also kept our theory that the use of APRI and FIB-4 causes a possibility of overrating the fibrosis stage due to the influence of neuroinflammatory activity on transaminases [25,103] and the indicative precision of FIB-4 foreseeing liver fibrosis was found to be equivalent to or superior to that of APRI.[104]

The SWE is a readily available, repeatable, and cost-effective modality. It can be used as a non-invasive alternative to the biopsy for grading liver fibrosis and follow-up of chronic viral hepatitis patients. Biopsy is a gold standard and invasive test that can be reserved for specific clinical settings and baseline evaluation of fibrosis. SWE correlates more with APRI, King's Score, and FIB-4 markers for differentiating F0-F1 from clinically significant F2-F4 fibrosis. The serological indices can be combined with SWE for post-treatment follow-up of liver fibrosis patients, thus avoiding repeated biopsy.

CONCLUSION

CONCLUSION

With advancing fibrosis, liver size and stiffness significantly change. Increased liver echogenicity with smooth echotexture suggests mild fibrosis, while coarse liver texture correlates with advanced fibrosis stages.

Type of liver disease is significantly associated with fibrosis stages. Cases of alcoholic liver disease predominantly showed advanced stage of liver fibrosis. Meanwhile, the cases of NAFLD showed mild stages of fibrosis.

These findings suggest liver echotexture and disease pathology significantly influence fibrosis stages, and elastography, along with 2D and colour Doppler imaging, can serve as a crucial parameter in fibrosis progression assessment.

Based on shear wave elastography, complications are significantly associated with fibrosis stages, and severe complications are associated with higher fibrosis stages.

APRI, FIB 4, and King's scores strongly correlate with fibrosis progression. These values show significant correlations with shear wave elastography findings. Overall, liver elastography, along with serological indices, serves as a promising tool for assessing the severity of liver fibrosis and assisting the treating doctor in making comprehensive, well-informed decisions regarding patient care and long-term management of liver disease.

SUMMARY

SUMMARY

Liver fibrosis is a progressive disorder that can be diagnosed early and staged accurately. Grading hepatic fibrosis is crucial for prognosis, therapy planning, and follow-up. Non-invasive serological techniques and APRI, King's Score, and FIB-4 scores are used for grading liver fibrosis. A cross-sectional study at R.L. Jalappa Hospital and Research Center in Kolar included 91 patients with liver diseases, including alcoholic and non-alcoholic fatty liver disease, deranged liver function tests, and infective/autoimmune/drug-induced factors. Ultrasound examinations, SWE findings, and serological values were used to classify patients. This study examined the role of shear wave elastography in liver fibrosis prediction.

Younger groups (<45 years) show higher proportions of fibrosis stages. Older groups (>45 years) show lower proportions in each stage. Males are more frequently affected across all stages, possibly due to more exposure to toxic agents and viral infections.

Increased echogenicity is more common in advanced stages. With advancing fibrosis, there are significant changes in liver size and stiffness. There is a significant correlation between coarse echotexture, nodularity, surface irregularity, and advanced fibrosis stages. Normal texture declined from 35.0% in F0-F1 to 3.6% in F4. Hence, the liver echotexture is predominantly normal in the early stages, but the coarse texture becomes more prevalent as fibrosis advances.

ALD is most prevalent in advanced stages (92.9% in F4). Hepatitis B and C show significant presence in early and intermediate stages but none in F4. NAFLD is more common in early stages (50.0% in F0-F1). The type of liver disease is significantly associated with different stages.

APRI and King's scores demonstrate strong correlations with fibrosis progression. Hepatitis C patients show the largest spleen sizes. Significant differences in liver damage and fibrosis levels are noted.

High AUC values indicate strong discriminatory power in comparing stages (F0-F1) against F2, F3, and F4. High accuracy in distinguishing between minimal or no fibrosis (F0-F1) and advanced fibrosis (F3) with a sensitivity of 95% and a specificity of 90% at a cut-off value of ≥ 6.60. Outstanding discriminatory ability in distinguishing between minimal or no fibrosis (F0-F1) and severe fibrosis/cirrhosis (F4) with a sensitivity of 96.4% and a specificity of 91.4% at a cut-off value of ≥7.50.

Good discriminatory performance in differentiating between moderate (F2) and advanced fibrosis (F3) with a sensitivity of 95% and a specificity of 77.6% at a cut-off value of ≥8.0. Strong accuracy in distinguishing between moderate fibrosis (F2) and severe fibrosis/cirrhosis (F4) with a sensitivity of 92.9% and a specificity of 79.8% at a cut-off value of ≥ 9.0. Diagnostic accuracy decreases when distinguishing between adjacent stages, such as F2 vs. F3 and F3 vs. F4.

Strong positive correlations with shear wave elastography with APRI, King's, and FIB 4 scores suggest a significant score increase as the fibrosis stage increases. Moderate positive correlations with portal vein diameter and spleen size suggest a moderate direct relationship with these parameters. Also, there is a strong positive correlation between APRI, King's, and FIB 4 scores, indicating a significant association between these scoring systems for liver fibrosis assessment.

Patients without complications were predominant in the early stages but decreased significantly in F4. Patients with complications show a substantial increase in advanced fibrosis stages. Hematemesis is the most common complication, especially in advanced stages consistent with SWE results.

LIMITATION

- Liver biopsy is considered the gold standard for assessing fibrosis, but it was not done in our study due to deranged liver function tests, coagulation profiles, and patient noncompliance. Confirming our findings with liver biopsy can further confirm the results obtained in our study.
- In our study, the cut-off derived for differentiating mild (F1) disease from moderate (F2) disease is narrow in range, which makes it challenging to differentiate practically. Further testing with a larger sample size is necessary.
- Generated shear waves become weak due to dissipation after spreading a few millimetres. Hence, evaluating liver stiffness using shear wave elastography in patients with gross ascites is less reliable, and the ascitic component needs to be tapped and then assessed.
- Inadequate breath holding can sometimes occur during the examination in patients with concomitant pleural effusion or any pulmonary disease, making the acquired values less reliable.

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BIBLIOGRAPHY

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ANNEXURE

ANNEXURE I

PROFORMA

"ROLE OF SHEAR WAVE ELASTOGRAPHY IN ASSESSING FIBROSIS IN PATIENTS WITH LIVER DISEASES AND ITS CORRELATION WITH SEROLOGICAL INDICES"

Hospital number:

Consent taken: Yes / No

SUBJECT EVALUATION

Date:

Time:

Demographic Variables

Age:

Sex:

Occupation:

Disease Details

Diagnosis of liver disease ☐

If yes then specify:

Liver disease complications ☐

If yes then specify:

Conventional B - mode Ultrasound Features

Liver size:

Liver echotexture: 1. Surface irregularity - Yes / No

2. Nodularity – Yes / No

Portal vein diameter:

Spleen size:

Shear Wave Elastography

ROI size:

ROI location:

Elastography values of liver parenchyma:

S1	S2	S3	S4	S5	S7	S8	S9	S10

Average reading:

Biochemical Parameters

AST:

ALT:

Platelet count:

INR:

Shear wave elastography correlation with serological indices: YES / NO

Remarks:

ANNEXURE II

INFORMED CONSENT FORM

I Miss/Mrs. _____ have been explained in my own understandable language, that I will be included in a study which **"ROLE OF SHEAR WAVE ELASTOGRAPHY IN ASSESSING FIBROSIS IN PATIENTS WITH LIVER DISEASES AND ITS CORRELATION WITH SEROLOGICAL INDICES".**

I have been explained that my clinical findings, investigations, will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have been explained about the interventions needed possible benefits and adversities due to interventions, in my own understandable language.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place:

ANNEXURE III

PATIENT INFORMATION SHEET

STUDY TITLE: "ROLE OF SHEAR WAVE ELASTOGRAPHY IN ASSESSING FIBROSIS IN PATIENTS WITH LIVER DISEASES AND ITS CORRELATION WITH SEROLOGICAL INDICES".

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that,

We are conducting this study to assess role of sonoelastography in assessing Liver in patients with liver diseases.

If you are willing to be enrolled in this study, we perform elastography and other relevant investigations needed to assess the liver.

This will facilitate in deriving cut off values of elastography of Liver stiffness in patients with liver diseases. It will also benefit other patients with liver diseases undergoing medical therapy in the future. You are free to opt-out of the study at anytime if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are part of the study

Your identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact Dr. Guru Yogendra M or any other member of the above research team for any doubt or clarification you have.

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MASTER CHART

KEY TO MASTER CHART

M- MALE

F- FEMALE

ALD – ALCOHOLIC LIVER DISEASE

NAFLD – NON-ALCOHOLIC FATTY LIVER DISEASE

KPA – KILOPASCALS

SWE – SHEAR WAVE ELASTOGRAPHY

APRI – AST PLATELET RATIO INDEX

PV – PORTAL VEIN

FIB 4 – FIBROSIS 4 INDEX

KING – KING FIBROSIS SCORE

UHID – UNIQUE HEALTH IDENTIFICATION NUMBER

SL NO	AGE	UHID NO	SEX	DIAGNOSIS	LIVER SIZE	LIVER ECHOGENICITY	LIVER ECHOTEXTURE	P V DIAMETER	SPLEEN IN CM	LIVER SWE IN KPA	SWE STAGE (F)	APRI	KING	FIB 4	COMPLICATIONS	COMPLICATIONS IF ANY
1	45	654744	M	ALD	12.3 CM	INCREASED	COARSE	15.6 MM	12.1	12.1	4	1.5	21.1	2.2	YES	HEMATEMESIS
2	43	663226	M	HEPATITIS B	14.5 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.1 MM	10.2	8.1	4	0.7	12.9	1.54	NO	NIL
3	54	693718	M	ALD	11.4 CM	INCREASED	COARSE	16.8 MM	13.1	8.6	3	1.2	13.1	1.65	YES	HEMATEMESIS
4	51	667827	M	ALD	14.5 CM	INCREASED	COARSE	12.1 MM	9.6	13.8	4	1.4	14.9	1.82	NO	NIL
5	45	690191	F	NAFLD	14.1 CM	INCREASED	COARSE	13.1 MM	9.7	8.8	3	0.6	12.1	14.8	NO	NIL
6	54	568798	M	NAFLD	15.6 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.8 MM	9.9	12.9	4	1.8	18.1	1.74	NO	NIL
7	45	652839	M	ALD	12.1 CM	INCREASED	COARSE	14.1 MM	10.1	9.1	3	0.9	12.1	1.56	YES	ASCITES
8	36	562819	M	ALD	11.2 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	15.5 MM	14.7	11.3	4	1.7	18.9	1.98	YES	HEMATEMESIS
9	39	345654	M	ALD	11.0 CM	INCREASED	COARSE	15.4 MM	14.9	21.1	3	1.3	21.9	1.76	YES	HEPATORENAL SYNDROME
10	56	872638	M	NAFLD	15.6 CM	INCREASED	NORMAL	12.1 MM	12.5	6.2	1	0.4	10.9	0.4	NO	NIL
11	45	563728	F	ALD	15.2 CM	INCREASED	COARSE	12.9 MM	12.8	9.8	4	1.6	16.8	1.67	NO	NIL
12	43	637291	M	HEPATITIS B	14.9 CM	INCREASED	NORMAL	11.1 MM	10.8	7.5	2	0.8	12.9	0.9	NO	NIL
13	39	127060	M	NAFLD	15.9 CM	INCREASED	NORMAL	12.6 MM	12.1	6.2	1	0.5	3.5	0.8	YES	NIL
14	45	564123	M	ALD	12.6 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	11.0 MM	11.9	9.6	4	1.7	17.2	1.69	YES	ASCITES
15	48	654123	M	ALD	11.5 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.9 MM	13.5	14.2	4	1.9	16.9	1.7	YES	HEMATEMESIS
16	43	142653	F	HEPATITIS B	16.1 CM	INCREASED	COARSE	12.3 MM	12.3	8.9	3	1.5	12.9	1.48	NO	NIL
17	47	154365	M	NAFLD	18.7 CM	INCREASED	COARSE	11.0 MM	12.7	8.8	3	1.6	15.8	1.6	NO	ASCITES
18	54	342569	M	ALD	12.1 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	16.2 MM	17.2	10.6	4	2.1	18.3	1.7	YES	HEMATEMESIS
19	45	324512	M	ALD	12.6 CM	INCREASED	COARSE	12.1 MM	12.5	12.6	4	1.5	18.9	1.9	YES	ASCITES
20	49	342323	M	ALD	12.1 CM	INCREASED	NORMAL	15.3 MM	12.8	7.8	2	0.6	12.5	0.9	YES	ENCEPHALOPATHY

SL NO	AGE	UHID NO	SEX	DIAGNOSIS	LIVER SIZE	LIVER ECHOGENICITY	LIVER ECHOTEXTURE	P V DIAMETER	SPLEEN IN CM	LIVER SWE IN KPA	SWE STAGE (F)	APRI	KING	FIB 4	COMPLICATIONS	COMPLICATIONS IF ANY
21	39	342331	F	ALD	14.8 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.1 MM	13.6	8.3	4	1.1	15.9	1.3	NO	NIL
22	54	543114	M	HEPATITIS C	13.6 CM	INCREASED	COARSE	13.9 MM	12.2	11.9	4	2.2	17.9	1.67	NO	NIL
23	55	543355	M	HEPATITIS C	13.9 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	16.9 MM	14.1	8.3	4	0.9	12	1.51	YES	HEMATEMESIS
24	35	345612	M	ALD	13.2 CM	INCREASED	COARSE	12.4 MM	9.3	12.1	4	1.4	16.3	1.8	YES	ASCITES
25	43	143935	M	HEPATITIS B	15.4 CM	INCREASED	NORMAL	13.4 MM	9.8	8.3	3	1.1	16.8	1.48	NO	NIL
26	41	453234	M	NAFLD	16.8 CM	INCREASED	NORMAL	11.9 MM	9.3	5.5	1	0.4	9.8	0.8	NO	NIL
27	40	654986	F	ALD	11.9 CM	INCREASED	COARSE	15.9 MM	10.4	11.5	4	1.6	16.9	1.65	YES	HEPATIC ENCEPHALOPATHY
28	42	651245	M	ALD	14..9 CM	INCREASED	NORMAL	12.5 MM	12.1	6.1	1	0.5	5.8	0.7	YES	JAUNDICE
29	45	654783	M	NAFLD	16.4 CM	INCREASED	NORMAL	12.1 MM	11.1	8.7	3	0.7	13.9	1.54	NO	NIL
30	51	543566	M	ALD	12.0 CM	INCREASED	COARSE	16.1 MM	12.9	14.1	4	2.2	19.6	2.1	YES	HEMATEMESIS
31	45	432345	M	ALD	12.3 CM	INCREASED	NORMAL	15.6 MM	12.1	6.4	1	0.3	7.1	0.7	YES	HEMATEMESIS
32	43	324213	M	HEPATITIS B	14.5 CM	INCREASED	COARSE	12.1 MM	10.2	8.9	3	1.2	16.2	1.56	NO	NIL
33	54	432343	M	ALD	11.4 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	16.8 MM	13.1	8.8	4	1.2	11.9	1.58	YES	HEMATEMESIS
34	51	654876	M	ALD	14.5 CM	INCREASED	COARSE	12.1 MM	9.6	12.8	4	1.9	18.2	1.9	NO	NIL
35	45	180262	F	NAFLD	14.1 CM	INCREASED	NORMAL	13.1 MM	9.7	5.5	1	0.3	9.6	0.3	NO	NIL
36	54	453123	M	NAFLD	15.6 CM	INCREASED	NORMAL	12.8 MM	9.9	5.4	1	0.5	7.9	0.5	NO	NIL
37	45	456322	M	ALD	12.1 CM	INCREASED	COARSE	14.1 MM	10.1	9	3	0.9	15.7	1.6	YES	ASCITES
38	36	456431	M	ALD	11.2 CM	INCREASED	COARSE	15.5 MM	12.7	10.8	4	1.7	20.9	1.2	YES	HEMATEMESIS
39	39	123223	M	ALD	11.0 CM	INCREASED	NORMAL	15.4 MM	12.5	6.7	2	0.7	12.1	1.2	YES	HEPATORENAL SYNDROME
40	56	123443	M	NAFLD	15.6 CM	NORMAL	NORMAL	12.1 MM	12.5	6.2	1	0.4	6.9	0.4	NO	NIL
41	45	126754	F	ALD	15.2 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.9 MM	12.8	12.1	4	1.8	16.9	1.67	NO	NIL
42	43	142236	M	HEPATITIS B	14.9 CM	INCREASED	COARSE	11.1 MM	10.8	8.2	3	0.8	13.1	1.56	NO	NIL
43	39	152244	M	NAFLD	15.9 CM	INCREASED	NORMAL	12.6 MM	12.1	5.9	1	0.5	9.3	0.9	YES	NIL
44	45	143232	M	ALD	12.6 CM	INCREASED	COARSE	11.0 MM	11.9	10.9	4	1.7	18.3	1.9	YES	MILD ASCITES

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45	48	170145	M	ALD	11.5 CM	INCREASED	COARSE	12.9 MM	11.8	8.6	3	1	15.9	1.56	YES	HEMATEMESIS
46	43	234367	F	HEPATITIS B	16.1 CM	NORMAL	NORMAL	12.3 MM	12.3	6.1	1	0.8	3.9	0.58	NO	NIL
47	47	342123	M	NAFLD	16.7 CM	NORMAL	NORMAL	11.0 MM	12.7	6.9	2	0.9	12.1	1.2	NO	NIL
48	54	234541	M	ALD	12.1 CM	INCREASED	NORMAL	16.2 MM	13.1	7.1	2	0.7	13.1	0.8	YES	HEMATEMESIS
49	45	234516	M	ALD	12.6 CM	NORMAL	NORMAL	12.1 MM	12.5	5.7	1	0.3	5.4	0.7	YES	ASCITES
50	49	242134	M	ALD	12.1 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	15.3 MM	12.8	9.8	4	1.8	17.5	1.9	YES	ENCEPHALOPATHY
51	39	134275	F	ALD	14.8 CM	NORMAL	NORMAL	12.1 MM	13.6	7.6	2	1.1	12.8	1.3	NO	NIL
52	54	256845	M	HEPATITIS C	13.6 CM	NORMAL	NORMAL	13.9 MM	12.2	9.1	3	1.3	16.1	1.6	NO	NIL
53	55	197638	M	HEPATITIS C	13.9 CM	INCREASED	COARSE	16.9 MM	14.1	8.3	3	1.1	12.1	1.58	YES	HEMATEMESIS
54	35	562346	M	ALD	13.2 CM	NORMAL	NORMAL	12.4 MM	9.3	6.9	2	0.8	12	1.1	YES	JAUNDICE
55	43	542654	M	HEPATITIS B	15.4 CM	NORMAL	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	13.4 MM	9.8	8.5	4	0.9	16.3	1.56	NO	NIL
56	41	246212	M	NAFLD	16.8 CM	NORMAL	NORMAL	11.9 MM	9.3	5.5	1	0.4	9.6	0.8	NO	NIL
57	40	543212	F	ALD	11.9 CM	INCREASED	NORMAL	15.9 MM	10.4	6.4	1	0.9	9.8	0.6	YES	HEPATIC ENCEPHALOPATHY
58	42	453763	M	ALD	14..9 CM	INCREASED	NORMAL	12.5 MM	12.1	6.1	1	0.5	7.9	0.7	YES	JAUNDICE
59	45	353121	M	NAFLD	16.4 CM	INCREASED	NORMAL	12.1 MM	11.1	6.8	2	1.1	13.9	1.1	NO	NIL
60	51	342134	M	ALD	12.0 CM	INCREASED	NORMAL	16.1 MM	12.9	5.3	1	1.9	5.4	0.7	YES	HEMATEMESIS
61	40	421242	F	ALD	11.9 CM	INCREASED	NORMAL	15.9 MM	10.4	6.9	2	0.8	13.4	1.59	YES	HEPATIC ENCEPHALOPATHY
62	45	456321	M	ALD	12.3 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	15.6 MM	12.1	6.4	4	1.5	7.1	0.9	YES	HEMATEMESIS
63	43	524521	M	HEPATITIS B	14.5 CM	INCREASED	NORMAL	12.1 MM	10.2	6.9	2	0.7	12.3	1.1	NO	NIL
64	54	322428	M	ALD	11.4 CM	INCREASED	NORMAL	16.8 MM	13.1	7.8	2	1.2	14.1	1.6	YES	HEMATEMESIS
65	51	522311	M	ALD	14.5 CM	INCREASED	NORMAL	12.1 MM	9.6	7.9	2	0.9	16.1	0.9	NO	NIL
66	45	452345	F	NAFLD	14.1 CM	INCREASED	NORMAL	13.1 MM	9.7	5.5	1	0.3	4.1	0.3	NO	NIL
67	54	134343	M	NAFLD	15.6 CM	INCREASED	NORMAL	12.8 MM	9.9	7.4	2	0.5	10.9	1.47	NO	NIL
68	45	524324	M	ALD	12.1 CM	INCREASED	NORMAL	14.1 MM	10.1	6.7	2	0.67	14.8	0.9	YES	MILD ASCITES

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69	36	421344	M	ALD	11.2 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	15.5 MM	12.7	12.1	4	1.1	16.2	1.9	YES	HEMATEMESIS
70	39	141431	M	ALD	11.0 CM	INCREASED	COARSE	15.4 MM	12.5	10.9	4	1.9	18.6	1.8	YES	HEPATORENAL SYNDROME
71	56	154323	M	NAFLD	15.6 CM	NORMAL	NORMAL	12.1 MM	12.5	6.2	1	0.4	6.9	0.4	NO	NIL
72	45	424341	F	ALD	15.2 CM	INCREASED	COARSE	12.9 MM	12.8	7.9	2	1	14.9	1.2	NO	NIL
73	43	141411	M	HEPATITIS B	14.9 CM	INCREASED	NORMAL	11.1 MM	10.8	7.2	2	0.8	16.1	0.9	NO	NIL
74	39	545422	M	NAFLD	15.9 CM	INCREASED	NORMAL	12.6 MM	12.1	7.9	2	0.5	13.5	1.5	YES	NIL
75	45	254234	M	ALD	12.6 CM	INCREASED	NORMAL	11.0 MM	11.9	8	3	0.7	17.9	1.5	YES	MILD ASCITES
76	48	253522	M	ALD	12.4 CM	INCREASED	COARSE	12.9 MM	11.8	9.8	4	1.1	17.5	1.4	YES	HEMATEMESIS
77	43	141439	F	HEPATITIS B	16.1 CM	NORMAL	NORMAL	12.3 MM	12.3	6.1	1	0.7	6.8	0.7	NO	NIL
78	47	354524	M	NAFLD	16.7 CM	NORMAL	NORMAL	11.0 MM	12.7	6.9	2	1.6	10.9	1.2	NO	NIL
79	54	524452	M	ALD	12.1 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	16.2 MM	13.1	9.1	4	1.2	18.7	1.7	YES	HEMATEMESIS
80	45	378768	M	ALD	12.6 CM	NORMAL	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	12.1 MM	12.5	9.9	4	1.5	10.7	1.9	YES	MILD ASCITES
81	49	367855	M	ALD	12.1 CM	INCREASED	COARSE	15.3 MM	12.8	9.7	4	2.1	16.4	1.8	YES	ENCEPHALOPATHY
82	39	557887	F	ALD	14.8 CM	NORMAL	NORMAL	12.1 MM	13.6	7.6	2	1.1	11.9	1.3	NO	NIL
83	54	234216	M	HEPATITIS C	13.6 CM	NORMAL	NORMAL	13.9 MM	12.2	5.7	1	0.8	7.2	0.6	NO	NIL
84	55	356431	M	HEPATITIS C	13.9 CM	INCREASED	COARSE	16.9 MM	14.1	8.9	3	0.6	13.1	1.1	YES	HEMATEMESIS
85	35	625232	M	ALD	13.2 CM	NORMAL	NORMAL	12.4 MM	9.3	7.9	2	0.7	12.5	0.8	YES	ASCITES
86	43	433411	M	HEPATITIS B	15.4 CM	NORMAL	NORMAL	13.4 MM	9.8	7.2	2	0.9	14.7	0.9	NO	NIL
87	41	413243	M	NAFLD	16.8 CM	NORMAL	NORMAL	11.9 MM	9.3	7.8	2	1.1	12.4	0.8	NO	NIL
88	40	134345	F	ALD	17.1 CM	INCREASED	COARSE	15.9 MM	10.4	13.2	4	1.6	18.3	1.6	YES	HEPATIC ENCEPHALOPATHY
89	42	431234	M	ALD	14.9 CM	INCREASED	COARSE	12.5 MM	12.1	11.9	4	1.8	16.8	1.5	YES	HEMATEMESIS
90	45	323412	M	NAFLD	16.4 CM	NORMAL	NORMAL	12.1 MM	11.1	6.7	2	0.7	13.1	1.1	NO	NIL
91	51	324123	M	ALD	11.0 CM	INCREASED	COARSE ECHOTEXTURE WITH NODULARITY AND SURFACE IRREGULARITY	16.1 MM	12.9	9.2	4	1.2	22.1	2.1	YES	HEMATEMESIS