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Value of Shear Wave Elastography in Liver Cirrhosis

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Abstract:
Background: Chronic liver disease associated with viral hepatitis (mainly hepatitis B and C) or other etiologies, is clinical problem. It can cause various parenchymal liver injuries, lead to development of liver fibrosis and its various complications, from those portal hypertension and hepatocellular carcinoma being the most important. Liver biopsy is the most commonly used method for the diagnosis of liver fibrosis. The biopsy specimen size varies from one to three centimeters in length and between one to two millimeter in diameter, therefore the sample represents 1/50000 of all liver tissue.**Objective:** To assess the diagnostic value of two-dimensional shear wave elastography in evaluation of liver fibrosis.**Patients and method**: A prospective study included one hundred patients, fifty patients clinically confirmed as had liver fibrosis, the other fifty patients were normal (taken randomly with no history of liver disease and have normal ultrasound), the age of patients ranging from 20-55 years old. This study is single hospital study done in Baghdad teaching hospital in medical city, from November 2019 to march 2020.**Results:** The shear wave elastography measurements value in liver fibrosis was 11.165 kPa (range 3.8 to 23 kPa), whereas the median liver elasticity for normal subjects was 4.885 kPa (range 3.2 to 7.2 kPa) . A significant correlation was found between shear wave elastography and fibrosis (p=0.0006) with sensitivity of 80%. A significant correlation also seen between shear wave elastography and exclusion of fibrosis (sensitivity 76%) (sensitivity 76%) (p= 0.003). **Conclusion:** Shear wave elastography examination is a promising noninvasive method for the evaluation of liver fibrosis, with good diagnostic performance
Keyword: liver cirrhosis, two-dimensional shear wave elastography, noninvasive method

Introduction:

Chronic liver disease associated with viral hepatitis (mainly hepatitis B and C) or other etiologies, is clinical problem [(1)]. It can cause various parenchymal liver injuries, lead to development of liver fibrosis and its various complications, from those portal hypertension and hepatocellular carcinoma being the most important [(2)]. Liver biopsy is the most commonly used method for the diagnosis of liver fibrosis [(3)]. The biopsy specimen size varies from one to three centimeters in length and between one to two millimeter in diameter, therefore the sample represents 1/50000 of all liver tissue [(4)]. However, the biopsy is an invasive procedure with secondary effects, and about 1- 3% of patients may need hospitalization for complications [(5)]. The mortality rate among patients following liver biopsy is approximately 1 in 10000 to 1 in 20000, thus it cannot be repeated frequently to monitor liver fibrosis [(6)]. Moreover, biopsy

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sampling error and sample size are major sources of bias during liver fibrosis assessment [7]. Therefore, there is increasing interest in developing new, non-invasive methods to evaluate chronic liver disease as an alternative to biopsy, with focus on elastographic methods. 2 Ultrasound imaging plays increasing role in the diagnosis, monitoring and decision of therapy in chronic liver diseases [8].

It has several clinical indications [9]:

1. morphological examination of the liver parenchyma.
2. assessment of the risk of development of chronic disease by investigating the signs of dysmorphism and /or portal hypertension.
3. detecting and characterizing lesions in the liver.
4. monitoring local treatments (i,e percutaneous radiofrequency)
5. assessing treatment response. Conventional ultrasound cannot differentiate accurately the stages of liver fibrosis which is considered limitation to ultrasound [10].ShearwaveelastographyPrinciple's shear wave elastography was introduced in 2005 on the diagnostic imaging apparatus, called Aixplorer. It depends on measurement of the shear wave propagation speed in soft tissue.itdoes not require external vibrator to generate the shear wave.it is based on the generation of radiation force in the tissue to create the shear wave. The ultrasound probe of the device produces a very localized radiation force deep in the tissue of interest [11]. An acoustic radiation force is focused at successively greater depths on an axial line to produce multiple sequential spheric wave fronts. These interfere constructively to create a Mach cone with greater displacement magnitudes than those produced by the individual wave fronts. By analogy with supersonic planes, the Mach cone is produced because the rate of sequential wave front production is greater than the speed of the resulting shear waves. In the commercial implementation of shearwaveelastography, several Mach cones are produced at different lateral positions of the image. An ultra-high frame rate (up to 15,000 images per second) is used to scan the entire imaging plane in one acquisition with high temporal resolution. The combination of Mach cone generation and fast imaging allows real-time generation of elastograms. The results are reported as meters per second or converted to the Young modul in kilopascals [12]. A comparison of two consecutive ultrasound images allows the measurement of displacements induced by the shear wave and creates a movie showing the propagation of the shear wave whose local speed is intrinsically linked to elasticity. The propagation speed of the shear wave is the estimated from the movie that is created and two-dimensional color map is displayed, for which each color codes either the shear wave speed in meters per second (m/s), or the elasticity of the medium in kilopascals (kPa) This color map is accompanied by the anatomic reference gray scale (or B mode) image.this quantitative imaging technique is a real time imaging mode. Quantitative measurements can be performed in the color window by positioning one or more region of interest, called Q –Box. The Q-Box are variable in size (from 3 mm2 to 700 mm2)[13]. Measurements can be performed retrospectively from the saved image or cineloop. The measurements provided by Q-Box are the mean, standard deviation, and minimum and maximum elastography values. Results are given in m/s or kpa[13]. Figure 1.

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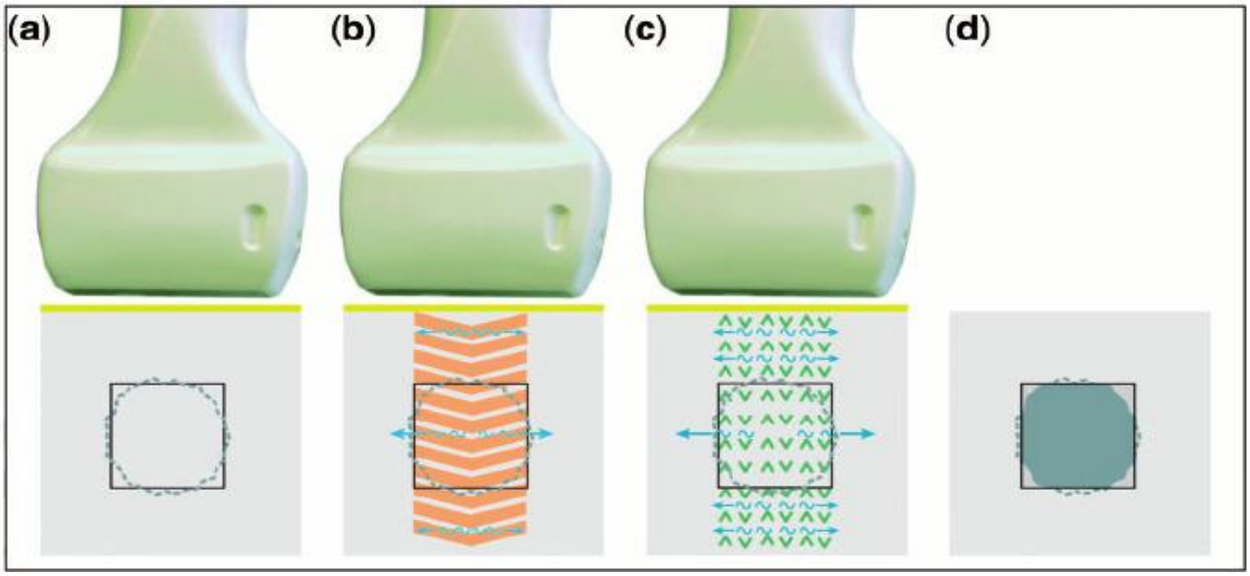

Figure 1: schematic illustration of shear wave imaging .(a) an elastography region of interest (black box) is placed over the liver .(b) high intensity acoustic impulse (orange arrows) are transmitted to the tissue , which induce shear waves (blue) .(c) diagnostic impulses (green arrows) track shear wave propagation(14) .

Liver stiffness evaluation with S-Shearwaveelastography Samsung’s S-Shearwave is a technology that detects the velocity of the shearwave propagated through a targeted area in liver tissue, then displays the numerical measurement of stiffness in kPa or m/s. The ―shearwave is a perpendicular wave produced as a result of multiple, focused, highintensity, short-duration acoustic pulses generated lateral to the area of interest (Fig. 3). The shearwaves are tracked as they travel through this region of interest. The shearwave propagation speed is used to calculate the stiffness of the tissue. Shearwave displays the numerical measurement of elasticity (stiffness) as either shearwave velocity (m/s) or as Young’s Modulus in kPa. Shearwaves travel faster in stiffer tissues. In the liver, the loss of elasticity corresponds closely to the amount of hepatocellular damage (fibrosis).[15]

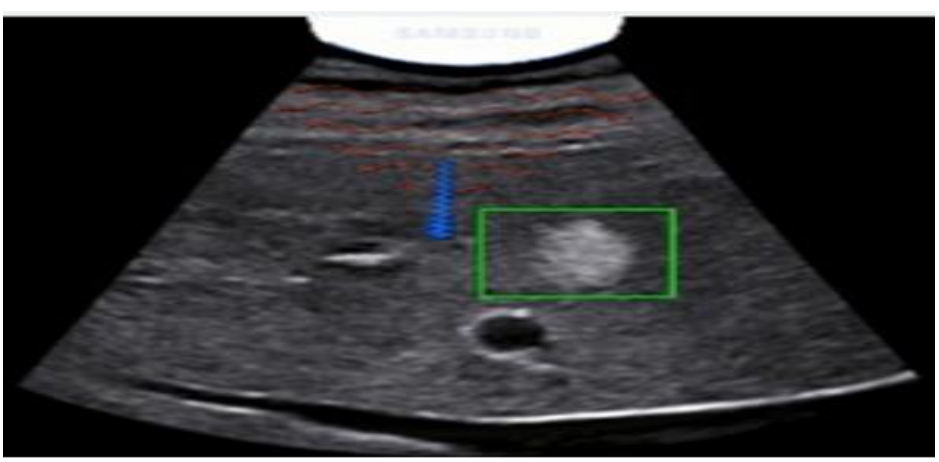
Figure 2: Graphic depiction of an ultrasound pulse (blue arrow)and resultant shear waves (red perpendicular waves)used during shear wave elastography . The shear waves propagate through the region of interest (green box) to determine the stiffness of the liver tissue /lesion[16].

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Shearwave on Samsung's HS70 is conducted on the liver by first using B-Mode imaging to locate the area of interest. The Region of Interest (ROI) box is then placed in an area of the right lobe of liver and several S-Shearwave measurements are taken (Fig. 3). The measurements are conducted while the patient suspends respiration. The region of interest box should not be placed in or immediately lateral to any vasculature. The velocity of the shearwaves are used to calculate the stiffness (kPa) of the targeted area within the ROI.[15]

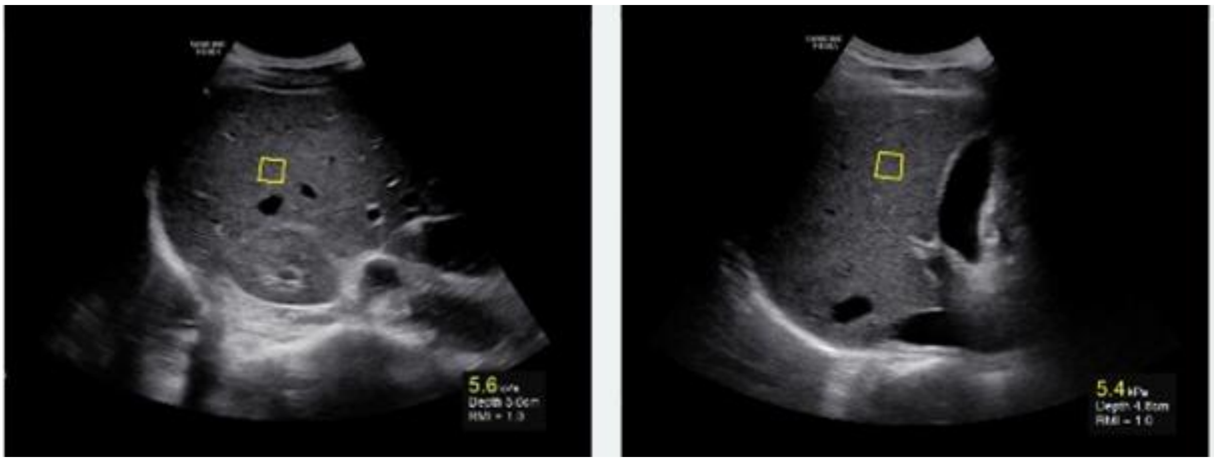

Figure 3: several shear wave measurements taken on a patients liver .After each sample , shear wave indicates the stiffness measured in kilopascal , the depth of the region of interest ,and the reliable measurement index (RMI)[16]

The average of the measurements is used to estimate the degree of liver stiffness (Fig. 4). Additionally, the Reliability Measurement Index (RMI) and Variation Range (VR) are provided in the Shearwave Profile. The RMI (reliability of the measurement) is a quality control parameter that is calculated by the weighted sum of two factors: the residual of the wave equation, and the magnitude of the shearwave. Therefore, high RMI values are strongly correlated with reproducible measurements. An RMI of 0.0 would indicate significant error, whereas an RMI of 1.0 would indicate no error). While in the Shearwave Profile display, the user can easily deselect any unreliable measurements depending on its RMI [16].

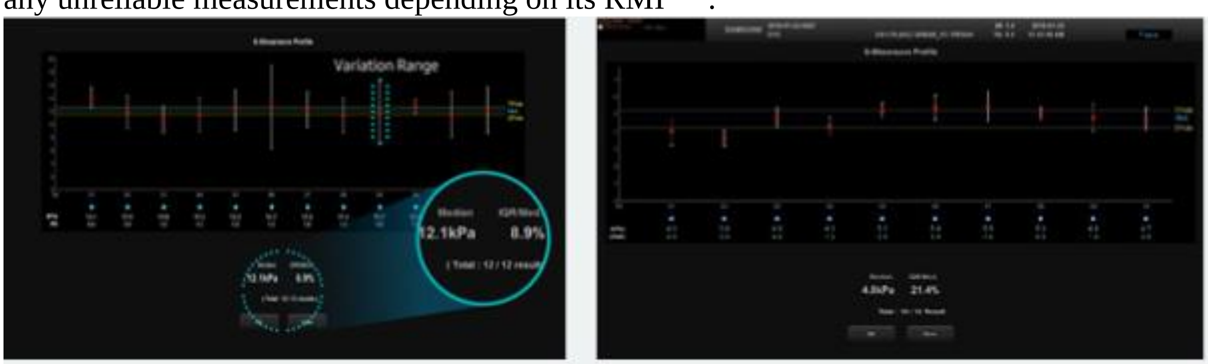

Figure 4: the shear wave profile graphs the measurements including kPa, RMI, percentiles , and median values. Additionally , an interquartile range (IQR)of all successful measurements of median value is calculated[16]

Advantages [14]

•it is an easy,painless, rapid technique

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•good intra-operator reproducibility with an intra-class correlation coefficient of 0.95 when measurements are taken at the same day and 0.84 when they are taken at different days by same operator.

•goodinteroperatorreproducibility.

•the result is immediately available.

•shear wave elastography is incorporated onto a conventional ultrasound diagnostic imaging device, which allows the combination, in one exam of quantitative elastography assessment of the liver fibrosis and /or tumor after the morphological ultrasound examination of the liver (to investigate for signs of cirrhosis, portal hypertension and to identify focal lesions).

•quantitative assessment of soft tissue elasticities in kPa or in m/s.

•real-time two-dimensional map of tissue elasticities.

• visual control of measurement location with the ability to avoid vascular structures when performing acquisition, study regions of interest (area of steatosis, liver with tumor) and visualize the special distribution of fibrosis , correlate elasticity to the tissue architecture seen (necrosis , steatosis), study the right and left lobe of the liver(16) .

•the ability to select measurement depth, and an area free of shear wave elasticity artifact (due to vessels,Glisson'scapsule, or other lesions).

•the ability to perform several measurements retrospectively on saved images on the device.

•the ability to choose the size of the Q-Box. •results expressed and displayed in kPa or m/s

•ultrasound based elastography samples a liver volume 150 times largest than a biopsy specimen (17).

Aim of the study:

To assess the diagnostic value of two-dimensional shear wave elastography in evaluation of liver fibrosis.

Patients and methods

Patients

This is a prospective study included one hundred patients, fifty patients clinically confirmed as had liver fibrosis, the other fifty patients were normal (taken randomly with no history of liver disease and have normal ultrasound), the age of patients ranging from 20-55 years old. This study is single hospital study done in Baghdad teaching hospital in medical city, from November 2019 to march 2020. All the patients underwent a general abdominal ultrasound and shear wave elastography examination. Inclusion criteria for the cirrhotic patients is patient with known cirrhosis according to laboratory tests with increase liver enzyme level, exclusion criteria include association of the cirrhosis with ascites.inclusion criteria for normal patients include no history of liver disease and normal ultrasound study, exclusion criteria include any history of liver diseases or hepatitis.

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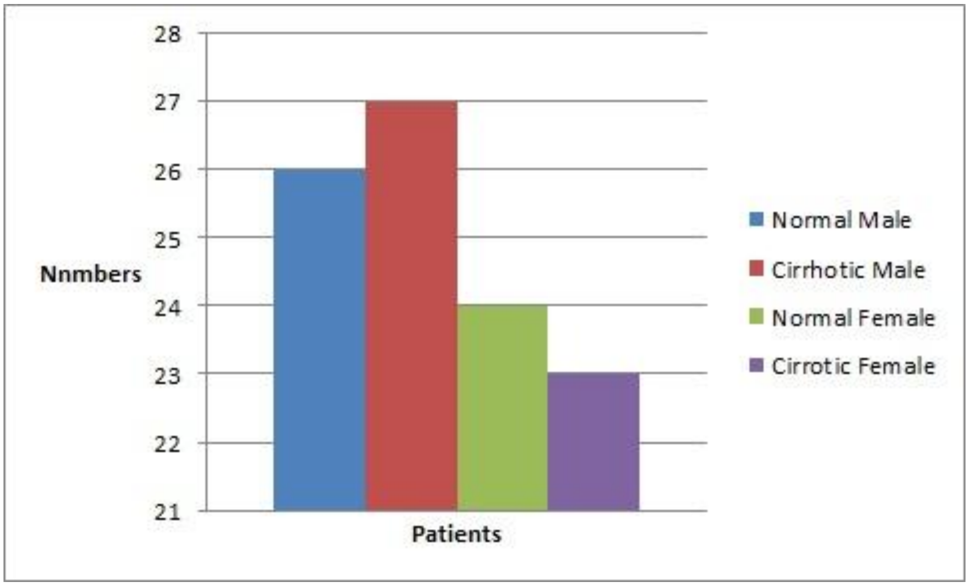

Figure 5: illustrate number of patients according to gender

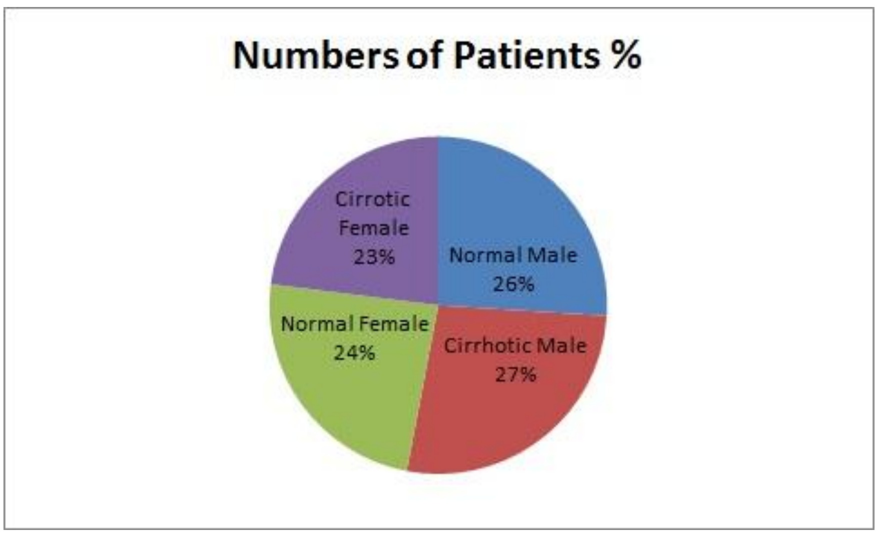

Figure 6: number of patients percent

Shearwaveelastography examination

Shear wave elastography examination was performed using Samsung HS70A equipment (figure 7).the patient was lying in the lateral decubitus position with the right arm extended above the head in aim to get access to the right hypochondrium and to increase the intercostal acoustic shadow. The probe was placed parallel to the intercostal space with gel applied sufficiently to minimize rib shadowing.

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Figure 7: Samsung HS 70 apparatus

The region of interest (ROI) with a box size of 1-2cm was positioned with in the liver parenchyma under two-dimensional B mode using depth of at least 2cm below the capsule of the liver in the right lobe, taking care to avoid including large vasculature or biliary structures. During scanning no pressure was applied to the liver, and the patient was asked not to breath for a few seconds to minimize motion artifacts.

Measurements of liver stiffness were performed on same area of liver parenchyma. The equipment listed the shear wave velocity (m/s) in the region of interest as well as the depth at which the measurements was performed. The tissue stiffness is computed in kilopascal (kPa), the shear wave velocity (v) was converted into shear Modulus G= t/y, in which the t is the shear stress and y is the shear strain based on relationship $G = pv^{2,}$ in which the p is the density of the tissue .

Ten to fifteen measurements were collected at the same location and reports was generated when success rate of at least 80% was obtained

Statistical analysis

Data are expressed as means ± standard error. Statistical analysis was performed using two-way analysis of variance (ANOVA) and then subjected to the least significant difference test (LSD). The significance level considered was ($p < 0.05$). table 1

Table 1:Measurements of liver stiffness according to gender in the studied groups

sex	N	Control group	N	Fibrosis group
male	26	4.57 ± 0.25^{aA}	27	9.63 ± 0.95^{aB}
female	24	5.21 ± 0.51^{aA}	23	12.70 ± 1.88^{bB}

M±SE=mean+ standard error
Different small letters represent significant differences within groups ($P<0.05$).
Different capital letters represent significant differences between groups ($P<0.05$).

Results

We analyzed data from fifty patients with liver fibrosis and fifty normal subjects without history of liver disease.valid shear wave elastography measurements were obtained from all

patients.from those mean age 26.6 ± 7.1 (range 20-60 years) , from the normal subjects 26 male (52%) and 24 female (48%) , and those with fibrosis 27 male (54%) and 23 female (46%)
The shearwaveelastography measurements value in liver fibrosis was 11.165 kPa (range 3.8 to 23 kPa) ,whereas the median liver elasticity for normal subjects was 4.885 kPa (range 3.2 to 7.2 kPa) . A significant correlation was found between shear wave elastography and fibrosis (p=0.0006) with sensitivity of 80% . A significant correlation also seen between shear wave elastography and exclusion of fibrosis (sensitivity 76%) (sensitivity 76%)(p= 0.003).

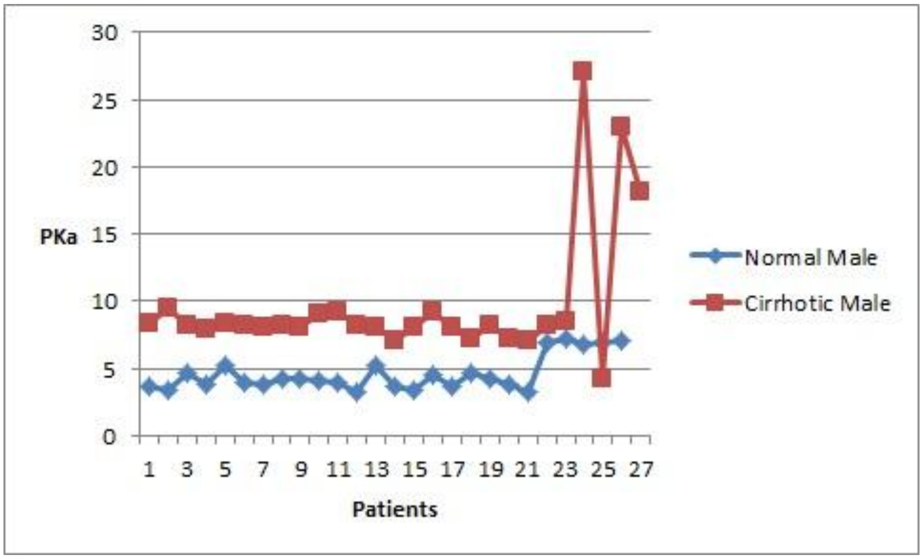

Figure 8: Number of normal and cirrhotic male and their measurement in kPa

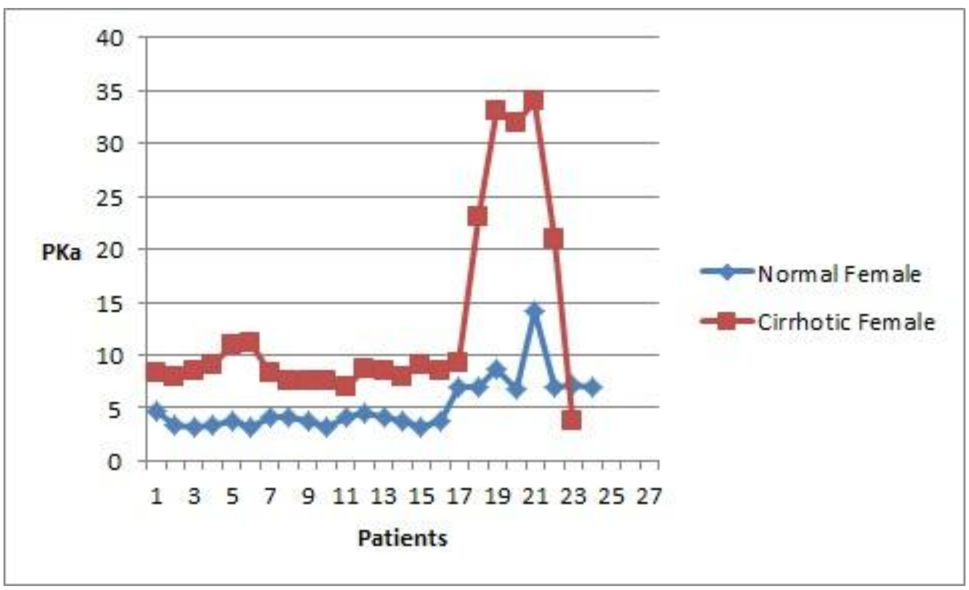

Figure 9: number of normal and cirrhotic female and their measurement in kPa

Discussion

Two-dimensional shear wave elastography is relatively new ultrasound technique that allows integrated liver stiffness measurement to non-invasively assess liver stiffness.Although, the

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method is easy to learn and fast to perform, validated normal values for healthy individuals as well as cirrhotic patients are largely missing and may differ between various high ends ultrasound devices [19].

Studies on two-dimensional shear wave elastography are starting to emerge but mostly have been confined to the supersonic ImgineAixplorer system (the first system used shear wave), with mean liver stiffness measurments ranging from 4.29 [20] to 6 ± 1.4 kPa [21].

In our study, the mean liver stiffness measurement of all subjects without liver disease was 4.88 kPa (range 3.2 to 7.2) which is lower than measurement produced by Chong Hyun Suh et al[22] , who evaluate normal value in 196 subjects with potential donor for living donor liver transplantation using biopsy verified normal liver value and identified a cut off of 6.2 kPa.

In our study the mean liver stiffness measurement in cirrhotic patients was 11.165 kPa (range 3.8 to 23 kPa) which is close to the result produced by Gomez –Domin-guez et al [23] which is 11 kPa (range from 5-16 kPa) and Fraquelli et al [24] who produce measurement of 10.3 kPa (range from 7.9 to 11.93 kPa) .

our measurement is lower than that produced by Rigamonti et al [25] who produce measurement of 12 kPa (range 7.8 to 19 kPa). Our study is higher than that produced by Ziol et al [26] which produce measurement of 9.6 kPa (range 8.8 to 14.6 kPa) and castera et al [27] who produce measurement of 9.5 kPa (range 7.1 to 12.5 kPa). The reason of differences in the reading may be due to intra- and inter-observer variability, readings is higher in patient with hepatitis C; Acute hepatitis can have false positives. In patients with a high body mass index, erroneous values may be obtained. A very practical pitfall is confounding factors such as edema, inflammation, cholestasis and congestion. All these must be put in context and a multidisciplinary clinical approach used in the interpretation of the results [28].

Table 2: comparison of the measurement between our study and other study.

study	Measurement (kPa)	Range (kPa)
Our study	11.165	3.8 -23
Gomez-Domin-guez et al	11	5 - 16
Fraquelli et al	10.3	7.9 – 11.93
Rigamonti et al	12	7.8 - 19
Ziol et al	9.6	8.8 – 14.6
Castera et al	9.5	7.1 – 12.5

Interestingly, our study revealed that sex had an impact on liver stiffness measurements in patient with liver cirrhosis, showing higher liver stiffness values in female which is differs from Bende F Mulbecirovic a sporea I et al [29] which shows significantly higher liver stiffness measurements in male participants. In contrast, we found no significant differences regarding sex in healthy liver subjects similar to Mulbecirovic a sporea I et al. this finding could have been due to the heterogenicity of this cohort because of the various underlying morbidities.

Therefore, on the basis of our data we can roll out cirrhosis in patients with normal liver stiffness values but no cut off values for cirrhosis can be derived at present. Further studies with higher numbers of patients had a homogenous etiology with histologic findings as the reference's standard are warranted.

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Our study had several limitations.First, we did not provide evidence of normal liver enzyme and bilirubin levels in the healthy volunteer group, potentially missing asymptomatic liver disease. Second, histologic conformation was only available for the liver cirrhosis cohort, whereas no histologic findings were obtained for the healthy subjects.third, the investigator performing liver stiffness measurement where aware of the cirrhotic status of the patients, introducing a potential risk of bias.

Conclusion and recommendation

Shear wave elastography examination is a promising noninvasive method for the evaluation of liver fibrosis, with good diagnostic performance.further studies in larger series of patients with uniform underlying liver disease are needed to validate these results.

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