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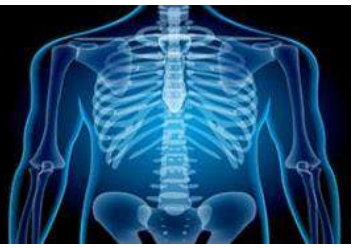

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Evaluation of acoustic radiation force impulse (ARFI) elastography as a tool for non invasive detection and grading of liver fibrosis with histopathology correlation

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Abstract
Background: Chronic insult caused by viral infection, autoimmune disease, alcohol and other toxins can damage the liver parenchyma and ultimately lead to liver fibrosis and cirrhosis. Acoustic Radiation Force Impulse (ARFI) elastography is emerging as a valuable tool in the detection and grading of fibrosis in liver.
Materials and Methods: It is a prospective comparative study performed in 36 patients between December 2016 and March 2018 who presented with deranged liver function test and referred for ultrasonography, ARFI elastography of liver followed by liver biopsy. The findings of Elastography were correlated with histopathology.
Results: When compared with histopathology ARFI had a sensitivity of 82%, specificity of 85%, positive predictive value of 90% and negative predictive value of 75% in detecting liver fibrosis when we used optimum cut values of ARFI.
Conclusion: ARFI elastography is a valuable tool in non-invasively detecting liver fibrosis and can be included as part of routine ultrasonic examination protocol of liver. ARFI technology allows the quantification of liver fibrosis and can be effectively used to stage fibrosis. Hence ARFI can be used as an alternative to liver biopsy and it might substitute liver biopsy in future.

Keywords: Elastography, ARFI, liver fibrosis grading

Introduction
The incidence of chronic liver parenchymal disease is constantly on the raise. The major underlying causes are alcoholism and viral hepatitis [1]. In response to continuous inflammation and injury there is fibrosis [2, 3, 4] and regeneration which result in liver cirrhosis and the attendant complications like portal hypertension, variceal bleed, ascites, liver failure, hepatic encephalopathy and even development of hepatocellular carcinoma[1]. Generally cirrhosis is considered to be irreversible, however accumulating evidence suggests that it could be reversible to some extent, especially when targeted therapy is given [1, 3, 5]. Hence, early detection and grading the severity of liver fibrosis is of utmost importance for treatment. The degree of hepatic fibrosis is an important factor which influences the treatment and determines the prognosis of the underlying liver disease [1]. Therefore, there is tremendous need for quantitative assessment and grading of hepatic fibrosis. The method used traditionally for assessing the degree of liver fibrosis is liver biopsy. Which is considered as gold standard method for determining the extent of liver fibrosis. However it is an invasive procedure which is associated with patient discomfort and occasionally severe complications like bleeding, infection and rarely death [1]. Histopathological examination (HPE) of liver fibrosis is greatly dependent on the size of the sample and segment from which the sample is obtained. Generally a biopsy specimen of size 1.5-2cm is required by the pathologist for accurate evaluation. The distribution of fibrosis within the liver is very non-uniform and sampling errors are bound to happen. [4, 6, 7]These disadvantages associated with liver biopsy have been the thrust behind pursuing alternate methods to assess liver fibrosis. ARFI Elastography is a recently introduced technology to evaluate tissue stiffness non-invasively.

The technology of ARFI Elastography involves the mechanical excitation of tissue using short-duration acoustic pulses (push pulses) in a region of interest, producing shear waves that spread away from the region of interest, perpendicular to the acoustic push pulse, generating localized, micron-scale displacement of the tissue [8, 9]. Simultaneously, detection waves of lower intensity than that of the push pulse (1:100) are generated. By recording the shear wave front at several locations and correlating these measurements with the elapsed time, the shear wave velocity (SWV) can be quantified in meter per second unit. Generally, the stiffer a region in the tissue, the greater the SWV as it travels through this region. This technique can be used in various organs and it is well suited for liver in view of the size and relative superficial location of the organ. The advantage of this technology is that it is incorporated in an ultrasound machine and the operator can use the ultrasound to measure the stiffness of the tissue of interest in real time.

Materials and Methods

It is a prospective study performed from December 2016 to March 2018. Before starting the study necessary clearance was obtained from the institutional ethics committee and informed written consent was obtained from the patients. The study population includes 36 patients with clinical and laboratory features of altered liver function who were referred to radiology department for further evaluation with ultrasound. All the patients underwent liver sonography, ARFI Elastography and subsequently, with in a period of two weeks, liver biopsy. The findings of Elastography were correlated with HPE. Inclusion criteria: patients under evaluation for altered liver function parameters, nonalcoholic-steatohepatitis, chronic viral infections, patients undergoing liver biopsy for assessment of fibrosis. Exclusion criteria: Patients with bleeding disorders, altered coagulation parameters, patients unable to hold their breath and uncooperative. Ultrasound protocol: Examination was performed in SEIMENS S2000 machine in supine position. B mode Ultrasound: to assess the size, echogenicity and echo-texture of liver. ARFI Elastography: Total of 8 measurements of shear wave velocity were taken, at least 2 from each segment of right lobe. Measurement was calculated by placing a 0.5 x 1cm box at least 1.5 to 2cm deep to the liver capsule (Fig. 1) and away from major vessels. The velocity was calculated in meter per second and the mean and median velocity of all 8 measurements were used to grade the stiffness of the liver.

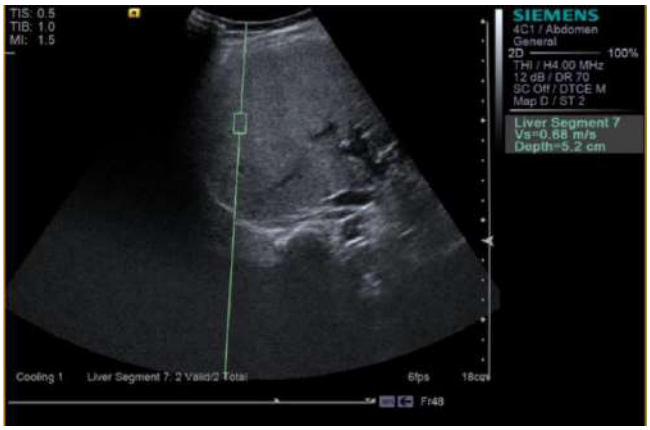

Fig 1: Measurement of ARFI by placing an ROI in each segment of the right lobe of liver.

Biopsy: Biopsy of the liver was obtained using 18G fully automatic gun (Bard MaxCore) with 22mm long cutting needle harvesting a 20mm long core. The specimen was fixed in formalin and sent for HPE. Fibrosis was scored in histopathology using the METAVIR scoring system. The cut of value [10] of shear wave velocities corresponding to METVIR grades is shown in Table 1:

Table 1: METAVIR Score and corresponding mean SWI in ARFI

Metavir Score	Histopathology	Mean Shear Wave Velocity
F0	No fibrosis	1.09+/- 0.42m/s
F1	Portal fibrosis without septa	1.22+/- 0.41m/s
F2	Portal fibrosis with few septa	1.37+/- 0.48m/s
F3	Numerous septa without cirrhosis	1.70+/- 0.59m/s
F4	Cirrhosis	2.23+/- 0.71m/s

Results

In this study 36 patients were evaluated with Ultrasonography and Elastography, the findings were compared with the HPE findings. In our study out of 36 patients 10 (28%) patients were female and 26 (72%) were male who presented with liver disease and altered liver function tests with different underlying pathologies like Nonalcoholic steatohepatitis (NASH), chronic viral hepatitis, storage disease and Cryptogenic cirrhosis. Our study had patients ageing from 11 years to 60 years with an average of 30 years. We had 14 (39%) patients below the age of 30 and 22(61%) patients more than 30 years of age. The distribution of various grades of fibrosis in the study population is shown in figure 2. The number of patients in the study population with various grades of fibrosis in ARFI and HPE is shows in table 2.

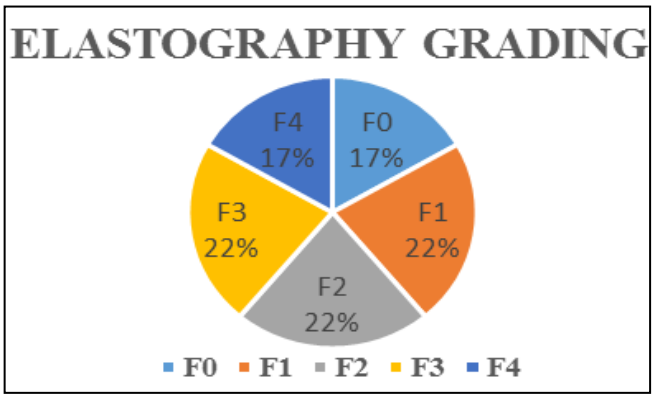

Fig 2: Distribution of various degrees of fibrosis in the study population in ARFI.

Table 2: Grading of fibrosis

	ARFI		HPE	
	Frequency	Percent	Frequency	Percent
F0	6	17	10	28
F1	8	22	4	11
F2	8	22	8	22
F3	8	22	4	11
F4	6	17	10	28
Total	36	100	36	100

B mode ultrasound findings of liver are shown in Table 3. Out of the 36 patients 4 had normal appearing liver, majority showed diffuse fat infiltration in the liver and 8 patients had altered echo-texture of liver parenchyma.

Table 3: Ultrasound findings in study population

Frequency		Percent
Normal	4	11
Steatosis	24	67
Altered echo texture	8	22
Total	36	100

In our study of 36 patients, ARFI showed clinically insignificant fibrosis in 16 patients with a METAVIR score of F0, F1 which was commonly seen with patients of acute hepatitis and nonalcoholic steatohepatitis. Clinically significant fibrosis (F2, F3, and F4) was seen in 20 patients with a majority of them affected by chronic viral hepatitis. (Tables 4).

Biopsy showed clinically insignificant fibrosis (F0, F1) in 14patients (39%) and clinically significant fibrosis (F2, F3, F4) in 22 patients (61%). Of the 14 patients who had insignificant fibrosis, different underlying etiologies such as NASH, storage diseases and autoimmune hepatitis were found, patients with significant fibrosis had viral hepatitis. (Tables 4).

Table 4: Significance of fibrosis in ARFI and HPE

	ARFI		HPE	
	Frequency	Percent	Frequency	Percent
Significant fibrosis	20	56	22	61
Insignificant fibrosis	16	44	14	39
Total	36	100	36	100

The cross tabulation comparing various grades of fibrosis in ARFI and HPE are shown in table 5.

Table 5: Elastography Grade Vs Histopathology Grade Cross Tabulation

			HPE Grade					Total
			F0	F1	F2	F3	F4	
ARFI Elastography Grade	F0	Count	2	0	2	0	2	6
		% with ARFI grade	33.3	0	33.3	0	33.3	100%
	F1	Count	4	4	0	0	0	8
		% with ARFI grade	50%	50%	0	0	0	100%
	F2	Count	4	0	4	0	0	8
		% with ARFI grade	50%	0	50%	0	0	100%
	F3	Count	0	0	2	4	2	8
		% with ARFI grade	0	0	25%	50%	25%	100%
	F4	Count	0	0	0	0	6	6
		% with ARFI grade	0	0	0	0	100%	100%
Total		Count	20	8	8	4	10	36
		% with ARFI grade	27.8%	11.1%	22.2%	11.1%	27.8%	100%

Table 6: Chi-Square Test

P value	
Pearson Chi-Square	0.028

The Chi square test shows a P = .028 which is statistically significant and proves elastography as a reliable tool for prediction of fibrosis and grading of liver fibrosis.

The cross tabulation comparing significant and insignificant fibrosis in ARFI and HPE is shown in table 7.

Table7: Significant Vs insignificant fibrosis in elastography and histopathology cross tabulation

			Histopathology		Total
			Significant	Insignificant	
ARFI	Significant fibrosis	Count	18	2	20
		% with ARFI	90%	10%	100%
	Insignificant fibrosis	Count	4	12	16
		% with ARFI	25%	75%	100%
		Count	22	14	36
		% with ARFI	61.1%	38.9%	100%

Table 8: Chi-Square Test

	P value
Pearson Chi-Square	0.005

The Chi square test shows a P = .005which is statistically significant.

Table 9: Sensitivity and specificity calculation

ARFI	Histopathology	
	Disease	No disease
Test positive	18(a)	2(b)
Test negative	4(c)	12(d)

Sensitivity: 82%, Specificity: 85%

Positive predictive value: 90%, Negative predictive value: 75%

Discussion

Generally fibrosis is thought to be an irreversible process till the discovery of hepatic stellate cells (HSC) in the 1980s. HSCs play an important role in fibrosis. Following chronic liver injury HSC under inflammatory milieu proliferate and activate to produce pro inflammatory and fibrogenic factors. Activated HSC produce large amounts of extracellular matrix (ECM). The extracellular matrix accumulates and distorts the liver architecture and forms a fibrous scar along with regeneration of hepatic tissue which subsequently lead to formation of the nodules. Studies carried out in the 1990s demonstrated that hepatic fibrosis was a reversible process if the cause was to be treated [2, 3, 4]. Since then researchers have taken keen interest in developing therapies for reversing/slowing down progression and severity of liver fibrosis. Thus, assessing the stage and severity of fibrosis precisely has taken the center stage in the management of chronic liver disease. In fibrosis and cirrhosis the pathological changes in tissue lead to alteration of mechanical properties like stiffness which can be measures noninvasively. The gold standard for assessing liver fibrosis

is biopsy and HPE. Liver biopsy, though safe, is an invasive procedure with a small risk of complications like severe hemorrhage. The risk of significant bleed is more when there is alteration of the coagulation parameters or in the presence of significant ascites. Both these risk factors are seen more frequently in patients with liver parenchymal disease, which in the first place is the indication for doing a biopsy. Percutaneous liver biopsy yields only a tiny fragment of the liver (1 in 50000 of the total volume of the liver) [11] which may lead to errors in staging of fibrosis, since there can be non-uniform distribution of fibrosis with in the liver. Bedossa *et al* [12] proved that the chance of under diagnosis of the stage of fibrosis, when the length of biopsy core is less than 2.5 cm can reach up to 25%. They have also proved that in almost half of the cases where liver fragments obtained from both the lobes of liver in the same session showed different stages of fibrosis. Hence in many ways liver biopsy is a flawed gold standard. For the past 10-15 years, enormous efforts have been made by several groups for establishing a reliable and reproducible noninvasive marker for liver fibrosis as a substitute to the invasive liver biopsy technique. In our study of 36 patients we have attempted to study the efficacy of ARFI compared to histopathology. The accuracy of ARFI elastography for assessing the severity of liver fibrosis and grading was evaluated. Calculating the sensitivity, specificity, positive predictive value and negative predictive value of the noninvasive test ARFI demonstrated a good sensitivity and specificity. Accurately grading and quantifying the severity of hepatic fibrosis secondary to an underlying disease is of great importance for planning appropriate treatment strategies. Studies comparing the non-invasive methods for evaluating the severity of fibrosis in chronic liver disease to liver biopsy are being performed to assess if these techniques would replace the invasive test. Virtual touch tissue imaging application enables ARFI technology to evaluate the deep tissues. SWI in meter per second can be quantified in a region of interest with ARFI technology in a precise anatomical location, which represents the elasticity property of the tissue. In our study we encountered 4 false negative patients. One of them was hepatitis B patient and another one patient with Hepatitis C. In these cases we presume values taken in the areas of necrosis may have contributed to low values. Another 2 patients were cases of alcoholic hepatitis, in whom the steatosis may have contributed to the falsely low values. We also had 2 false positive patients encountered in our study. One of them had hepatitis B acute stage and another one patient had hepatitis A. Hepatitis is known to have both inflammation and fibrosis, one of which may predominate depending upon the stage of disease [13, 14]. In acute stage because of inflammation, we can get erroneous high values [15, 16]. There are no possible means to differentiate the high values due to inflammation from that due to fibrosis. This may explain the false positivity in the hepatitis patients.

A study by Takahashi *et al*. [17] of 80 patients with mixed etiologies using ARFI (Siemens Healthcare), had a sensitivity and specificity of 91% and 80% respectively for F>2 stage of fibrosis. This is in concordance with the results in our study. In a similar study by Sporea at al. [18] using 114 patients with mixed etiologies, also had a sensitivity and specificity of 89% and 68% respectively. We attempted to study whether ARFI was sensitive in patients with NASH, who form the majority of the mixed etiology liver disease without viral hepatitis group. 10%-15% of NASH patients show a progression in the severity of fibrosis and architectural remodeling, and liver cirrhosis is seen in 15%-25% of cases. Three to 5% of people with fatty liver may develop cirrhosis. Cirrhosis due to NASH and cryptogenic cirrhosis have risk of developing HCC. HCC may rarely occur in a non-cirrhotic NASH patient. Hence lies the importance of detecting early fibrosis in patients with NASH [18, 19]. In a study conducted by Fraqueli *et al* [20] using 200 patients with mixed etiology liver diseases other than viral hepatitis, the sensitivity and specificity of ARFI was 72% and 84% respectively. In a study of 106 patients with HBV and HCV conducted by Friedrich-Rust *et al* [21] the sensitivity and specificity was 69% and 92% respectively. In our analysis of 28 HBV and HCV patients, we had a sensitivity of 90% and specificity of 75%. The liver stiffness assessment is challenging in patients with viral hepatitis because of the nature of underlying disease. There may be increased necro-inflammatory changes in the acute phase of the disease which undergoes fibrosis later on. The necrotic areas will give lower stiffness values compared to the other areas of inflammation thus may decrease overall sensitivity. The higher sensitivity in our study may be because these patients were assessed in the advanced stage of the disease. Review of previous publications and our own study has shown that US elastography definitely has a role in the staging of fibrosis where it has the potential of replacing liver biopsy. Another upcoming and exciting non-invasive modality to evaluate liver fibrosis is MR Elastography which has the advantage of avoiding sampling errors and operator variability. New MR imaging contrast agents that target specifically the collagen and other extracellular matrix macromolecules may be developed in the near future. A collagen-specific MR imaging contrast agent and also contrast agents that selectively target hepatic stellate cells and other cells involved in the pathogenesis of liver fibrosis may permit imaging of fibrogenesis or fibrolysis. All such data may provide valuable information for guiding antifibrotic therapy development and monitoring patients in clinical trials. Thus these noninvasive methods may help in the assessing the severity of fibrosis.

Conclusion

Acoustic Radiation Force Impulse (ARFI) elastography is a promising noninvasive tool to quantify liver fibrosis. It also has the advantage of routine ultrasound assessment of the liver during the same session of elastography study. ARFI measurements are done in real time under vision. As many number of measurements as the operator wishes can be obtained in a single study. The assessment can be repeated frequently as and when required. The technique has good sensitivity and specificity and less operator dependent when compared with other ultrasound techniques as the calculation is done automatically by the system and there are tools which are useful to obtain a good quality study. The technique has good sensitivity and specificity which has the potential to replace invasive biopsy. Limitations: Our study is limited by the relatively small sample size. The small sample size is primarily due to limitation in the number of patients undergoing biopsy. ARFI elastography is a relatively new technology that has not been extensively investigated, hence large prospective studies are needed to ascertain its efficacy and to form strict cut off values for the shear wave velocity. Different technologies and

measurement calculations are adopted by different ultrasound venders. Because of this standard values are not available for comparison across different ultrasound systems [22], which needs to be addressed by various ultrasound manufacturing vendors and an amicable consensus to be arrived at.

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