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NON INVASIVE ASSESSMENT OF LIVER FIBROSIS USING ULTRASOUND POINT SHEAR WAVE ELASTOGRAPHY

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ABSTRACT **Aim:** To prospectively determine the sensitivity, specificity and accuracy of point shear wave elastography as a non-invasive method in the diagnosis of clinically significant hepatic fibrosis with various etiologies of liver using liver biopsy as gold standard.To determine the stiffness cut-off values for point shear wave elastography (pSWE) diagnosis of clinically significant hepatic fibrosis.

Methods: Fifty patients with elevated liver enzymes were examined by point shear wave Elastography and they subsequently underwent percutaneous liver biopsy. Ultrasound Elastography findings were correlated with the histopathology fibrosis staging (METAVIR / Brunt Scoring)

Results: Liver stiffness value of >7.6 kPa was cut-off for clinically significant fibrosis and had a sensitivity of 92%, a specificity of 78.3% and an accuracy of 86%.

Conclusions: ElastPQ is a non-invasive and sensitive technique for determining the clinically significant liver fibrosis in patients with various etiologies.

KEYWORDS : Elastography, Hepatitis, Cirrhosis, Liver , Fibrosis.

INTRODUCTION

The term liver fibrosis refers to the excessive deposition of collagen, proteoglycans, and other macromolecules in the extracellular matrix in response to repetitive liver injury from various causes (1). Originally thought to be irreversible, a marker of injury, hepatic fibrosis is now considered as a dynamic process with potential for regression (2). The accumulation of proteins in the extracellular matrix promotes the formation of scar tissue that bridge together adjacent portal triads and central veins. Ultimately, progressive hepatic fibrosis leads to cirrhosis, in which fibrous bands carve the liver parenchyma into nodules of regenerating hepatocytes, a typical feature in almost all end-stage liver diseases (2).

The current clinical standard of reference for assessing liver fibrosis is liver biopsy. However, owing to its invasiveness, costs, possible complications, and sampling variability, biopsy is not an ideal tool for screening and assessing therapeutic response (3). Cross-sectional imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) have limited capability for detection of liver fibrosis. In recent years, a number of imaging-based methods for noninvasively assessing liver fibrosis have emerged like ultrasonography (US)–based transient elastography and magnetic resonance (MR) elastography.

US elastography has been here for a few years and is available easily and not very time consuming. It encompasses a wide spectrum of techniques such as strain based elastography and shear wave based elastography. In this study we have attempted to study the sensitivity, specificity and accuracy of elastography point quantification (ElastPQ, Philips healthcare), which is a type of point shear wave elastography (pSWE) which is in turn a type of shear wave elastography, as a non-invasive method for the diagnosis of clinically significant hepatic fibrosis with various etiologies of liver using liver biopsy as gold standard. We also attempted to determine the stiffness cut-off values for point shear wave elastography (pSWE) diagnosis of clinically significant hepatic fibrosis.

MATERIALS AND METHODS

Institution review board approval was taken for this prospective study. An informed consent was taken from all the patients included in the study. We prospectively included 50 patients (male 33, females 17, age group: 18 – 80 years) with altered liver enzymes wither because of non alcoholic steatohepatitis (NASH), hepatitis or due to idiopathic cause over a span of 2 years. Patients with aspartate aminotransferase (AST)/ alanine transaminase (ALT) > 3 x upper normal limit, patients not willing for liver biopsy and patients with decompensation were excluded. All patients underwent routine blood tests (Complete blood counts, PT/INR, Liver function tests) ultrasound abdomen with pSWE before liver biopsy. All patients included in the study underwent technically successful US guided liver biopsy with no major complications like intraperitoneal bleed, sub capsular hematoma and pneumothorax.

Techniques

Ultrasound Elastography technique

ElastPQ (Elastography point quantification) was performed on a Philips IU 22 x Matrix (Bothell WA, USA) ultrasound system. Liver stiffness (LS) measurements were performed in a fasting patient using C5-2 probe with the patient in supine position with the right arm in maximum abduction, by intercostal approach in the right lobe of liver, 1-2 cm under the liver capsule, breath held in expiration. We aimed for 10 ElastPQ measurements in each patient (expressed in kilopascals). ElastPQ technique uses a box with predefined size (15 x 5mm), which was placed in the liver avoiding the area immediately under the liver surface and near the major vessels. The median value of 10 valid measurements (4, 5) expressed in kPa were taken as the LS measurement. The optimal liver stiffness cut-off for clinically significant liver fibrosis (F=2 METAVIR or a comparable scoring system) was more than or equal to 7.6 kPa based on the meta-analysis by Friedrich-Rust et al (6).

Liver biopsy Technique

Liver biopsy was performed via the percutaneous route in all patients. Biopsy samples were taken via a right intercostal space from the right lobe. The right lobe was chosen because of its larger size and easy accessibility through the intercostal space. First sonography was performed to find the safest and best accessible intercostal space from which to obtain a biopsy sample. After disinfection and local anesthesia of the skin, intercostal space, peritoneum and liver capsule, liver biopsy was performed. This was performed using 18G BARD®MAX-CORE® disposable core biopsy instrument (Bard Peripheral vascular Inc., USA). The liver specimens (Median length of 1.8 mm) were fixed in formalin. The specimens were graded for fibrosis according to the METAVIR classification (or a related classification like Brunt classification): No fibrosis (F0), portal fibrosis without septa (F1), portal fibrosis with septa (F2), numerous septa without cirrhosis (F3), cirrhosis (F4) (7, 8, 9).

STATISTICAL ANALYSIS

Validity parameters – sensitivity, specificity, positive predictive value, negative predictive value. Accuracy of pSWE with respect to liver biopsy was computed. Statistical significance of association of two methods of diagnosis with reference to different grades were studied

applying McNemar's test. Appropriate cut-off point for F2 stage of fibrosis with respect to gold standard was computed by doing receiver operating curve (ROC) analysis.

RESULTS

Out of the 50 patients considered in the study, 33 (66%) were males and 17 (34%) were females age range of 21- 66 years (average age of 42.46 years). All the patients had AST, ALT and ALP values <3 times the upper normal value at the time of biopsy. The total bilirubin, direct bilirubin, total platelet count, PT/INR were within normal limits at the time of biopsy. Out of the 50 patients who underwent elastography and biopsy, 43 (86%) were to evaluate elevated liver enzymes at initial presentation and 7 (14%) were to assess liver stiffness as part of pretransplant workup. Out of the 50 patients, 36 (72%) patients had a clinical diagnosis of NASH/alcoholic hepatitis, 5 (10%) patients had a diagnosis of hepatitis B, 9 (18%) patients had a diagnosis of hepatitis C. Pre procedure elastography showed clinically insignificant fibrosis (<7.5 kPa) in 20 patients (40%) and clinically significant fibrosis (>7.6 kPa) in 30 patients (60%). Out of these 20 patients with clinically insignificant fibrosis, 4 patients (8%) had viral hepatitis. Out of the 30 patients with clinically significant fibrosis, 10 patients had viral hepatitis (20%).Biopsy showed clinically insignificant fibrosis (F0, F1) in 23 patients (46%) and clinically significant fibrosis (F2, F3) in 27 patients (54%). Of the 23 patients who had insignificant fibrosis, 4 patients (8%) had viral hepatitis and of the 27 patients with significant fibrosis, 10 patients (20%) had viral hepatitis. ElastPQ had a sensitivity of 92.6%, specificity of 78.3%, positive predictive value of 83.3%, and negative predictive value of 90% and accuracy of 86% in determining the clinically significant fibrosis (Table 1).

Table 1.Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of point shear wave elastography in determining clinically significant fibrosis

		Biopsy results		"p" value
		Clinically significant fibrosis (F2, F3) n (%)	Clinically insignificant fibrosis (F0, F1)n (%)	
Elastography	Clinically significant (>7.6 kPa)	25(92.6)	5(21.7)	0.453
	Clinically insignificant (<7.5 kPa)	2(7.4)	18(78.3)	

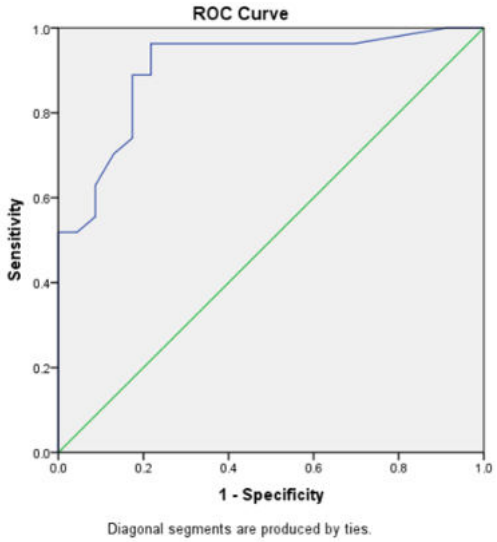

Figure 1. AUROC curve generated from the elastography values

DISCUSSION

The correct evaluation of liver fibrosis in chronic liver disease is of paramount importance for the appropriate management of the underlying diseases. Liver biopsy is still considered the gold standard for the diagnosis and staging of severity of fibrosis. Liver biopsy is an expensive and invasive procedure with a small risk of complications like severe hemorrhage. Also liver biopsy captures only a small fragment of the liver (about 1/50000 of the total volume of the liver) which may lead to misdiagnosis and understaging of fibrosis since the fibrosis is heterogeneously distributed. Hence in many ways liver biopsy is a 'flawed gold standard'. Studies comparing the various non-invasive methods of evaluation in chronic liver disease with liver biopsy have been conducted to assess whether they can replace it. In our study we attempted to assess the sensitivity, specificity and accuracy of ElastPQ (Philips Healthcare), which is a variant of point shear wave elastography (pSWE) as a non-invasive method for assessing of liver fibrosis.

In our study, ElastPQ had a sensitivity of 92.6%, specificity of 78.3%, positive predictive value of 83.3%, and negative predictive value of 90% and accuracy of 86% in determining the clinically significant fibrosis (Table 1). The performance of ElastPQ in our study population as assessed by area under the receiver operating curve (AUROC) was 0.906 with 95% confidence limit of 0.821 and 0.991 (Figure 1). The cut-off value for clinically significant fibrosis obtained from the AUROC was 7.6 kPa having a sensitivity and specificity of 96.3% and specificity of 78.3%. This cut-off value is similar to the value we used in our study based on the meta-analysis by Friedrich-Rust et al (6). In our study we encountered 2 (7.4%) false negative patients. One of them was a hepatitis B patient, hence LS values taken in the areas of necrosis may have contributed to low LS values. The second patient was a case of NASH, in whom the steatosis may have contributed to the false low values. In our study we also encountered 5 (21.7%) false positive patients. One of them was a hepatitis B patient and the remaining 4 were patients with suspected NASH. Hepatitis is known to have both inflammation and fibrosis, one of which may predominate depending upon the stage of disease (10, 11). In acute stage because of inflammation, we can get erroneous high LS values. There are no possible means to differentiate the high LS values due to inflammation from that due to fibrosis. This may explain the false positive value in the hepatitis patient. Four of these patients were suspected to have NASH based on their transaminitis and USG finding of fatty liver. Ultrasound elastography showed clinically significant fibrosis in these patients. However as liver biopsy showed steatosis with no fibrosis/inflammation, they were considered as false positive. One of these patients was put on only strict lifestyle and diet modification and the other three were put on lifestyle modification and Udiliv (ursodesoxycholic acid) and were followed up. Follow up laboratory evaluation showed resolution of the transaminitis. Improvement of major histological features of disease severity, grade of steatohepatitis and occasionally of fibrosis following therapy using different agents have been reported in NASH (12).These cases may stand as an example where the fibrosis was staged incorrectly by biopsy because of "sampling errors". However further studies comparing ultrasound elastography, MR elastography and biopsy are required to substantiate this observation.

A study by Takahashi et al. (13) of 80 patients with mixed etiologies using ARFI (Siemens Healthcare) which is another variant of pSWE, 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. (14) using 114 patients with mixed etiologies, also had a sensitivity and specificity of 89% and 68% respectively.

In a study by Fraqueli et al (15) using 200 patients with mixed etiology liver diseases other than viral hepatitis, the sensitivity and specificity was 72% and 84% respectively. In our study of 36 patients with mixed etiology liver diseases other than viral hepatitis, the sensitivity and specificity was 94.1% and 78.9%. The reason for higher sensitivity in our study may be because of the pSWE technique which we used as compared to transient elastography (TE) technique used in the previous study. The disadvantages of TE are that it has limited role in obese patients and patients with narrow intercostal space. Also since TE has no anatomic images, the values recorded may be from an area adjacent to a major vessel resulting in lower values. However our study population was smaller compared to the previous study. A study with larger cohort undergoing pSWE may be helpful to assess the advantage of pSWE over transient elastography.

In a study of 106 patients with HBV and HCV conducted by Friedrich-Rust et al. (16) the sensitivity and specificity was 69% and 92% respectively. In our analysis of 14 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 maybe because these patients were assessed in the advanced stage of the disease.

Fibrosis is a heterogeneous process. We used liver biopsy as a gold standard which mentioned earlier captures only 1/50000th of the liver volume while elastography was done multiple areas of the right lobe. Hence there may be a "sampling error" for biopsy.

The review of previous papers and our own study has shown that US elastography definitely has a role in the staging of fibrosis of liver especially in cases of non-viral hepatitis liver diseases where it has the potential of replacing liver biopsy. But this is not true in case of viral hepatitis, where elastography can only play the role of an adjunct tool to guide biopsy from areas of "stiff" liver. 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. In the future, new MR imaging contrast agents that specifically target collagen or other extracellular matrix macromolecules may be developed.

CONCLUSION

ElastPQ is a non-invasive and sensitive modality for detecting clinically significant liver fibrosis in patients with various etiologies.

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