ORIGINAL ARTICLE

TRANSIENT ELASTOGRAPHY OF LIVER FIBROSIS IN CHRONIC HEPATITIS C PATIENTS: DIAGNOSTIC IMPORTANCE

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ABSTRACT

OBJECTIVE: To determine the diagnostic accuracy of transient elastography (TE) of liver in assessing fibrosis in adult chronic Hepatitis C patients keeping liver biopsy as gold standard. **SUBJECTS AND METHODS:** This cross-sectional study was conducted at the Radiology department of Civil Hospital Karachi, Pakistan from May 2014 to January 2015. Consecutive adult patients aged 18 to 60 years with presence of HCV RNA in serum according to polymerase chain reaction, and minimum of 6 months duration of known Hepatitis C were included in the study. All patients underwent transient elastography of liver by a consultant radiologist and the Principal investigator. Ten valid measurements were taken and mean value was classified accordingly (F0-F4). The elastography scores were correlated with METAVIR scores of liver biopsy. Diagnostic accuracy was determined in terms of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). **RESULTS:** Transient elastography correctly identified presence of fibrosis in 190 (95.4%) out of 199 patients with fibrosis and ruled out fibrosis in 63 (88.7%) of 71 patients with normal liver on histopathology. The diagnostic accuracy of transient elastography in determining the presence of fibrosis was: Sensitivity 95.5%, specificity 87.5%, PPV 95.5% and NPV 88.7%. However, for assessing the stage of fibrosis the sensitivity and specificity respectively were 80% and 95.23% for F1, 79.6% and 96.29% for F2, 88% and 96.61% for F3, and 98% and 99.54% for F4. **CONCLUSION:** Transient elastography has high diagnostic accuracy in determining the presence of fibrosis as well as in assessing late fibrosis and cirrhosis (F3-F4). However, the sensitivity was comparatively less in identification of early fibrosis (F1-F2) in the studied group of patients.

Keywords: Transient Elastography (TE), Fibroscan, METAVIR, Liver Fibrosis, chronic hepatitis

Introduction

Chronic liver injury is the result of various viral, autoimmune, drug-induced, cholestatic, and metabolic etiologies.[1] Patients with chronic hepatitis are at increased risk for liver fibrosis, cirrhosis and its complications including hepatic failure and primary liver malignancy.[2,3] Hepatitis C Virus (HCV) infects approximately 185 million or 2.8% of the world's population.[4] It has become a major source of disease burden in developing countries, particularly in Pakistan, having the second highest prevalence rate of hepatitis C,[5] ranging from 2.2-14% or approximately 10 million HCV infected individuals in the country.[6]

Determination of the degree of liver fibrosis is imperative in chronic viral hepatitis patients for prognosis, surveillance and treatment decisions by clinicians.[7] Liver biopsy is still considered the gold standard for assessment of liver fibrosis and cirrhosis.8 Its drawbacks include procedural complications, sampling error, and requiring special expertise for performing liver.[9]

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Various hematological tests, serum markers, and scoring systems have been devised; however, failure to quantify liver fibrosis is seen in about 50% of patients. Detection of intermediate fibrosis has been the most difficult for most assays.[10,11]

Imaging techniques are promising attempts in the assessment of liver fibrosis; these include measurement of liver stiffness with ultrasound transient elastography.[12,13]

Ultrasound transducer probe on the axis of vibrator is used in transient elastography. Vibration transmitted through this transducer propogates through the tissues in the form of an elastic "shear wave". This is followed by pulse-echosonographic acquisitions and liver stiffness in kilopascals is measured.[14]

In a number of studies, positive correlation between TE and stage of liver fibrosis has been reported, however, a high rate of non- interpretable results have also been documented.[15] Liver stiffness evaluation (LSE) is considered reliable when all of these criteria are met: (i) Ten valid measurements; (ii) LSE success rate of 60%; (iii) and LSE interquartile range / median (IQR/ M) of 0.30.[16]

Transient elastography (Fibroscan) is a novel technology for assessment of liver fibrosis in chronic hepatitis C patients for diagnosis as well as follow-up. It is reasonably accurate, cost effective, quick and widely applicable and can reduce the need for liver biopsy.[17] The objective of this study was to determine the diagnostic accuracy of Transient Elastography (Fibroscan) in staging of fibrosis in chronic hepatitis C patients with liver biopsy as the gold standard.

Material and Methods

A descriptive cross sectional study was conducted from April 2014 to January 2015 at Radiology Department of Civil Hospital Karachi. Study was duly approved by Hospital Review Committee.

Adult patients (aged 18-60 years) with Hepatitis C virus (HCV) ribonucleic acid (RNA) in serum positive with real-time polymerase chain reaction, and a minimum of six months duration of infection were consecutively included. Whereas all patients with ascites, history of alcohol consumption, co-infection with other viruses such as hepatitis B virus, other liver diseases such as primary biliary cirrhosis were excluded. Obese patients (BMI >30 kg/m^2) were also excluded from the study since this is known to limit the accuracy of transient elastography.

Informed consent was sought from all patients. Clinical parameters included weight, height, past history of ascites or bleeding varices, and hepatocellular carcinoma were recorded on the proforma.

Transient elastography (Fibroscan) was performed by consultant radiologist with training in elastography procedure, assisted by the principal investigator. Patients had liver biopsy after the liver stiffness measurement (usual indications for liver biopsy), liver biopsy was fixed in formalin and paraffin embedded. All biopsy specimens were analysed independently by an experienced pathologist blinded to the clinical data and the results of the liver stiffness measurements.

Patients were positioned in the dorsal decubitus position with right arm in maximal abduction. All measurements were acquired on the right lobe with transducer placed in intercostal space. Measurement depth was between 25 mm to 65 mm below the skin surface. The operator reviewed an ultrasonic time-motion image and located to locate a 6 cm portion of liver free of large vascular structures. Once the region of interest was located, the operator pressed the probe button to start an acquisition. Measurements which did not have a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software. Up to 10 successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. The results are expressed in kilopascal (kPa). Median value of the successful measurements was kept as representative of liver stiffness. Only liver stiffness measurements obtained with at least ten successful measurements and a success rate of at least 60% were considered reliable.

Staging of liver fibrosis on transient elastography was according to defined cut-off values,18 with no fibrosis (F0) cut off value of <5.5KPa, minimal fibrosis (F1) <7.0KPa, significant fibrosis (F2) <9.5KPa, severe fibrosis (F3) <12.5KPa and cirrhosis (F4) >12.6KPa.

Staging of liver biopsy specimens was according to METAVIR score with F0 = no scarring, F1= minimal scarring, F2= scarring extending outside the areas in the liver containing blood vessels, F3= bridging

fibrosis, F4= cirrhosis or advanced scarring of the liver.

A database was developed on SPSS for windows version 19.0 and mean and standard deviations were calculated for quantitative variables like age, weight, height, and duration of disease. Frequency and percentage were calculated for gender. The diagnostic accuracy of transient elastography was determined in terms of sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy against the gold standard of liver histopathology

Results

A total of 304 patients were enrolled in the study. Thirty four patients (11.2%) were excluded because of unsuccessful liver stiffness measurement (less than 10 valid measurements or success rate of less than 60%). Therefore, 270 patients were analyzed, including 144 (53.3%) males and 126 (56.6%) females. The age range was between 18 and 60 years with mean age of 35.4 years.

The duration of hepatitis C infection was between 6 months and 8 years with mean duration of 2.1 years. The body mass index (BMI) of patients ranged from 18 kg/m^2 to 30 kg/m^2 with mean BMI of 25.2 kg/m^2.

On histopathology, fibrosis stage distribution was such that 71 patients had no fibrosis (F0), 60 mild (F1), 54 moderate (F2), 34 severe fibrosis (F3), and 51 had cirrhosis (F4). (Fig. 1)

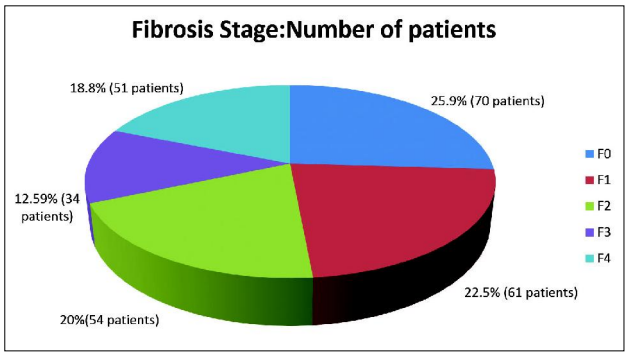

Figure 1: Stage of fibrosis according to histopathology

For stage F0 or no fibrosis, there were 190 true positive cases, 9 false positive, 8 false negative and 63 true negative cases. Thus, Fibroscan for this stage had a sensitivity of 95.5%, specificity of 87.5%, positive predictive value of 95.47% and negative predictive value of 88.73%.

For mild fibrosis (F1), there were 48 true positives, 10 false positives, 12 false negative and 200 true negative cases, thereby the calculated diagnostic accuracy is: sensitivity of 80%, specificity of 95.23%, positive predictive value of 82.75% and negative predictive value of 94.33%.

There were 43 true positive, 8 false positive, 11 false negative and 208 true negative cases for stage F2 or moderate fibrosis. Diagnostic accuracy was calculated: sensitivity - 79.6%, specificity - 96.29%, positive predictive value - 84.31%, negative predictive value 94.97%.

Severe fibrosis or F3 stage consisted of 30 true positive cases, 8 false positive, 4 false negative and 228 true negative cases. Diagnostic accuracy was: sensitivity 88%, specificity 96.61%, positive predictive value of 78.94% and negative predictive value of 98.27%.

There were 50 true positive, 1 false positive, 1 false negative and 218 true negative cases for cirrhosis or stage F4, therefore, sensitivity was 98%, specificity was 99.54%, positive predictive value was 98% and negative predictive value was 99.54%. (Tab. 1)

	Sensitivity	Specificity	PPV	NPV
F0	95.5%	87.5%	95.47%	88.73%
F1	80%	95.23%	82.75%	94.33%
F2	79.6%	96.29%	84.31%	94.97%
F3	88.0%	96.61%	78.94%	98.27%
F4	98.0%	99.54%	98%	99.54%

Table 1: Sensitivity, specificity, positive and negative predictive values of Fibroscan

Overall diagnostic accuracy of transient elastography in determining liver fibrosis in hepatitis C patients was found to be 93.7%. (Fig. 2)

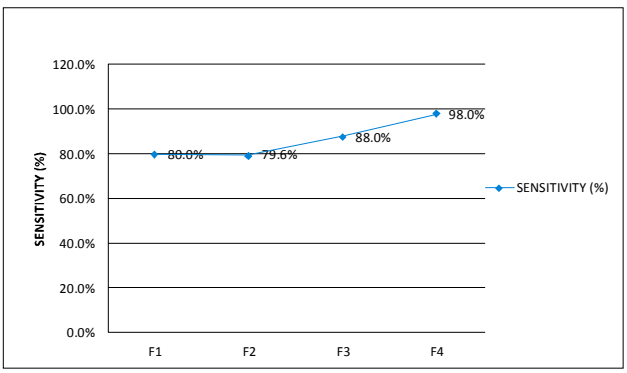

Figure 1: Sensitivity for each stage of fibrosis

Discussion

Hepatic fibrosis is presently and preferably followed up by non-invasive means employing either biochemical means or utilizing physical principles of elasticity in imaging. The concept is that fibrosed tissue has lost elasticity, and allows the strain wave to travel more rapidly and thus produce echoes that can be translated into measurable units. The imaging modalities include the better-known technique of ultrasound elastography, the strain wave technique called TE or Fibroscan, and the magnetic resonance (MR) elastography. To the author's knowledge, this study is the first local study to evaluate TE validity in patients with Hepatitis C. Most studies have not evaluated the diagnostic accuracy for each stage of fibrosis in hepatitis C patients.

A recent meta-analysis of 24 articles reported high sensitivity (84%) and specificity (90%) of transient elastography (TE) for assessing liver cirrhosis in hepatitis C patients with subgroup analysis of patients with HCV alone, sensitivity and specificity of 91% and 92%.[19] This is slightly lower compared to our study with values of 98% and 99.54% respectively for liver cirrhosis (F4).

A recent study in Egyptian population conducted by Lamiaa Mobarak et al reported that Fibro-Scan was able to predict significant fibrosis at cut-off value 7.5 KPa with sensitivity 88%, specificity 100%.[20] This was comparable to the results in our population.

A meta-analysis conducted in chronic Hepatitis B patients showed the diagnostic accuracy of transient elastography as: sensitivity of 74.3% and specificity of 78.3% for F2 with cut-off value of 7.9 kPa, 74.0% and 63.8% for F3, the cutoff value was determined to be 8.8 kPa, and 84.6% and 81.5% for F4 with cut-off value of 11.7 kPa.[21] A similar trend of improved diagnostic accuracy with increasing stage of fibrosis was also observed in our study, however, better results were obtained in chronic hepatitis C patients.

Our findings support the previous studies carried out internationally suggesting that the degree of liver fibrosis impacts the diagnostic accuracy. Transient elastography has better performance for diagnosis of cirrhosis and lower diagnostic accuracy for lower-stage of fibrosis.

A higher diagnostic accuracy of transient elastography is likely due to exclusion of technically difficult obese patients, and patients in whom the success rate of obtaining measurements was less than 60%. A significant limitation of this technique is lack of real time scanning as it requires the use of ultrasonography to find the good window because there is no B-mode.

Liver elastic property can also be measured by other non invasive modalities - magnetic resonance (MR) elastography, compression elastography, acoustic radiation force impulse imaging, and supersonic shear wave imaging. Mobarak et al found the overall diagnostic accuracy of FibroScan to be 94%, while that of real time elastography to be 83%. However, real time elastography was useful for liver fibrosis assessment in chronic hepatitis C patients especially in cases with technical limitations for Fibroscan.[20]

MRI uses many diffusion based chemical shift and elastography techniques for evaluation of fibrosis.[22] MR elastography is reported to have an even greater ability than DWI to distinguish between the stages of fibrosis.[23] However its use is restricted as it is expensive and not widely available.

Conclusion

Transient elastography has high diagnostic accuracy in evaluation of cirrhosis. Further improvement in the technology and hands-on experience may go a long way in improving our understanding of managing liver fibrosis.

Conflict of Interest: None declared by all authors

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