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Original Research Paper

Radio-Diagnosis

EVALUATION OF FIBROSIS STAGE IN CHRONIC LIVER DISEASE BY USE OF LOW AND HIGH FREQUENCY ULTRASOUND AND ITS COMPARISON WITH HISTOPATHOLOGY

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ABSTRACT The stage of fibrosis is a key factor in defining the prognosis and management of chronic liver diseases with a viral infection. The gold standard for the diagnosis of the fibrosis stage has been a histological liver evaluation based on specimens taken either by a needle biopsy or at operation. Aim of this study was to evaluate the accuracy of the liver fibrosis stage by utilizing the techniques of advanced ultrasound in patients with chronic liver disease as an non- invasive and reliable alternative to the histological staging in chronic liver diseases by biopsy. Ultrasound assessment for parameters of liver edge, liver surface regularity and parenchymal echotexture using high and low frequency transducers and resultant scoring system depending on the severity of findings was undertaken. Finally, a cumulative score was assigned by adding the individual ultrasound score of the three parameters. Subsequently, comparison with the histopathological grade of fibrosis present in each case was carried out. Statistical analysis showed that the parameters of liver edge, surface irregularity, parenchymal echotexture and the cumulative ultrasound score showed sensitivity reaching upto 100% in detecting upto early stages of fibrosis. The specificity of all these parameters except for parenchymal echotexture ranged from 77.7% to 83.3.%. Also, the negative predictive value of these parameters was reaching upto 100% indicating the role of ultrasound in predicting absence of fibrosis in patients with accuracy at par with histopathology.

KEYWORDS : Hepatitis B, Ultrasound, Fibrosis

INTRODUCTION

Chronic liver diseases result in varying degrees of hepatic parenchymal changes ranging from varying stages of fibrosis to cirrhosis. The stage of fibrosis plays an important role in prognostication and management of chronic liver diseases with a viral infection.

Fibrosis of the liver results due to extracellular matrix proteins accumulates in excess including collagen. This occurs in most types of chronic liver diseases.[1]The resultant distortion of hepatic architecture can lead to a fibrous scar, and regenerating hepatocytes forms cirrhosis defining nodules. Cirrhosis produces hepatocellular dysfunction resulting in hepatic insufficiency[2].

Initially, due to distortion of hepatic parenchyma and replacement by collagen predominant tissue, fibrosis was thought to be a passive and permanent process.[3,4]. It is postulated to indicate wound-healing response to chronic liver injury[5]. Liver fibrosis may progress rapidly to cirrhosis in several clinical settings[6].

Liver biopsy is the 'gold standard' for the assessment of liver fibrosis. Among the various classification systems, METAVIR scores and Ishak (modified Knodell score) are the most widely accepted scoring systems [7].

The staging of liver fibrosis has an important bearing not only for further risk assessment of developing complications but also from the therapeutic management of the patient. For most patients infected with HCV genotypes 2 or 3, antiviral treatment is indicated. However, the treatment for in HCV genotype 1–infected which is considered difficult to treat , management is based on additional prognostic factors like degree of hepatic fibrosis at the time of liver biopsy[8]. Liver biopsy is thus recommended to aid in the decision to treat patients, but its value is being questioned because of its potential risks and the concern of sampling error.Therefore, noninvasive tests for hepatic fibrosis like serum biomarkers, transient elastography and MR-applications have been proposed in the assessment of liver fibrosis either as single methods or as combinations.[9,10]

Ultrasound (US) is a non-invasive, cost effective and reproducible modality and has been used as the most valuable tool in assessment of hepatic status in chronic liver disease.Various sonographic parameters studied for the assessment of stage of fibrosis are liver surface[11,12,13,15,18], parenchymal echotexture[13],liver edge[19,20], caudate lobe hypertrophy[13], spleen size[10,13,14], gall bladder thickness[15]. Moreover, most of these studies have also combined Doppler parameters such as portal venous flow velocity[16,10,13,15] along with B- mode parameters.

MATERIAL AND METHODS

This cross sectional descriptive study was carried out at Department of Radiodiagnosis, Armed Forces Medical College, Pune for a duration of two years. The study was approved by institutional ethics committee.

Study Population and sample size:

One hundred patients (100) with chronic hepatitis who are being considered for liver biopsy were taken up for study. The sample size was based on the average OPD and in-patient data of the hospital.

Inclusion criteria

Patients with chronic hepatitis who were being considered for liver biopsy.

Exclusion criteria

Any clinical and/or biochemical signs of decompensated liver disease and coagualpathy.

Study protocol

1. Clinical data including demographic data, complete blood counts, biochemical data, coagulation profiles and serologic data obtained before US and liver biopsy.

2. Equipment used :

All patients were evaluated using real time ultrasound system (LOGIQ P5 (GE Medical Systems,USA)) with a 2–5 MHz convex array transducer (low frequency probe) and a 7-12 MHz Linear transducer (high frequency probe) within an interval of no more than 15 days prior to the biopsy examination. The patients were kept in supine, left lateral

oblique and left lateral decubitus positions and scanning performed with quiet respiration.

3. Parameters studied:
Following parameters were studied and a score was determined (for each parameter and a cumulative score) using low and high frequency probes. The final cumulative score (if> 0) was determined by the sum of individual scores detected by the mode (low frequency or high frequency probe)showing discernible findings. The scores were calculated as follows:

a. Liver edge:
score 0 for sharp; score 1 for mildly blunted; score 2 for blunted.

b. Liver surface:
score 0 for smooth; score 1 for mildly irregular; score 2 for irregular; score 3 for highly irregular; and

c. Liver parenchymal texture:
score 0 for fine; score 1 for mildly coarse; score 2 for coarse; score 3 for highly coarse.

4. Histological findings :
Liver biopsy specimens were obtained from each patient. All of the histologiclal slides were reviweed as per the modified histological activity index grading and staging system.

Statistical analysis:
US scores (Cumulative as well as scores of individual paramemters) were compared with the histopathological grading of fibrosis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and inter-observer variability (kappa) were calculated. Statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 19.0. *P*-value was calculated for each of the criteria separately using Chi Square test or Fisher's exact test as appropriate. *P*-value < 0.05 was considered statistically significant.

RESULTS

100 patients with chronic hepatitis awaiting liver biopsy were taken up for the study. The age of the patients ranged from 22 – 46 years with maximum patients in the 31-40 year age bracket. Majority of the patients were males (80%). The etiology of chronic hepatitis in the patients were HBV (72%), HCV (26%) and Autoimmune hepatitis (2%).

Liver biopsy specimens were obtained in each patient and the staging of fibrosis was assigned as per the modified histological activity index grading and staging system. 64% of the patients were found to be in early stages of fibrosis (28 % in stage 0 and 36% in stage 1).

Likewise, those who were found to have stage 2 fibrosis (26 patients) and stage 3 fibrosis (10 patients) comprised 36% of the total sample population. Therefore, the statistical evaluation pertaining to these two groups was carried out and the US parameters with their significance were considered for these groups of early/ mild and late/ moderate fibrosis stage separately.

The patients were examined by ultrasound for parameters of liver edge, liver surface irregularity and parenchymal echotexture using low and high frequency probes.

This assessment was separately given a score based on severity of findings and correlation of the individual score of these parameters as well as combined score with the staging of fibrosis obtained on histopathology was carried out. (Figures 1-3)

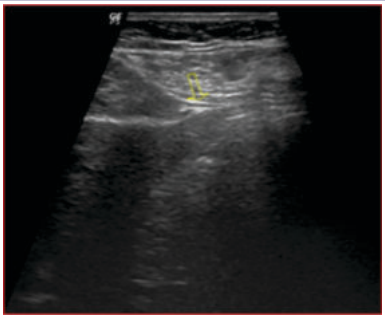

Fig 1: USG B Mode shows mild irregularity of the liver surface(yellow arrow) only on high frequency probe and was given a score as 1. The low frequency scores were 0. The cumulative score was 1 suggesting early fibrosis (detected by high frequency probe). The corresponding liver biopsy showed Stage 1 (early) fibrosis for this patient.

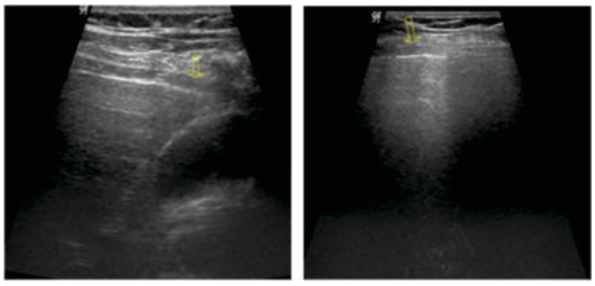

Fig 2(a) **Fig 2(b)**

Fig 2 (a-b): USG B Mode using High Frequency probe showing parameters of liver edge & parenchymal echotexture **(a)** and surface **(b)**. The score for each parameter was given as 1 on high frequency probe. The low frequency scores were 0. The cumulative score was 3 suggesting mild fibrosis (yellow arrows). The corresponding liver biopsy showed Stage 2 mild fibrosis for this patient.

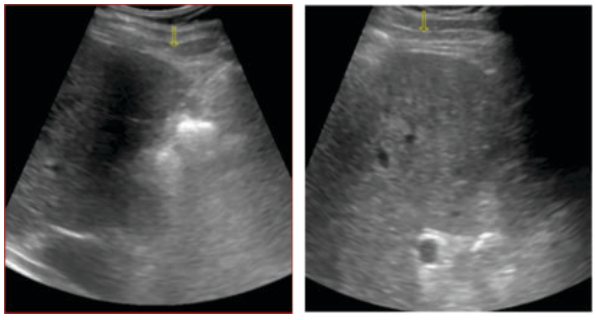

Fig 3 (a) **Fig 3 (b)**

Figure 3(a-b): USG B Mode probes showing parameters of liver edge **(a)** , surface **(b)** and parenchymal echotexture. The score for each parameter was given as 3 on high as well as low frequency probes. The cumulative score was 6 suggesting moderate fibrosis(yellow arrows). The corresponding liver biopsy showed Stage 3 (moderate) fibrosis for this patient.

The correlation between the cumulative USG score as well as score for individual parameters and stage of fibrosis is tabulated below:

Table 1: Correlation between the cumulative US score and fibrosis stage

Cumulative US score	Histopathological Stage			
	0+1	2+3	Total	Chi square test P
0-3	64	8	72	30.8,<0.001 HS
4+	0	28	28	
Total	64	36	100	

Table 2: Correlation between the score for liver edge and fibrosis stage

Liver edge score	Histopathological Stage				
	0+1	2+3	Total	Chi square Df=1	P
0+1	62	6	68	30.5	<0.001 HS
2	2	30	32		
Total	64	36	100		

Table 3: Correlation between the score for liver surface and fibrosis stage

Surface irregularity score	Histopathological Stage				
	0+1	2+3	Total	Chi square Df=1	P
0+1	64	8	72	30.8	<0.001 HS
2 +3	0	28	28		
Total	64	36	100		

Table 4: Correlation between the score for liver parenchymal echotexture and fibrosis stage.

Parenchymal echotexture	Histopathological Stage			
	0+1	2+3	Total	Fisher Exact Test P
0+1	64	26	90	0.004 Sig
2	0	10	10	
Total	64	36	100	

The cumulative US score had sensitivity of 100%, specificity of 77.7%, PPV of 88.9% and NPV of 100%. The parameter of liver edge score showed sensitivity of 96.8%, specificity of 83.3%, PPV of 91.1% and NPV of 93.7%. The liver surface score showed sensitivity of 100%, specificity of 77.7%, PPV of 88.8% and NPV of 100%. The parameter of liver parenchymal showed sensitivity of 100%, specificity of 27.7%, PPV of 77.7% and NPV of 100%.

DISCUSSION

The irregularity of liver surface has been shown to correspond to those of nodular regeneration for diagnosis of cirrhosis in patients of chronic liver disease. The sensitivity of liver surface nodularity has been shown to range from 82-100% and specificity from 54%- 89%[10,11,12,18].Our study has shown a comparable specificity and sensitivity regarding this parameter for detection of fibrosis in early stages being 77.7% and 100% respectively.

A common interpretation by various studies have been a single ultrasonographic parameter is limited in sensitivity and specificity for the diagnosis of early cirrhosis which can be detected using 2 or 3 quantitative and qualitative parameters with greater sensitivity and specificity[13,14,19,20].

There have also been studies proposing a scoring system on sonographic parameters. Study conducted by Hung et al[14] in 2003 used US score consisted of liver surface, parenchyma, vascular structure, and splenic size to describe the severity of hepatic parenchymal damage. US score of 7 was the best cut off point for the prediction of HBV-related cirrhosis, with sensitivity, specificity, positive predictive value and negative predictive value of 77.8% , 92%, 87.5% and 86.0% respectively. The US scores were significantly correlated with the hepatic fibrosis scores ($P < 0.05$) in their study. In our study also the cumulative scores showed significant correlation with the stage of fibrosis.

Few recent studies using low and high frequency probes[17]and parameters similar to our study[19,20]have shown statistically significant correlation coefficients ranging from 0.6668 (liver edge), 0.9007 (liver surface) and 0.8853 (parenchymal echotexture). In our study, the corresponding coefficients were 0.774, 0.870 and 0.753 respectively which is in agreement with the similar studies. Also, the accumulated US score of all the three parameters were found to be most reliable indicator (rs: 0.9524) with average sensitivity of 68.68%.,specificity of 53.6%. In our study, the sensitivity of cumulative US score was 100% and specificity of 77.7% in predicting upto mild fibrosis (stage 0 and 1) which is comparable to similar studies.

Therefore, it is likely that using sonographic parameters of liver edge, liver surface irregularity and parenchymal echotexture by appropriate high or low frequency probes can predict the stage of fibrosis in chronic liver disease with sensitivity at par compared with the gold standard of liver biopsy. The overall cumulative score of all these parameters can reliable predict early stages of fibrosis with sensitivity as high as 100%. Further, the absence of abnormal findings(NPV of 100%) in the sonographic examination can rule out the presence of fibrosis and in this subset of patients with chronic liver disease invasive procedure like liver biopsy can be replaced by ultrasonography.

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