Original Article

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FIBROSCAN: A NON INVASIVE TOOL FOR PREDICTING EARLY ESOPHAGEAL VARICES IN CHRONIC LIVER DISEASE SECONDARY TO HEPATITIS C VIRUS INFECTION

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ABSTRACT

Aim: To determine the values of liver stiffness measurement as a non invasive tool in predicting the early esophageal varices (EV).

Materials and Methods: This is a cross sectional comparative study carried out at MH Rawalpindi where 233 adults patients of hepatitis C, >20 and <80 years of age, were randomly included. All patients were subjected to endoscopy for esophageal varices and Transient Elastography for Liver Stiffness Measurement (LSM). The results were analyzed statistically using SPSS-17.0.

Results: The results showed that the optimal cut off point of LSM for predicting presence of esophageal varices (EV) is ≥18.82±4.42kpa with sensitivity 91% (95% CI 84-95%), specificity 71% (95% CI 67-78%), PPV 84% 95%CI 77-90%), NPV 82% (95% CI 78-84%) and AUROC value 0.76 .The optimal cut off values 31.53kpa± 7.76kpa and 46.21kpa±10.96kpa predicts for presence of large varices (≥F2, ≥F3 respectively) with AUROC value 0.83 and 0.94. Child Pugh score A for absence and B for presence of EV (≥F1) has sensitivity 83%, specificity 53%, PPV 67% and NPV 78% with AUROC value 0.67 which is lower than LSM 18.84kpa AUROC value of 0.76 (p <0.003).

Conclusion: Liver stiffness measurement is a reliable screening method which can help in patient's selection for endoscopy with high probability of EV, thus avoiding unnecessary endoscopies.

Keywords: Child Pugh, Cirrhosis, Esophageal Varices, Hepatitis C, Liver Stiffness.

INTRODUCTION

Cirrhosis is the end result of almost all progressive chronic liver diseases. Approximately 60-80% patient suffering from active chronic hepatitis C infection present with clinical features of liver cirrhosis and its complications[1]. Increased liver stiffness is a recognized hallmark of cirrhosis for centuries. Transient Elastography (TE) makes it easier to translate the feeling of hard liver into numerical measurement in a totally non invasive way[2].

Development of esophageal varices (EV) is an important consequence of chronic liver disease and it develops at a rate of 5% per year. The development of EV is a clinically silent process and currently there is no effective non invasive method of screening early EV. For this reason, the Beveno IV, consensus report recommended screening of all cirrhotic patients with endoscopy for EV[3].

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But a generalized program of endoscopy is neither cost effective nor hazard free. For these reasons various non-invasive screening modalities have been proposed for patients with high probability of EV, but they are poorly discriminative and are hardly useable in clinical practice. Fibro Scan is a non invasive and a simple parameter of detecting the degree of liver stiffness and its various cut off values can predict the presence of early and large EV with significantly high sensitivity and specificity and thus may help to select the patients requiring endoscopic screening, and limiting unnecessary endoscopies[4].

The risk of upper gastro intestinal (UGI) bleed is clearly related to the size of EV. Hence primary prevention applies to all those previously diagnosed with large EV by upper GI endoscopy. A generalized program of repeated upper GI endoscopy to detect early EV is not only cumbersome but a costly event for developed countries. Liver stiffness (LS) measurement may allow prediction of presence of early and large esophageal varices (EV) in patients with liver cirrhosis[5].

This study was designed to assess the efficacy of liver stiffness measurements by Fibroscan in predicting early and large esophageal varices in patients with chronic hepatitis C.

MATERIAL AND METHODS

The study was conducted in the Department of Gastroenterology at Military Hospital Rawalpindi from 12th January 2011 to 17th March 2011.

Patients fulfilling following inclusion criteria were inclueded, adult patients suffering from chronic hepatitis C virus infection, patients of Child- Pugh class A, B and C and BMI <30.

While patients with chronic liver disease other than hepatitis C viral infection, gross obesity (BMI>30) and gross ascities with positive fluid thrill, portal vein thrombosis and Budd Chiari syndrome were excluded.

A total of 310 patients positive for chronic hepatitis C virus infection were selected using non probability consecutive sampling from all outdoor and indoor departments of Military Hospital and Combined Military Hospital Rawalpindi. All patients were clinically assessed and subjected to lab tests for serum bilirubin, ALT, albumin, prothrombin time, platelets count and abdominal sonography and were classified in Child Pugh class A, B and C. Only 249 patients met the inclusion criteria and out of them 16 patients did not report and the rest 233 were subjected to the study. About 10-15 patients were called upon in endoscopy unit daily where endoscopy was performed by GIF 160 Olympus endoscope by 4 experienced endoscopists.

Endoscopy findings were classified according to the guide lines of the American Association of Study of Liver Disease (AASLD) as follows.

- Grade 0 (F0)—no varices
- Grade 1 (F1)---small straight sub mucosal veins
- Grade II (F2)---enlarged tortuous veins occupying <1/3 of esophageal circumference
- Grade III (F3)---large coiled shaped veins occupying >1/3 of the luminal circumference

The Fibroscan (Echosense, Paris) was used for the measurement of liver stiffness and METAVIR scoring system was used for calculating liver stiffness measurement (LSM) values ranging from 3.5-75 kilopascals (kpa) with normal liver stiffness value 5.5 kpa and LS value 7.1 kpa was considered for exclusion of fibrosis. The Fibroscan was placed in the endoscopy unit in a separate room. Both the endoscopists and fibroscan operator were blind of each others findings. Liver Stiffness (LS) measurements were performed by one independent operator in the right lobe of liver through intercostal space with patient lying in dorsal decubitus position and right arm in full abduction. The tip of transducer was covered with coupling gel and placed on the skin in the intercostal space at the level of right lobe of liver. The operator located a portion of liver about 6 cm thick devoid of vasculature for the measurement. Once the area had been selected the operator pressed the button for measurements. Ten successful measurements were performed in each patient and the success rate was calculated by as the ratio of number of successful measurements over the total number of acquisitions. The results were expressed in kilopascals and the median value of successful measurements was considered as representative of LSM. Only LS measurements with success rate (SR) >60% and inter quartile ratio IQR <30% were considered reliable.

Statistical Analysis

The relation between LSM and presence of early and large esophageal varices was studied. The collected data was analyzed using the statistical microsoft package SPSS 17.0. Quantitative variables with normal distribution were expressed as mean ± standard deviation (SD). Mann Whiteny (U) test was applied to analyze variables that were not normally distributed and student t-test was applied to analyze variables that were normally distributed. Qualitative data were expressed as numbers and percentage. The diagnostic performance of LS by using Receiver Operating

Characteristic (ROC) curve. ROC curves were plotted as sensitivity over (1-specificity) for each parameter and Area Under Receiver Operating Characteristic (AUROC) was calculated. The optimal cut off values were chosen to maximize the sum of sensitivity and specificity. The correlation of Child Pugh scores for predicting no/early and large (≥F2) EV was also assessed and a *p*-value of <0.05 was considered to be statistically significant.

RESULTS

Results of the overall patients' characteristics are shown in table-1

The demographic results of patients showed that 121(52%) patients were male and 112 (48%) were female with mean age of the patients is 48±12 years. Out of 233 patients 99 (42%) were in Child class A, 84 (36%) were in Child Pugh class B and the rest 50 (21.5%) were in Child class C. Out of 233 patients 77 (33%) have no esophageal varices, 52 (22.3%) have grade I (F1) varices and the rest 104 (46.7%) have grade II (F2) or more (>F2) varices as shown in the table-1. The mean values of liver stiffness measurements (LSM) with their standard deviations (SD) for predicting the various grades of esophageal varices were determined as shown in table-3, fig-1. The mean value of LS in patients (n=129) with no varices (F0) or small varices (F1) is significantly lower (24.36±3.42 kpa) than LS value (56.34±7.56 kpa) in patients (104) with large (F2) varices (p<0.001)The best optimal cut off value of fibro scores (LSM) for the presence of early (F1) esophageal varices was 18.82±4.68 kpa and it had 91% sensitivity (95% CI 84-95%), specificity 73% (95%CI 67-78%) with positive predictive value (PPV) 85% (95% CI 77-90%) and negative predictive value (NPV) 92% (95% CI 78-84%) and AUROC value is 0.76 (p<0.003) (table-4 and fig-2a). Similarly the optimal cut off value of liver stiffness values (LSM) 31.53±7.76 kpa and LSM 46.21±10.7kpa studied for the presence of grade II (F2) and grade III (>F2) EV respectively and their sensitivity, specificity, NPV and PPV values are in tab-5 and AUROC values in fig-2b and 2c.

Similarly Child Pugh class has significant correlation (p=0.005) with the presence of esophageal varices but it is less sensitive as compared to LSM value for prediction of EV. The overall results indicate that fibroscan is a useful non invasive tool for screening patient with significantly good predictive value for presence of early EV and high predictive value for large EV.

DISCUSSION

Transient Elastography (TE) (FibroScan,

Table-1: Patient characteristics (mean age ± SD = 48±12).

	No	Percentage
Sex		
Male	121	52
Female	112	48
Child Pugh class		
A	99	42.5
B	84	36
C	50	21.5
State of esophagegeal varices		
F0	77	33
F1	52	22.3
≥F2	104	46.7

Table-2: Correlation of Child Pugh with EV.

Grades of varices	No Varices (F0)	Small varices (F1)	Large varices (≥F2)	Total	p-value (student t-test)
	n=72	n=52	n=104	n=233	
Child Pugh class					
A	45	24	30		<0.002
B	24	17	43		<0.005
C	08	11	31		<0.005

Echosens, Paris, France) is a novel technique that allows measuring liver stiffness and it can easily be performed at the bedside or in the outpatient clinic with readily available results. They are expressed in kilopascals (kPa) with normal liver stiffness values around 5.5 kPa. Thus, using a cut off of 7.1 kPa significant fibrosis and cirrhosis can be excluded with a very high negative predictive value (NPV)[6]. Positive predictive value (PPV) for the diagnosis of cirrhosis is lower using just a single scan but increases to 90% if high stiffness values are confirmed by a second independent scan. However the presence of fatty liver, acute liver injury and metabolic syndrome slightly increases the readings with the risk of overestimating liver stiffness values[7,8]. Another advantage of TE is that the liver stiffness values correlate with disease severity[9].

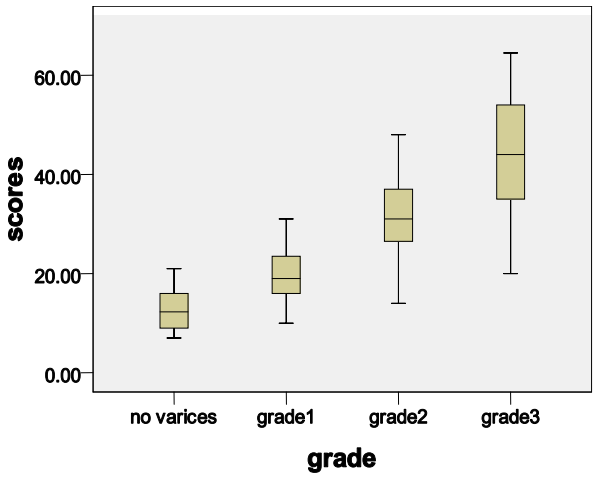


Fig. 1: Liver stiffness values for each grade of esophageal varicess. Box express the mean values and overall ranges.

Table-3: Correlation of LSM with EV and Child Pugh class

Studied parameter		No	LSM	U-test	p-value
Grade of varices	F0	77	15.5±2.14		<0.0001bet
1,2 & 3	F1	52	21.36±4.27	18.54	<0.0001bet
2 & 3	≥F2	104	36.18±6.76		
Child Pugh Class	A	99	24.71±13.74		
Bet 1, 2 & 3	B	84	33.32±14.62	40.56	<0.0002 bet
2 & 3	C	50	52.38±18.67		

Table-4: Predictive values of different LSM cut off point for EV.

Cut off value (LSM)	Sensitivity	Specificity	NPV	PPV	AUROC
13.46kpa	91%	54%	71%	87%	0.63
18.52kpa*	91%	73%	85%	92%	0.76
26.64kpa	81%	86%	89%	76%	0.58

EV(Esophageal Varices),PPV(Positive Predictive Value),NPV(Negative Predictive Value),AUROC(Area Under Receiver Operator Curve). *best cut off value for prediction of early EV.

Table-5: Optimal cut off values for various grades of EV

State of EV	LSM (kpa)	Sensitivity	Specificity	NPV	PPV	AUROC
F1	18.82+_4.68	91%	73%	85%	92%	0.76
F2	31.6 +_7.76	92%	78%	96%	75%	0.84
F3	46.21+_10.7	91%	96%	96%	67%	0.94

Various studies of TE for predicting portal hypertension and esophageal varices has proposed a wide range of cut offs, varying from 13.9 to 21.3 kPa for small EV (≥F1) and from 19 to 30 KPa for large (≥F2) esophageal varices(EV) [9]. In some studies, LS values < 19 kPa were highly predictive of the absence of significant EV (≥F1) whereas, the cut off values for presence of significant varices (≥F2) ranging from 27.5 to 35kPa were proposed and the cut off value of 62.7kPa suggested the presence of large varices with high risk of bleeding[10]. Our study results suggest that the LSM value of >18.82 kpa predicts presence of esophageal varices with 91 % sensitivity, 71% specificity, with PPV 84%, NPPV 81% and AUROC value 0.76. The cut off value 31.42 kpa predicts for large EV(≥F2) and significant liver cirrhosis

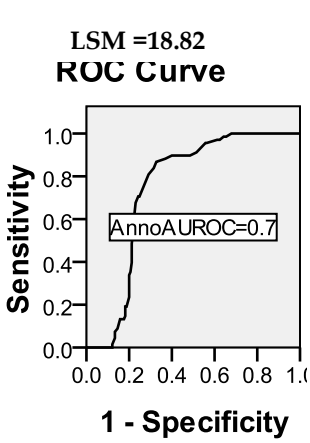


FIG-2(a)

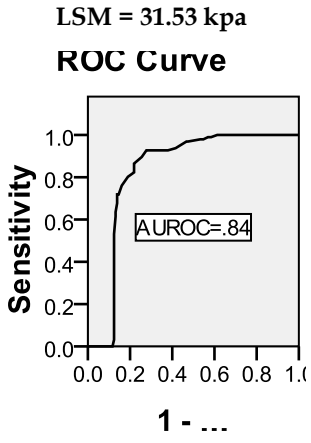


FIG-2(B)

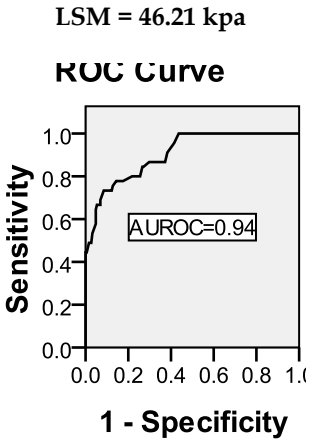
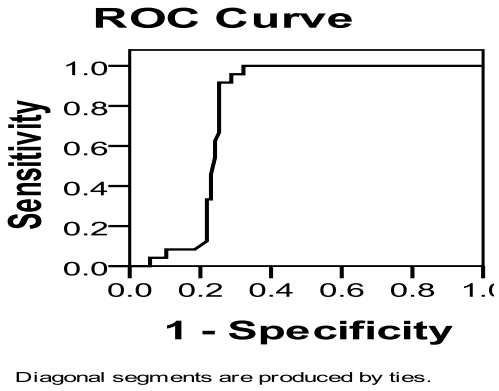
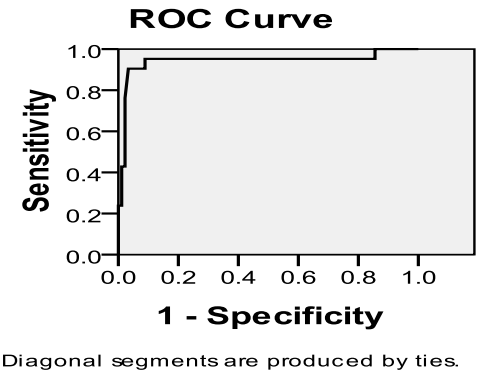


FIG-2(c)





with 92% sensitivity, 78% specificity, PPV 75% NPV 96% and AUROC value 0.84 whereas cut off value 46.21 kpa predicts for the presence of large(≥F3)) EV with 91% sensitivity, 96% specificity PPV 67% NPV 96% and AUROC value 0.94.

Kezmi et al found in their analysis that values of LSM by TE are highly predictive of the presence and the size of esophageal varices. They concluded that value below 19kpa has very low risk of bearing large EV which is close to our study[11]. Another study by Jang et al concluded that LSM cut off value above 19.7 kpa predicts the presence of early EV (F1) and cut off value 42.7 for large (≥F2)) EV[12]. Sporea et al support these observations by predicting the LS score of >31kpa for the presence of large (≥F2) EV[13].

Data from literature is inconclusive due to multiple reasons. Conditions such as metabolic syndrome and etiology of liver cirrhosis affect the liver stiffness value. Castera et al studied that patients with chronic hepatitis C and the same stage of fibrosis had increased liver stiffness if they had concomitant fatty liver[14]. The optimal values cut off of LSM, therefore vary and are still to be re-defined in fatty liver[15]. Raised liver transaminase level during acute on chronic phase also increase liver stiffness[16].

Mele et al concluded in his study that TE is a valuable tool for predicting early esophageal varices and portal hypertension with high sensitivity and specificity (71%-96% respectively), but moderate positive and negative predictive values[17]. Another study assessed the correlation between LSM values and HVPG in diagnosing significant portal hypertension in 150 patients. The cut off value of 21 kpa accurately predicted significant portal hypertension in 92% of patients for whom HVPG measurements were successful[18].

The sensitivity and specificity of Child Pugh scores is less in predicting EV as

compared to fibroscan scores (p<.0005). The mean liver stiffness values were 24.71±,10.74 kpa 33.32 ± 13.61kpa and 52.38 ± 18.67 kPa in Child Pugh class A, B and C patients respectively, with a significant correlation between liver stiffness and the Child-Pugh scores (p<.005). The more advanced the liver disease (as reflected by Child-Pugh scoring), the stiffer the liver tissue will be. In a study by Foucher et al. Child score B or C was one of the independent factors associated with LSM > 50 kpa[19].

CONCLUSION

LSM has reasonably good predictive value for EV. Therefore, it is reasonable to recommend endoscopic screening to determine early EV and deciding prophylactic therapy (banding, β-blocker) in patients with chronic liver disease with high LSM value. On the other hand, in patients with LSM values < 18 kPa, chances of significant esophageal varices are less therefore these patients should not be subjected to unnecessary endoscopies and do not require prophylactic therapy for EV.

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