ORIGINAL ARTICLES

Prediction Of Oesophageal Varices In Cirrhotic Patients By Measuring Liver Stiffness With Fibroscan.

Shahinul Alam[1], Ahmed Lutful Moben[2], AKM Khorshed Alam[3]

[1] Associate professor, [2] Resident, [3] Chairman & Professor, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Abstract:

Background : Repeated endoscopy is required to detect & follow up of esophageal varices (OV) in cirrhotic patients. **Objective :** For discomfort and unwillingness to do the endoscopy directed us to evaluate liver stiffness measurement (LSM) for the prediction of OV. **Methods:** A cross sectional observational study was conducted between July'2010 to July'2011. A total of 50 patients with cirrhosis were divided into three groups. Group-I patients had no varix (n=4), group-II had Grade-I OV (n=23) and group-III had Grade-II/III OV (n=23) at endoscopy. Liver stiffness was measured by fibroscan & data was analyzed by SPSS. **Results :** Mean age were 35.20 ± 11.36 years with highest frequency 19 (38 %) in 21-30 years age group. Etiologies were different with leading causes includes HBV (76%) followed by HCV (6%), alcohol (2%) and 14% were unknown. Liver stiffness did not significantly differ from group-I & group-II, but was significantly higher in group III than group-II & group I. Liver stiffness was not accurate in the prediction of grade-I oesophageal varices [Area under the curve (AUC)] = 23.6%. Liver stiffness at a cut off value 32.52 kPa with sensitivity, specificity, positive predictive value, negative predictive value, accuracy respectively 82.6%, 77.8 %, 76 % , 84%, 80% can predict the Grade-II-III oesophageal varices (AUROC = 85.2%). **Conclusion:** Liver stiffness may be suitable for prediction of Grade-II-III oesophageal varices, not for the screening of the presence of oesophageal varices.

Key Words : Oesophageal varices, Liver stiffness measurement, Cirrhosis of liver.

Introduction:

Portal hypertension and its consequences are progressively debilitating complications of cirrhosis. Variceal hemorrhage is the most common lethal complication of portal hypertension. Presence of oesophageal varices (OV) correlates with the severity of liver disease; while only 40% of Child A patients has varices, they are present in 85% of Child C patients[1]. Patients without varices develop them at a rate of 8% per year[2,3]. Variceal hemorrhage occurs at a yearly rate of 5%- 15%, and the most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices[4]. It is recommended that patients with cirrhosis undergo endoscopic screening for varices at the time of diagnosis[5] and needs periodic follow up to predict development or progression of OV. So, repeated endoscopy is necessary for the treatment of patients with cirrhosis of liver.

Upper GI endoscopy is the gold standard to detect oesophageal varices. Repeated endoscopy is also poorly accepted by some patient, particularly when done without profound sedation. For this reason some patient refuses further follow up. Besides, it is difficult to perform repeated screening endoscopy in patients with some comorbid conditions like severe respiratory disease, cardiac arrhythmia, atlanto-axial subluxation etc. In these circumstances a non-invasive marker is to predict esophageal varices become concern to researcher now a day.

Transient elastography is an emerging technology that is more sensitive for staging hepatic fibrosis. This technique rapidly and noninvasively measures mean hepatic tissue stiffness[6,7]. Hepatic stiffness is related to the degree of fibrosis.

Address for Correspondence: Dr. Md. Shahinul Alam, Associate professor Department of Hepatology, Bangabandhu Sheikh Mujib Medical University Telephone: 01973007173. E-mail address: shahinul67@yahoo.com.

grade – I oesophageal varices (Fig-I). Grade II-III oesophageal varices can be predicted by considering cut off value as 32.35 kPa , sensitivity-82.6 %, Specificity 77.8 % , PPV 76 %, NPV 84%, Accuracy 80% (Fig-II). Here AUC was 85.2%. Fibroscan value of group-III is significantly higher than group-I and group-II.

Discussion :

In current study, utility of LSM by fibroscan is evaluated for the prediction of complications of cirrhosis particularly oesophageal varices in 50 cirrhotic patients. LSM by fibroscan can be useful for the prediction of increased portal pressure in cirrhosis. Eighty four percent patients belongs to Child A, 14% Child B and 2% Child C in this study. Ascites was one of the exclusion criteria therefore number of Child B/C patients were less enrolled. Mean age of the patients found (35.20 ± 11.36) years with the highest frequency at 21-30 years age group (38%). It may be due to early exposure of the subjects to HBV during perinatal period and consistent with finding 93.2% patients of CHB were less than 40 years[9]. Ninety eight percent of the cirrhotic patients were male. Though there is male predominance (4.6: 1) for CHB in Bangladesh[9].But, it does not explain such sex distribution.

Etiology of cirrhosis were different with leading cause HBV (76%) followed by HCV (6%), alcohol (2%) and in remaining 14% causes were unknown. Afroze et al[10] also found HBV as a leading cause of cirrhosis 61.15% in Bangladesh. In present study three (6%) patients were positive for anti-HBc (Total), negative for HBsAg. Two out of three were also positive for HBV-DNA (PCR). Chung et al[11] concludes HBV infection can persist even after the loss of hepatitis B surface antigen (HBsAg). Such patients demonstrated persistent HBV infection in serum and liver tissue of HBsAg-negative cirrhosis. Such phenomenon is particularly seen in areas where HBV infection is prevalent and therefore a substantial number of HBV-related liver diseases may be missed if HBsAg alone is used for the diagnosis in such areas. These are occult HBV.

LS positively correlates with size of the OV, S. bilirubin and negatively correlates with S. albumin, but there is no correlation with INR and platelet count. Zakareya et al[12]

describe LSM by fibroscan had negative correlation with S. albumin and platelate and a positive correlation with S. bilirubin and INR. Foucher et al[8] reported that the lower the serum albumin and platelet count and the higher the serum bilirubin and INR, the higher the liver stiffness. Increased liver stiffness significantly correlates with the stages of fibrosis[8] and reflects the increased hepatic vascular resistance that leads to portal hypertension in cirrhosis[13]. Fibroscan value differs from Group-I to Group-III (P = 0.004) and Group-II to Group-III (P = 0.000), not from Group-I to Group-II (P = 0.725) (Table-I).

In the current study found LSM by Fibroscan was not accurate in the prediction of grade-I oesophageal varices (AUROC = 23.6 %). Vizzutti et al[14] reported that LSM positively correlated with the presence of esophageal varices and determined 17.6 kPa as a cutoff value for the prediction of esophageal varices with a sensitivity of 90%. In contrast, Lim and Groszmann et al[15] reported that liver stiffness was not accurate in the prediction of esophageal varices. Castera et al[16] concluded that although transient elastrography could be a valuable tool for the detection of esophageal varices using a cut-off of 21.5 kPa with 76% sensitivity and 78% specificity, it cannot replace endoscopy for screening for varices.

LSM by Fibroscan at a cut off value 32.52 kPa with sensitivity, specificity, PPV, NPV , accuracy respectively 82.6%, 77.8 %, 76 % , 84%, 80% can predict the Grade-II & III oesophageal varices (AUROC = 85.2%). Foucher et al[8] reported a cut off value (27.5 kPa) for the presence of esophageal varices grade II/III with sensitivity 88%, specificity 53%, PPV 45% and NPV 90%. Kazemi et al[17] reported that liver stiffness measurement value < 19 kPa was highly predictive of the absence of esophageal varices grade $\geq$ II with sensitivity 84%, PPV 47% and NPV 93%. In contrast, Vizzutti et al[14] found no correlation between LSM and the size of the varices and limited the value of fibroscan in predicting the presence of the varices per se.

Conclusion :

This study has shown that liver stiffness can predict Grade-II & III oesophageal varices, but failed to predict

Fibroscan is painless, rapid (it takes less than 5 minutes) and easy to perform at the bedside or in the out patients clinic. The examination is performed on a non-fasting patient lying flat on his back. Given its excellent patient acceptance and simplicity; fibroscan may also be a useful tool for the screening of high-risk populations. Fibroscan may also be a valuable tool in the screening of high-risk populations (such as alcohol abusers, drug users and diabetics) to identify patients with liver disease.

Predicting the presence of oesophageal varices by noninvasive means would restrict the performance of endoscopy to those patients with a high probability of having significant varices. Establishing the value of LSM by fibroscan to predict the presence of varices, particularly more than grade-I (Grade II or III) varices, will pinpoint patients who will require closer follow up and endoscopic screening and who will require follow up and endoscopic screening less frequently. So, liver stiffness may be evaluated with fibroscan as a non-invasive predictor of oesophageal varices in cirrhotic patients.

Methods :

A cross sectional observational study was conducted to evaluate the liver stiffness measurement by fibroscan for the prediction of oesophageal varices found in upper GI endoscopy in patients with cirrhosis of liver in the Department of Hepatology, BSMMU, Dhaka between July'2010 and July' 2011. A total of 50 patients of cirrhosis of liver with and without esophageal varices were enrolled for the study. Liver stiffness measurement (LSM) was done by fibroscan within seven days of performing upper GI endoscopy. The patients were divided in three groups. Group-I includes patients with cirrhosis of liver but had no varix (n= 4), Group-II includes patients with cirrhosis of liver with G-I oesophageal varices (n = 23) and Group-III includes patients of cirrhosis of liver with G-II/III oesophageal varices (n = 23) at upper GI endoscopy. For group-I total of 21 patients with suggestive feature of cirrhosis were provisionally selected. After full explanation and written consent, liver biopsies were done. Among them histopathology describe 4 patients as cirrhosis and they are enrolled for the study. 15 out of rest 17 reveal F3 fibrosis 2 patients reveals F1 fibrosis. All collected were data recorded in a structured questionnaire and analyzed by SPSS (version 17), Pearson's correlation & comparison between the groups was done by one way ANOVA (Hochberg's and Games-Howell tests). Receiver operating characteristic (ROC) curve was constructed to determine the cut off values of fibroscan for the prediction of presence and size of oesophageal varices at different groups. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the tests were expressed in percentages.

Results:

The age range of the cirrhosis patients was 18-70 years and the mean age was (35.20 ± 11.36) years. The highest frequency of cirrhosis patients was found at 21-30 age groups. Thirty eight patients (76%) of cirrhosis were HBV related among them three patients had occult HBV infection. HCV related (anti-HCV positive) cirrhosis were 3 (6%), alcoholic cirrhosis were one (2 %), Wilson's disease was one (2%) and in rest of the seven (14 %) cases causes were unknown. Patients of cirrhosis due to unknown etiology were negative for HBsAg, anti-HCV, anti-HBc total, ANA, slit lamp examination for K-F ring and urinary copper < 100 µg in 24 hrs. Four of them were diabetic indicates a possibility of NAFLD in a certain proportion of unknown etiology of cirrhosis of liver. Among the 50 cases 42(84%) was Child class A, seven (14 %) were Child B & one (2%) were Child-C.

There was no significant (p >0.05) difference in laboratory parameters S. bilirubin, S. albumin, INR, platelet count and LSM by fibroscan between Group-I and group II. On the other hand S. albumin is lower and Fibroscan value is higher in Group-III in comparison to Group-II (P < 0.05) (Table-I). There was no significant difference in S. bilirubin, INR, and platelet count between these two groups.

Liver stiffness (LS) positively correlates with size of the OV (P = 0.000), S. bilirubin (P = 0.04) and negatively correlates with S. albumin (P = 0.000), but there is no correlation with INR (P = 0.492) and platelet count (P = 0.483).For prediction of grade-I OV, AUC were 23.6 % and found sensitivity, specificity 56.5 %, 18.5 % respectively considering cut off Value as 16.4 kPa to predict

Grade-II & III oesophageal varices, but failed to predict presence of Grade-I oesophageal varices. So, LSM by fibroscan may be suitable for prediction of Grade-II & III oesophageal varices, not for the screening of the presence of oesophageal varices.

Table-I

Comparisons of laboratory parameter between Group-I and Group-II.

	Group-I	Group-II	Group-III	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
S.Bilirubin (mg/dl)	1.30 ± 0.73	1.48 ± 0.88	1.79 ± 1.88	0.48
S.Albumin (gm/dl)	3.72 ± 0.68	3.23 ± 0.75	2.95 ± 0.62	0.03*
INR	1.18 ± 0.10	1.34 ± 0.27	1.41 ± 0.33	0.12
Platelet count (×10³/cu mm of blood)	120 ± 62	180 ± 89	135 ± 54	0.47
Fibroscan value (kPa)	14.57 ± 8.88	23.80 ± 17.55	48.18 ± 19.64	0.00*

One Way Anova test was done. $P < 0.05$ was considered as significant.
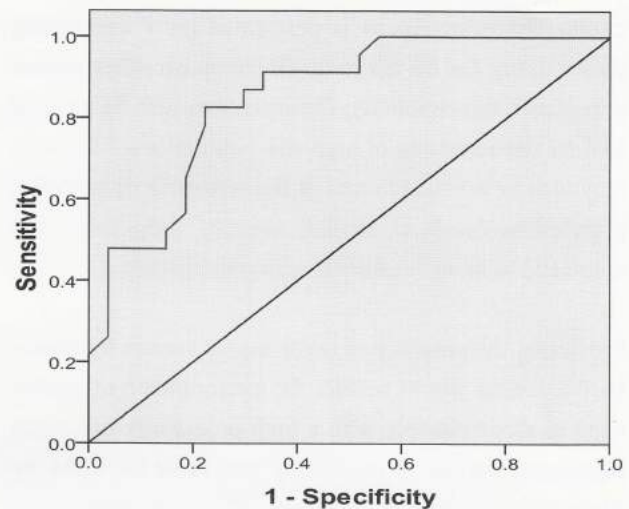

ROC Curve
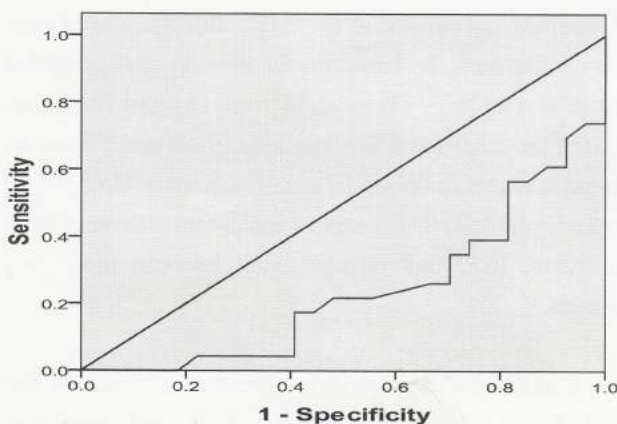
Diagonal segments are produced by ties.

Fig-1: *ROC curve to determine the cut off value of liver stiffness for the prediction of Grade-I Oesophageal varices.*

ROC Curve

Diagonal segments are produced by ties.

Fig-2: *ROC curve to determine the cut off value of liver stiffness for the prediction of Grade-II-III Oesophageal varices.*

References

1. Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis. Natural history. In: Bosch J, Groszmann RJ, editors. Portal Hypertension, Pathophysiology and Treatment: Oxford:Blackwell Scientific; 1994 .p. 72–92.

2. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. β-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med.2005; 353: 2254-2261.*

3. Merli M, Nicolini G, Angiolini S, Rinaldi V, De santis A , Merkel C. Incidence and natural history of small varices in cirrhotic patients. J Hepatol. 2003 ; 38: 266-272.

4. Brocchi E, Calrtti G, Brombilla G, Mantia LL, Lupinacchi G, Pisano G, et al. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med.1988; 319:983-989.*

5. Grace ND, Groszmann RJ, Garcia-Tsao G, Burroughs AK, Pagliaro L, Makuch RW, et al. Portal hypertension and variceal bleeding: an AASLD single topic symposium. *Hepatology.1998;28:868-880*

6. Sandrin L, Tanter M, Catheline S, Fink,M. Shear modulus imaging with 2D transient elastography. IEEE *Trans Ultrason Ferroelec Freq Control. 2002; 49: 426–435.*

7. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal,F, Christidis C, et al.Transient elastogaphy: a new noninvasive method for assessment of hepatic fibrosis.*Ultrasound Med Biol.* 2003; 29:1705-13.

8. Foucher J, Chanteloup E, Vergniol J, Carstera L, Bail BL, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (Fibroscan): a prospective study. *Gut.2006;55: 403- 408.*

9. Alam S, Ahmad N, Mustafa G, Alam K, KhanM. Characteristics of treatment naive chronic hepatitis B in Bangladesh: Younger populations are more effected; E antigen   are more advanced. *Saudi J Gastroenterol.2008;14: 15-19.*

10. Afroz S, Mahtab MA, Rahman S, Khan M. Hepatitis B virus is the leading cause of cirrhosis of liver in Bangladesh. *Hepatol Int.* 2007;1:120.

11. Chung HT, Lai CL, Lok AS. Pathogenic role of hepatitis B virus in hepatitis B surface antigen-negative decompensated cirrhosis.*Hepatology.*1995; 22: 25-9.

12. Zakareya T, Razek WA, Allam N, Gabal AA, Rewisha E, Waked I. The Utility of Transient Elastography in Predicting Complications of Chronic Liver Disease. *Nile liver journal.* 2010; 1: 49 – 57.

13. Hernandez-Guerra M, Garcia-Pagan JC, Bosch J. Increased hepatic resistance: a new target in the pharmacologic therapy therapy of portal hypertension. *J Clin Gastroenterol.*2005;39: S131–S137

14. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colarende S,et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology.* 2007; 45: 1290-1297.

15. Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? *Hepatology.* 2007; 45:1087-1090.

16. Castera L, Vergniol J, Foucher J, Bail, B, Chanteloup E, Haaserand M,et al. Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessment of fibrosis in chronic hepatitis C.Gastroenterol.2005;128: 343–50.

17. Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Trinchet J, Beaugrand M, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large esophageal varices. *J Hepatol.* 2006; 45: 230-235.