Use of Non-invasive markers in Predicting the Severity of Esophageal Varices in Liver cirrhosis: A Hospital Based Descriptive Observational Study

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Abstract

Introduction: Esophageal varices in patients with cirrhosis have serious clinical consequences. Though invasive, endoscopy is the gold standard for screening varices. Noninvasive tests are used to reduce the unnecessary endoscopies. The aim of the study was to assess the noninvasive markers of esophageal varices in cirrhotic patients.

Methods: This descriptive study analyzed eligible cirrhotic from January to June 2019. Clinical and laboratory parameters were assessed to grade the high risk varices according to severity of cirrhosis. Liver stiffness was measured by fibroscan and shear wave elastography. Analysis of these parameters was done to predict severity of esophageal varices.

Results: Seventy five patients were included, where the incidence of large and high-risk esophageal varices were 69% and 77% respectively. Independent predictors of large varices were splenic diameter >120 mm, portal vein diameter >13 mm, transient elastography ≥20 kPa and platelet count spleen diameter ≤909. The predictors for high-risk varices were shear wave elastography ≥22 kPa, platelet count spleen diameter ≤909 and liver stiffness-spleen size-to-platelet ratio risk score >2.2. The sensitivity, specificity, positive predictive value and negative predictive value for prediction of large varices were similar.

Conclusion: Strong noninvasive predictors were spleen size, portal vein diameter, transient elastography, platelet count spleen diameter ratio for large varices and shear wave elastography, platelet count spleen diameter ratio and liver stiffness-spleen size-to-platelet ratio risk score for high-risk varices. These parameters can be used to avoid unnecessary endoscopy and in resource limited settings.

Keywords: Esophageal varices, Splenomegaly, Portal vein, Transient elastography, Shear wave elastography

Introduction

Cirrhosis is the most common cause of portal hypertension leading to development of esophageal varices (EVs). EVs are present in almost fifty percent of cirrhosis patient at diagnosis.[1] The portal venous system decompresses into the systemic venous system mostly at distal esophagus and proximal stomach and rarely at other gastrointestinal sites. Varices are more common in Child-Pugh class C compared to Child-Pugh class A patients (85% versus 40%).[2] The rate of development and increase in grades of varices is 8% per year; the former is largely predicted by a hepatic venous pressure gradient (HVPG) >10 mm Hg and continuing

injury to liver.[3] The risk of first hemorrhage is 5–15% per year, highest with larger varices, severe liver disease and presence of endoscopic red wale signs with 20%-80% mortality depending on presence or absence of other decompensating events.[4]

Noninvasive markers are currently in use, and given resource limitations, cost, and availability, various societies recommend them to predict the varices with good reliablity.[5] Low platelet count, large spleen diameter, platelets count to spleen diameter ratio, Child Pugh Class (CTP) B/C and portal vein diameter are independent predictors for the presence of varices.[6,7] Upper gastrointestinal endoscopy (UGIE) remains the gold standard for screening for esophageal varices[6] but is invasive and is not readily available in many primary centers in our country. This study assesses the noninvasive predictors of esophageal varices to determine the severity of esophageal varices.

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Methods

This is a hospital based, prospective, descriptive observational study done at gastroenterology and liver units of Bir Hospital after ethical clearance from institutional review board. All patients ≥18 years diagnosed as liver cirrhosis with esophageal varices on UGIE were included regardless of etiology. Age <18 years, who refused to give consent, with ascites, non-cirrhotic portal hypertension, current or past treatment with beta-blockers, thrombocytopenia due to other causes, hepatocellular carcinoma and patients with endoscopic therapy were excluded. Clinical parameters assessed included Child-Pugh class (CTP), ascites and splenomegaly. Hemoglobin level, platelet count, international normalized ratio (INR), serum bilirubin, albumin as laboratory tests and splenic size, splenic vein diameter, portal vein diameter by ultrasonography were assessed.

The size was assessed during withdrawal of the endoscope and was defined as small if <5 mm or large if ≥5 mm in diameter. The low-risk varices were defined as small varices (for Child A and B cirrhosis). High-risk was defined as a) small varices with red color signs or b) large varices with or without red color signs (for Child A and B cirrhosis) and c) varices of any size with or without red color signs (for Child C cirrhosis).[8] The physical, biochemical and radiological parameters were then evaluated for their role as non-invasive predictors of large and high-risk EVs. Complete blood count was done by automated cell counter, Sysmex 550. Peripheral blood smear was done to rule any other hematological cause of thrombocytopenia. Liver function tests was done by Erba XL 300, automated analyzer. Prothrombin time and international normalized ratio were also calculated. All the blood investigations were verified by the pathologist before being dispatched.

The liver stiffness measurement (LSM) was done by 2-dimensional shear wave elastography (SWE) at gastroenterology unit and by TE (Fibroscan) at liver unit of Bir Hospital. The LSM was measured by both these methods on all patients. SWE value of ≥22 kPa and TE value of ≥20 kPa were used to predict the size and severity of esophageal varices. Real-time SWE studies were performed using the Aplio 400 system, Toshiba (Toshiba Medical Systems, Japan). TE was carried out by using FibroScan (Echosens, Paris, France), a dedicated medical device that provides a quantifiable estimate of liver stiffness (kPa).

APRI score is an index ratio of AST (aspartate aminotransferase) and platelets count. [(AST / ULN AST) x 100] / Platelets (109/L)]. A cut-off score value > 1.3 was used to predict the presence of large or high-risk EVs.[9] Platelet count spleen diameter (PC/SD) ratio was calculated by dividing the platelets count per mm^3 by splenic diameter measured in mm with a cut-off value of ≤909 to predict the size and severity of EVs.[10] The LSPS (Liver stiffness-spleen size-to-platelet ratio risk score) was calculated by TE (kPa), spleen size and platelet count (×103/mm3) with value >2.2 to predict the presence of severe varices.[11]

All statistical calculations were performed with SPSS version 20.0 for Windows. Differences between the two groups with continuous data were assessed using student-t test for normal and Mann-Whitney U test for non-normal distributions. Qualitative data were described using percentages and compared by the chi square, using Fisher test when needed. Logistic regression analysis was used to calculate the significant differences, if found, between the two groups in terms of outcome. Univariate and multivariate analysis was done on the data for predictors of large and high-risk EVs. A two-sided p value of less than 0.05 was considered statistically significant.

Results

A total of 75 cirrhotics with esophageal varices, irrespective of etiology were assessed. The mean age of the study population was 47.89±11.34 years. There were 57 men (76%) and 18 women (24%) with a male-female ratio of 3.17:1. There was no significant difference among age categories for the presence of large and small varices (p= 0.486). There was no difference in the prevalence of large and small varices among both the gender groups (p= 0.48) (Table 1). Alcohol was the most common cause of cirrhosis 43 patients (57.3%) followed by chronic viral infections (12 patients:16%).

Large sized varices were present in 52 patients (69%) and 23 patients (31%) had small varices. Red color signs were seen in 46 (88.5%) patients with large varices and in 6 (26.09%) patients with small varices. The large varices had significantly higher prevalence of red color signs as compared to those with small varices (p< 0.001). The prevalence of high-risk varices was 77% (58 patients) and that of low-risk varices was 23% (17 patients).

Table 1. Distribution of varices according to the age groups and gender

Parameters		No. of patients (n = 7 5) Large (%)	Esophageal varices		P value
			Large (%)	Small(%)	
Age (Years)	<30	2	0 (0%)	2 (100%)	0.486a
	31-40	22	16 (72.7%)	6 (27.3%)	
	41-50	24	12 (50%)	12 (50%)	
	51-60	18	15 (83.3%)	3 (16.7%)	
	>60	9	9 (100%)	0 (0%)	
Gender	Male	57	40 (70.2%)	17 (29.8%)	0.48b
	Female	18	12 (66.7%)	6 (333.3%)	

P value from a Fisher's exact test, b from Chi-square test.

On univariate analysis, patients in the high-risk varices group had significantly lower platelet level, hemoglobin levels, serum albumin and PC/SD ratio, as compared to those with small varices (Table 2). Patients with high-risk varices had significantly higher values of BMI, AST, INR, spleen diameter, portal vein diameter, splenic vein diameter, CTP, MELD, APRI, LSPS, shear wave elastography and transient elastography. We tried to find the association between these parameters and the formation of large varices.

Table 2. Relationship of various parameters with presence or absence of large esophageal varices on univariate analysis

Parameters	Large EV (N=52)	Small EV (N=23)	P value
Age (years) (Mean±SD)	49.87±11.82	43.43±12.78	0.037
BMI (kg/m2) (Mean±SD)	23.63±2.93	24.43±7.21	0.61
Platelet counts (x103/mm3) (IQR)	76 (60, 107)	122 (75, 161)	0.01*
Hb (gm/dl) (Mean±SD)	10.29±2.89	12.96±2.08	<0.001
ALT, Median(IQR)	50 (35, 76)	31 (27, 42)	0.02*
AST, Median(IQR)	66 (47,106)	38 (18, 68)	<0.001*
Albumin (Mean±SD)	3±0.59	3.74±0.68	<0.001
INR (Mean±SD)	1.46±0.60	1.0±0.00	<0.001
Spleen diameter (mm) (Mean±SD)	139.04±18.02	116.78±15.14	<0.001
Portal vein diameter (mm) (Mean±SD)	12.33±2.20	10.22±2.13	<0.001
Splenic vein diameter (mm) (Mean±SD)	7.85±2.21	6.91±2.11	0.09
CTP, Median(IQR)	8 (7, 9.75)	6 (5,6)	<0.001*
MELD (Mean±SD)	14.35±4.79	8.35±2.66	<0.001
APRI, Median(IQR)	3 (1,4)	1 (0,3)	<0.001*
PC/SD, Median(IQR)	535 (420, 738)	1017 (882, 1238)	<0.001*
LSPS, Median(IQR)	5 (2, 9.75)	1 (1, 3)	<0.001*
SWE, Median(IQR)	29(21,54)	13 (6,22)	<0.001*
TE, Median(IQR)	36 (16, 51)	15 (5, 20)	<0.001*

* Mann- Whitney test.

On bivariate analysis for the prediction of large varices: TE ≥20 kPa, SWE ≥22 kPa, splenic diameter ≥120 mm, portal vein diameter ≥13 mm, LSPS >2.2 and PC/SD ≤909 were positively associated. The platelet count <150x103/mm3, TE ≥20 kPa, SWE ≥22 kPa, splenic diameter ≥120 mm, portal vein diameter ≥13 mm, LSPS >2.2 and PC/SD ≤909 were significantly associated for formation of high risk varices (P <0.05). (Table 3)

Table 3. Bivariate analysis for the association between various variables and formation of high-risk esophageal varices

Variables	High-risk (% within group)	Crude OR	95% CI	P value
Age >40	37(72.5%)	0.38	0.97-1.46	0.15
Gender (male)	43(75.4)	1.63	0.41-6.46	0.48
Platelets < 150×103/mm3	52(82.5%)	1.65	0.97-2.9	0.014
TE (FIbroscan) ≥20 kPa	35(87.5%)	3.65	1.14-11.75	0.025
SWE ≥22 kPa	40(93%)	10.37	2.65-40.62	<0.001
Spleen diameter ≥120 mm	55(83.3%)	10.0	2.17-46.16	0.001
Portal vein diameter ≥13 mm	33(100%)	0.6	0.46-0.76	<0.001
Splenic vein diamter ≥11 mm	9(100%)	0.74	(0.64-0.85)	0.08
LSPS >2.2	37(86%)	3.23	(1.04-9.99)	0.03
PC/SD ≤909	45(88.2%)	6.35	1.97-20.46	0.001
Within Baveno VI	25(83.3%)	1.14	0.89-1.44	0.31

The independent predictors for the presence of large varices were splenic diameter >120 mm, portal vein diameter >13 mm, TE ≥20 kPa and PC/SD ≤909 on multivariate logistic regression analysis. All these predictors were significant in predicting the presence of large esophageal varices (P <0.05). (Table 4)

Table 4. Multivariate logistic regression analysis for predictors of presence of large esophageal varices

Variables	Adjusted OR	95% C.I.for Adjusted OR		P value
		Lower	Upper	
TE (Fibroscan) ≥20 kPa	18.665	1.542	225.961	0.021
SWE ≥22 kPa	6.130	0.864	43.507	0.070
Spleen diameter >120 mm	42.642	2.635	690.032	0.008
Portal vein diameter >13 mm	6.508	1.120	37.816	0.037
LSPS >2.2	0.576	0.081	4.113	0.582
PC/SD ≤909	41.781	3.096	563.820	0.005
Constant	0.001			0.002

Discussion

Our study demonstrated large varices with high risk features in more than two third of patients. Severe bleeding due to ruptured varices develops in about 30-40% of cirrhosis patients and is associated with significant morbidity, mortality and higher health care costs. Current literature emphasizes the application of screening tools in these patients to prevent rupture with

use of beta-blockers.[3,5] There is a need for noninvasive markers to detect the EVs in resource limited settings like ours to minimize the direct and indirect health care costs. In this study, we considered simple, commonly available and noninvasive parameters with less inter-observer variability as limited evidence exists in our country.

This study evaluated 75 cirrhotic patients with esophageal varices in 6 months, which is more than similar study (50 patients) conducted at Institute of Medicine, Nepal by Pathak R et al.[12] The mean age of this study population is similar to study done by Sharma S et al. with a median age of 45 years[13] and Sarangapani A et al[14] with the median age of 45 years. The study population was male-predominant similar to study by Pathak et al[12] demonstrated 72% of cirrhotics as male patients. This is probably due to high alcohol consumption habit among male in Nepalese society.

UGIE revealed 69% of patients to have large varices and 77% have high-risk varices. Red wale signs was seen in 88.5% of patients with large varices and in 26.09% of those with small sized varices. The large varices had significantly higher prevalence of red color signs as compared to those with small varices (p< 0.001). Similar studies from Nepal and India have demonstrated the presence of large varices in 67% (n=24 patients) and 41% (n=51 patients) respectively.[12,14] These findings suggest that most of the patients with cirrhosis, irrespective of etiology, suffered from esophageal varices thus suggesting the importance of screening.

On univariate analysis, the patients with large varices had significantly lower values of platelet counts, hemoglobin levels, serum albumin and PC/SD ratio and significantly higher values of ALT, AST, INR, spleen diameter, portal vein diameter, CTP, MELD, APRI score, LSPS, shear wave elastography and transient elastography. The age, BMI and splenic vein diameter were not significantly different between the large and small varices groups. Univariate analysis demonstrated a significantly lower values of platelet counts, hemoglobin levels, serum albumin and PC/SD ratio, significantly higher values of BMI, AST, INR, spleen

diameter, portal vein diameter, splenic vein diameter, CTP, MELD, APRI, LSPS, shear wave elastography and transient elastography for high risk varices.

The splenic size, portal vein size, a platelet count spleen

diameter ratio and TE were found to be predictors of large EVs. A splenic diameter >120 mm, portal vein diameter >13 mm, TE ≥20 kPa and PC/SD ≤909 were selected, as these represent the median values and offered the best discrimination. A similar study performed by Sarangapani A et al.[14] to predict large EVs reported that platelet count (<150000/mm^3), palpable spleen, splenic size (diameter >138mm), portal vein size

(> 13mm), and a platelet spleen diameter ratio (≤909) were found to be predictors of large EVs. Platelet spleen diameter ratio (≤909), SWE > 22Kpa and LSPS >2.2 were found to be predictors of high-risk EVs in this study similar to results reported by other studies. [8,11]

Our study showed that TE ≥20 kPa could independently predict the occurrence of large EVs. Other studies have reported a value range (19.0 kPa to 64.5 kPa) with corresponding PPV of 25–90% and NPV of 55–100% respectively.[15] The Baveno VI criteria suggests a combined TE <20 kPa and platelet count >150,000/mmm3 can avoid screening endoscopies[5,] which we analysed in our population, demonstrated that only 40% (30 out of 75) of patients would have undergone endoscopy. This would have led to missing out of 60% of EVs, who otherwise would have been benefited by UGI endoscopy. The present study demonstrated a simple, non-invasive techniques as reliable predictors for EVs among cirrhotics, however, endoscopy still remains the gold standard for management. Further larger prospective studies are needed to predict the varices to validate the findings of this study.

Conclusions

The predictors for the presence of large varices were splenic diameter >120 mm, portal vein diameter >13 mm, TE ≥20 kPa and PC/SD ≤909 whereas for the presence of high-risk varices were SWE ≥22 kPa, PC/ SD ≤909 and LSPS >2.2. Although UGI endoscopy remains the gold standard, use of noninvasive markers can be used in cirrhotic patients in limited resources and patients having high risk for bleeding.

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