Can Non Invasive Parameters Help us to Predict Large Esophageal Varices? Results from a Tertiary Medical Centre of South Rajasthan

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ABSTRACT

Introduction: Current consensus recommend screening cirrhotics patients with endoscopy to detect esophageal varices and to begin prophylactic management in patients having large esophageal varices. This study was aimed at finding non invasive parameters which could identify the presence of large esophageal varices.

Material and methods: In this prospective study 191 patients with liver cirrhosis without a history of prior gastrointestinal bleed were studied. Epidemiological, clinical, laboratory, and ultrasound parameters were assessed. Esophageal varices were divided as small and large on endoscopy. Univariate and multivariate analysis using binary logistic regression was done to find independent predictors for the presence of large esophageal varices.

Results: 191 patients (151 males; median age 43.5 yrs) with liver cirrhosis, [135 had large and 56 had small varices. on multivariate analysis Portal vein diameter >13mm, (Odd's ratio [OR] 62.495 95% Confidence Interval [CI] 10.583 to 369.038) P <0.001S, AUC 0.929], Splenic diameter>120mm, (OR 34.835 95% CI 8.791 to 138.032) P <0.001S,AUC 0.922 and Platelet count <1lakh/mm^3 (OR 11.871 (95% CI 2.515 to 56.036) (*P* =0.002 S), AUC 0.684] emerged as significant risk factors in the present study.

Conclusion: Low platelet count, spleen diameter, and portal vein diameter are significant predictors of large grade esophageal varices. They may be considered as non invasive predictors for large grade varices.

Keywords: Invasive Parameters, Predict Large Esophageal Varices,

INTRODUCTION

Esophageal varices develop secondary to portal hypertension in patients of chronic liver disease and are seen in around 50% of cirrhotics. Grade of esophageal varices increases with severity of liver disease. They are seen in 85% of child class C cirrhotics, while their prevalence in child A cirrhotics is around 45%.[1] Rate of development of new varices and increase in grades is determined by hepatic venous pressure gradient and presence of decompensate cirrhosis.[2-3]

Large size varices, red color signs (RCS), severe liver disease and hepatic venous pressure gradient (HVPG) more than 12 mm hg are predictor of increased bleeding risk.[4] Mortality of esophageal variceal bleed at 6 weeks is around 20%[5-6]

Current beveno consenses (beveno 6) recommends that screening endoscopy can be safely avoided in patients with a liver stiffness <20 kPa and with a platelet count >150,000. however liver stiffness measurement are not widly available in developing countries,therefore there is a requirement of simple, easily available tools for predicting the presence of varices

Predicting the grade of esophageal varices on detection of chronic liver disease may warrant prophylactic beta blocker therapy or endoscopic variceal ligation to prevent risk of variceal bleed. This study was under taken to determine the role of clinical, biochemical and imaging parameters in predicting the existence and grade of esophageal varices.

MATERIAL AND METHODS

Newly diagnosed cases of cirrhosis hospitalized in our gastroenterology department from February 2019 to May 2020 were enrolled in this prospective study. Individuals presenting with variceal bleed, past history of variceal bleed or on beta blocker therapy, history of variceal ligation, portal vein thrombosis, hepatocellular carcinoma were excluded from study. Patients clinical, biochemical, imaging and endoscopic features were recorded. Cirrhosis was diagnosed on the basis of clinical, biochemical and imaging parameters.[7]

History included amount, duration and pattern of alcohol intake, jaundice, gastrointestinal bleed, ascites, pedal edema, oliguria, hepatic encephalopathy and requirment for therapeutic paracentesis and repeated paracentesis(which is arbitarly defined as requirement of therapeutic paracentesis every weekly).

Examination included presence or absence of ascites, jaundice and spleenomegaly. Hematological profile included hemoglobin, platelets, blood urea, serum creatinine was recorded. Liver function test included serum bilirubin, albumin /globulin ratio, transaminase levels and PT/INR. Etiological work up included viral serology (HbsAg, anti HCV antibody assay), autoimmune markers (antinuclear antibody, anti smooth muscle antibody, anti liver-

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kidney-microsomal antibody), slit lamp examination, serum ceruloplasmin, 24 hour urine copper and iron studies.

Ultrasonography abdomen was done in all cases and liver echotexture, spleen and portal vein diameter, collaterals were recorded. Platelet count /spleen diameter ratio was determined. Endoscopy done in all cases by one expirenced endoscopist and were confirmed by another to minimize the inter observer variability. esophageal varices were graded as small (grade 1-2) or large(grade3-4), based on Paquet's grading system.[8-9]

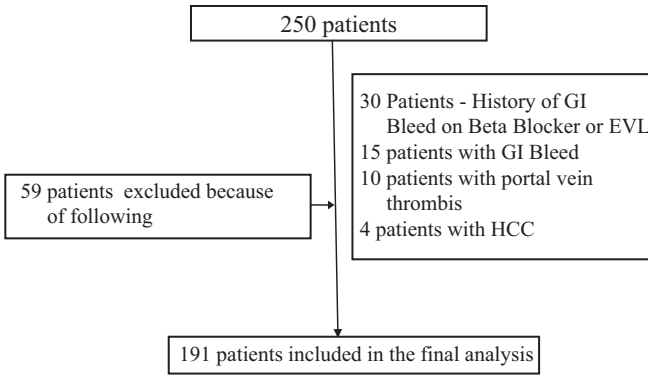
STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS, trial version 20 for Windows statistical software package (SPSS inc., Chicago, il, USA) and PRIMER. Qualitative data was presented as percentages, 95% CI, to assess any significant association. Chi Square test and and Odd's ratio were used. Quantitative data was expressed as mean ± standard deviation and were compared using students t-test. Binary Logistic regression was used to identify independent risk factors for large varices. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of significant variables. The diagnostic accuracy (specificity SN, sensitivity SP, negative predictive value NPV & positive predictive value PPV) was calculated. Significance level was set at $P < 0.05$.

RESULTS

Baseline characteristics

In the present study 250 patients were included. 59 patients were excluded because of various exclusion criteria. 191 patients were included in the final analysis.



Present cohort included 151(79%) males and 40(21%) females. Mean age of patients was 43.5 years. etiology of cirrhosis in majority of patients was alcohol related 110(57%), followed by cryptogenic 28 (14%), HBV related 26 (13.6%), autoimmune in 11(5.7%), NASH related in 9 (4.7%), HCV related in 6 (3.1%). CTP and MELD score was calculated in all the patients. The majority of patients belonged to child class B 53(27%) and child class C 122(63%) while 16(8%) patients belonged to child class A. Overall 191 patients had esophageal varices out of which 135(70%) patients had large esophageal varices and 56 (30%)had small esophageal varices (Table 1).

No significant difference was observed in age according to type of varices (Table 2). Among the laboratory features low hemoglobin, less Total Leukocytes Count (TLC), low platelet count were observed in large varies as compared to small varies (Table 2). However, there was no statistically significant relation between large varices and SGOT, SGPT, serum albumin, serum bilirubin, CTP and MELD score (table 3) On Ultrasonography splenic diameter was significantly more in large varies as compared to small varies (124.75 ±5.834 median 125 mm vs 112.09±11.428 median 112mm) P<0.001S, Portal vein diameter (16.17 ±1.949 median 16 mm vs 12.91±1.325 median 13 mm) P<0.001S was respectively (Table 2).

Risk factors for the presence of large varices

On univariate analysis the predictors of large varices were repeated paracentisis (with OR 2.944 95% CI 1.490 to 5.816), Platelet <1lakh/mm^3 (OR) 4.962 95% CI 2.440 to 10.087), Portal Vein Diameter >13mm (OR 89.51795% CI 28.136 to 284.805) and Splenic Diameter (mm) >120 (OR) 57.843 95% CI (21.542to155.31) (Table 4).

After multivariate logistic regression analysis with adjustment for age, Hb, MELD, PVD >13mm, SPD>120mm, PLT<1lac, Child Pugh Classification A vs b/c. The PVD >13mm, OR 62.495 (95% ci 10.583 to369.038) P <0.001S (SPD>120mm, OR 34.835(95% ci 8.791 to 138.032) P <0.001S and PLT<1lac OR 11.871 (95% CI 2.515 to 56.036) (*P* =0.002 S) emerged as significant risk factors in the present study [Table -5].

Using significant factors on multivariate analysis which predicted large varices portal vein diameter >13 mm was the most sensitive in picking up large grade varices at endoscopy. (sensitivity 97.04, specificity 73). When all the three parameters that is portal vein diameter, spleen diameter, and platelet count were considered portal vein diameter>13mm was most accurate(accuracy 90.5) in predicting large varices,

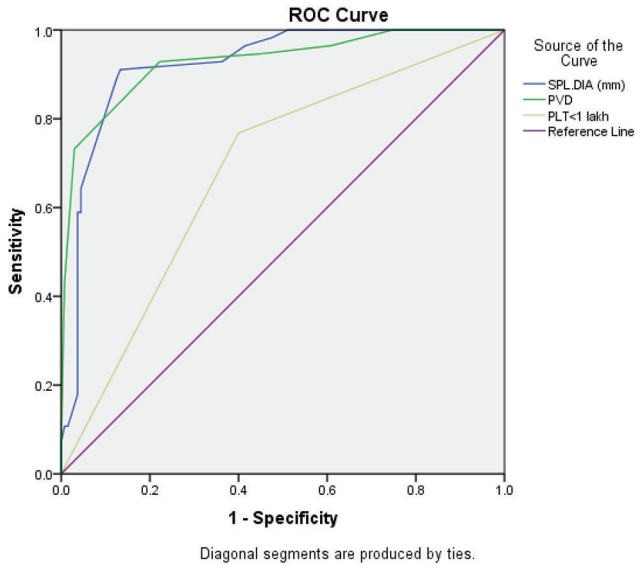


Figure-1: ROC Curve for Spleen Diameter in Predicting large Esophageal Varices

	Large (N%=135)	Small (N%=56)	Total	P value
Gender				
F	24(17.78)	16 (28.57)	40	0.141
M	111 (82.22)	40 (71.43)	151	
Etiology				
Alcohol	78 (57.78)	32 (57.14)	110	0.93
Autoimmune	5 (3.70)	6 (10.71)	11	0.12
BCS	1 (0.74)	0 (0.00)	1	0.64
Cryptogenic	22 (16.30)	6 (10.71)	28	0.44
HBV	20 (14.81)	6 (10.71)	26	0.60
HCV	5 (3.70)	1 (1.79)	6	0.81
NASH	4 (2.96)	5 (8.93)	9	0.16
Ascites	(0.00)	(0.00)		
No	17 (12.59)	6 (10.71)	23	0.62
Mild to Moderate	2 (1.48)	2 (3.57)	4	
Severe	116 (85.93)	48 (85.71)	164	
Child pugh				
A	14 (10.37)	2 (3.57)	16	0.29
B	36 (26.67)	17 (30.36)	53	
C	85 (62.96)	37 (66.07)	122	

Table-1: Comparative analysis of Demographic characteristics of the study population according to varices type(p<0.05 significant)

		Age	Hb	TLC	PLT	PT	INR	Spleen Diameter (mm)	Portal Vein Diameter (mm)	CTP
Large Varices (N=135)	Mean	43.91	8.58	8099.78	106081.48	17.18	124.75	16.17	10.52	1.63
	Std. Deviation	13.593	2.216	5924.877	110139.264	6.746	5.834	1.949	2.381	.651
	Median	45.00	8.60	6590.00	90000.00	15.30	125.00	16.00	10.00	1.40
small Varices (N=56)	Mean	42.79	9.33	10945.71	173392.86	17.61	112.09	12.91	10.77	1.65
	Std. Deviation	11.890	2.062	7962.890	124647.821	5.473	11.428	1.325	1.991	.552
	Median	40.00	9.40	8600.00	140000.00	16.50	112.00	13.00	10.50	1.50
Total Varices (N=191)	Mean	43.58	8.80	8934.19	125816.75	17.31	121.04	15.21	10.59	1.64
	Std. Deviation	13.096	2.194	6693.264	118307.863	6.388	9.757	2.324	2.271	.622
	Median	45.00	8.90	7000.00	100000.00	15.70	122.00	15.00	10.00	1.43
		0.59NS	0.03S	0.004*	<0.00*1S	0.452*	<0.001S*	<0.001S*	0.51*NS	0.733*

Table-2: Characteristics of the study population according to type of varices

	Large (N(%)=135)	Small (N(%)=56)	Total	Odds ratio	P value
HE	30 (22.22)	9 (16.07)	39	1.492 (0.657 to 3.389)	0.44NS
HRS	34 (25.19)	8 (14.29)	42	2.020 (0.869 to 4.694)	0.143NS
SBP	13 (9.63)	4 (7.14)	17	1.385 (0.431 to 4.449)	0.78NS
Paracentesis	70 (51.85)	15 (26.79)	85	2.944 (1.490 to 5.816)	0.003S
Platelet<1lakh/mm^3	81 (60.00)	13 (23.21)	94	4.962 (2.440 to 10.087)	<0.001S
Portal vein>13mm	131 (97.04)	15 (26.79)	146	89.517 (28.136 to 284.805)	<0.001S
Child A	14 (10.37)	2 (3.57)	16	3.124 (0.686 to 14.226)	0.20NS
Child B/C	121 (89.63)	54 (96.43)	175		
Splenic Diameter (mm) >120	118 (87.41)	6 (10.71)	124	57.843 (21.542 to 155.318)	<0.001S

Table-4: Univariate analysis for predicting the large esophageal varices via binary logistic regression

Parameter	P Value	Odds ratio	95% confidence interval	
			Lower	Upper
Portal vein diameter > 13mm	0.000	20.86	10.583	369.038
Spleen diameter > 120mm	<0.001	25.545	8.791	138.032
Platelet < 1 lakh/mm^3	.002	9.763	2.515	56.036

Table-5: Multivariate analysis for predicting the large esophageal varices via binary logistic regression

	Spleen diameter (mm) >120	Portal Vein Diameter > 13mm	Platelet <1 Lakh/mm^3
Sensitivity%	87.41	97.04	60
Specificity	89.29	73.21	76.79
Positive predictive value	95.16	89.73	86.17
Negative predictive value	74.63	91.11	44.33
Accuracy	87.95	90.05	64.92

Table-6: Diagnostic values for various significant predictors for diagnosing large varices

followed by spleen diameter >120mm (accuracy 87.4), while platelet count <1 lakh was least accurate (accuracy 64.9) (table 6)

ROC curve analysis was performed to determine the optimal cut-off values of splenic diameter, portal vein diameter and platelet count for the detection of large varices. At 121.50mm area under the curve (AUC = 0.922), optimal cut- off value of Splenic diameter, with a sensitivity of 91.1% and a specificity of 86.7%, was determined with SE 0.021and Youdon index 0.77 (Fig. 1)AUC for portal vein diameter >13 mm was determined to be 0.929(fig 1) with a sensitivity and specificity of 97.04% and specificity of 73.21%(table 6) while AUC for platelet count was 0.684(fig 1) with a sensitivity of 60% and specificity of 76.2% (table 6)

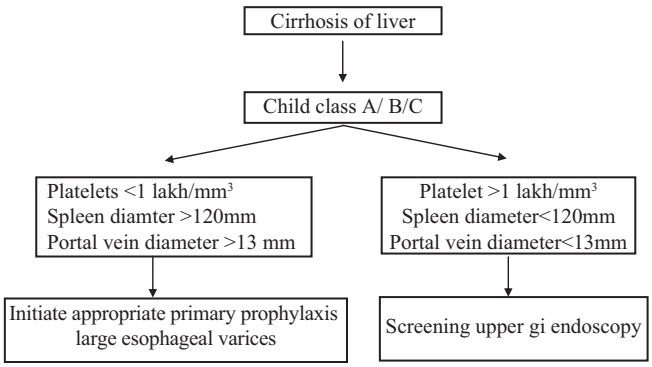
DISCUSSION

Studies in the past have shown independent parameters like spleenomegaly[9-13], ascites,[14], spider naevi[15], childs grade[16], platelet count[17-19], prothrombin time[15-18], portal vein diameter[18] platelet count/spleen diameter ratio[20-21], serum albumin[19] and serum bilirubin[19] as significant predictors for the presence of esophageal varices.

Our study was undertaken especially to assess the factors associated with presence of large varices. There are very few Indian studies which have assessed for non invasive predictors of large varices. Amrapurkar et al[9] reported that spleenomegaly alone was a significant predictor for the development of large esophageal varices. Sharma et al[13] in a prospective study have shown spleenomegaly and platelet count to be independent predictors of presence of large esophageal varices.

In our study portal vein diameter (>13mm), spleen size (>120mm), and platelet count (<100000/mm^3) emerged as a significant predictors for the presence of large esophageal varices. In previous studies[22] child class was found to be the most sensitive parameter for picking up large grade varices at endoscopy. But in our cohort the patients included were in patients with majority belonging to child class B or C and the number of patients in child A was very low. This may account for the exclusion of CTP class as a predictor of large varices in our study.

Based on present study patients of child class B/C who have above mentioned parameters present can be started on primary prophylaxis for large esophageal varices, however this non invasive model needs to be validated in future larger studies based on results of this study following algorithm can be proposed.



Algorithm for the initiation of primary prophylaxis for large esophageal varices based on the present study.

We believe that this non invasive model may be of help to the physician practicing in remote areas where endoscopic facilities are not available in helping them to start primary prophylaxis in these patients. In urban health care system with high endoscopic burden, a non invasive model like this can help us to initiate drug therapy while waiting for endoscopic procedure.

CONCLUSION

Low platelet count, spleen diameter, and portal vein diameter are significant predictors of large grade esophageal varices. They may be considered as non invasive predictors for large grade varices.

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