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Original Research Article

Non-invasive markers for prediction of varices in patients with portal hypertension

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ABSTRACT

Background: The incidence of esophageal varices in patients with cirrhosis ranges from 35 to 80%. Thus, screening all cirrhotic patients with upper gastrointestinal (UGI) endoscopy to detect the presence of varices implies a number of unnecessary endoscopies, which increase the workload of endoscopy units and UGI endoscopy has its own limitations. The present study was conducted to investigate series of non-invasive biochemical and radiological markers for prediction of esophageal varices in patients with portal hypertension.
Methods: Patients of either sex, aged 18-80 years with diagnosis of chronic liver disease, cirrhosis, extrahepatic portal vein obstruction or any other cause of portal hypertension were studied. Patients were subjected to UGI endoscopy within 2 weeks of investigation of laboratory parameters. All patients were subjected to detailed clinical history and physical examination and biochemical and radiological investigations. Endoscopy was done with an olympus gastroscope using 20% xylocaine spray.
Results: Out of 51 patients in the study, esophageal varices were seen in 34 (66.67%) patients and absent in 17 (33.33%) patients. On multiple logistic regression analysis, the variables independently linked to the presence of esophageal varices were; spleen diameter [odds ratio (OR): 1.137, 95% confidence interval: 1.033-1.255; p=0.009] and Portal vein size [odds ratio (OR): 41.531, 95% confidence interval: 1.858-928.304; p=0.019].
Conclusions: Non-invasive prediction for varices by biochemical and radiological methods are reliable methods for screening of cirrhotics patients because of increasing patient overload, when a major chunk of these patients do not show any evidence of varice.

Keywords: Cirrhosis, Noninvasive, Portal hypertension, Varices

INTRODUCTION

Cirrhosis is the end stage of every chronic liver disease, resulting in disorganization of liver architecture, and nodule formation, and development of portal hypertension. Portal hypertension is associated with development of a hyperdynamic circulation and complications such as ascitis, hepatic encephalopathy, and esophagogastric varices. About 50% of patients presenting with cirrhosis with ascites are reported to have varices. Development of esophageal varices may occur in up to 90% of patients with liver cirrhosis, being more common in child-pugh class C patients compared to child-pugh class A patients (85% versus 40%).[1] Once varices form, they enlarge from small to large at a rate of 5-12% per year and bleed at a rate of 5-15% per year.[2] Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis clearly show that the risk of variceal hemorrhage can be reduced by 50% to about 15% for large esophageal varices.[3] The Baveno IV Consensus Conference on portal hypertension recommended that all cirrhotic patients should be

screened for presence of esophageal varices. Endoscopy should be performed at 2-3 years intervals in patients without varices and at 1-2 years intervals in patients with small varices.[4] However, at a given point in time, a variable proportion of patients will not have varices; in fact, the reported prevalence of esophageal varices is variable, ranging in different series between 24 and 80%. Thus, screening all cirrhotic patients with upper GI endoscopy to detect the presence of varices implies a number of unnecessary endoscopies, which increase the workload of endoscopy units.[5] Upper gastrointestinal endoscopy remains the gold standard for screening, but this test is not without its own limitations. In recent years a number of clinical, laboratory and ultrasonography variables have been explored as non-invasive alternatives to endoscopy.[6] The present study was conducted to investigate series of non-invasive biochemical and radiological markers for prediction of esophageal varices in patients with portal hypertension.

METHODS

This prospective study was conducted in the Department of Medicine, Government Medical College Jammu, for a period of one year.

Patients of either sex, aged 18-80 years with diagnosis of chronic liver disease, cirrhosis, extrahepatic portal vein obstruction (EHPVO), NCPF or any other cause of portal hypertension were included. While those having history of variceal bleeding, prior variceal treatment or variceal bleeding prophylaxis (any form), patients of liver transplantation, those suffering from hepatocellular carcinoma, those with any coexistent illness were excluded from study. Presence of esophageal varices on endoscopy was the final endpoint. Patients were subjected to esophagogastroduodenoscopy (EGD) within 2 weeks of investigation of laboratory parameters. Endoscopy was done by an expert endoscopist and variceal size was recorded in red colour sign and portal hepatic gastropathy according to Japanese Research Society for portal hypertension classification and gastric varices according to the Sarin classification.[7,8]

All patients were subjected to detailed clinical history and physical examination and following investigations;

Ultrasonography for portal variceal size, maximum spleen bipolar diameter, complete haemogram, liver function tests, PT, PTI, international normalized ratio (INR). Kindey function tests, serum electrolyte, routine examination of urine and UGI endoscopy. For potential non-invasive cases, variables investigated in this study which could predict esophageal varices were: portal variceal size, maximum spleen bipolar diameter on USG, platelet count, platelet count/spleen diameter ratio, MELD score, AST/platelet ratio index (APRI), AST/ALT ratio, serum albumin, total bilirubin and INR. Endoscopy was done with an Olympus Gastroscope using 20% xylocaine spray.

Statistical analysis

The statistical analysis was done by using appropriate statistical methods with the help of Windows-based Excel and SPSS ver. 22 applications. A p-value of <0.05 was taken as statistical significant in all analyses.

RESULTS

Out of 51 patients in the study, esophageal varices were seen in 34 (66.67%) patients and absent in 17 (33.33%) patients. There were more male 34 (66.67%) patients as compared to female 17 (33.33%) patients in the study, with male to female ratio of 2:1. Mean platelet count, mean prothrombin activity value expressed as International Normalized Ratio (INR), mean portal vein size, mean spleen diameter, mean ratio of platelet count and spleen diameter (PC/SD), mean aspartate aminotransferase-to-platelet ratio index (APRI) and mean model for end stage liver disease (MELD) score in patients with esophageal varices compared to patients with esophageal varices absent, were statistically significant (Table 1).

Table 1: Comparison of non-invasive parameters in study population.

Variable	Esophageal varices		
	Present Mean±SD	Absent Mean ± SD	p-value
Mean platelet count	131.32±35.83	172.65±35.18	0.001
INR	1.75±0.74	1.26±0.50	0.01
Mean portal vein size	14.48±1.08	13.30±0.32	0.001
Mean spleen diameter	13.30±0.32	122.24±13.57	0.001
PC/SD[#]	122.24±13.57	1426.83±318.16	0.001
APRI[$]	2.34±1.28	1.26±0.85	0.003
MELD	15.91±6.37	10.19±4.90	0.003

platelet count/spleen diameter, $ mean aspartate amino transferase to platelet ratio index.

Mean aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio in patients with presence of esophageal varices was more as compared with those patients with esophageal varices absent. Portal hypertensive gastropathy was present in 33 (97.06%) and absent in 1 (2.94%) patients with esophageal varices, while it was present in 4 (23.53%) and absent in 13 (76.47%) patients with esophageal varices absent. On multiple logistic regression analysis, the variables independently linked to the presence of esophageal varices were; spleen diameter [odds ratio (OR): 1.137, 95% confidence interval: 1.033-1.255; p=0.009], PV size [odds ratio (OR): 41.531, 95% confidence interval: 1.858-928.304; p=0.019] (Table 2). Using coordinates of

AUROC and applying Youden's index, a cut off value of 13.75 mm for portal vein size was derived which implied that any patient with portal vein size above 13.75 mm on USG showed presence of esophageal varices on UGI endoscopy with a sensitivity of 79.4% and specificity of 88.2%. Spleen diameter had a cut off value of 141.5 mm above which study population showed presence of varices on endoscopy with a significant association. The sensitivity was 73.5% with specificity of 100%.

Table 2: Multiple logistic regression analysis of factors associated with presence of esophageal varices in study patients.

	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for Exp (B)
Spleen diameter	0.129	0.039	10.914	1	0.001	1.137	1.054
Constant	-16.921	5.188	10.639	1	0.001	0.000	
Portal vein size	3.726	1.585	5.526	1	0.019	41.531	1.858
Spleen diameter	0.130	0.050	6.785	1	0.009	1.139	1.033
Constant	-67.993	24.95	7.421	1	0.006	0.000	
Variables		**OR (95% Confidence interval)**			**p-value**		
Spleen diameter		1.139 (1.033 - 1.255)			0.009		
Portal vein size		41.531 (1.858 - 928.304)			0.019		

DISCUSSION

Portal hypertension constitutes the pathophysiological basis of most complications of cirrhosis. Early diagnosis of varices before first bleed is very essential as primary prophylaxis clearly decreases mortality in these patients. Given the variable prevalence of varices in portal hypertension and cirrhosis on endoscopy, there is a need to identify a high risk group of patients using some noninvasive methods which will reduce the burden and cost of endoscopy as well as discomfort to the patients which are at lowest risk of developing varices. Present study have demonstrated a significant difference in patients with varices as compared to patients without varices with regards to variables like platelet count, spleen diameter, portal vein size, platelet count / spleen diameter ratio, INR, MELD and APRI (AST to platelet ratio index) on univariate analysis. De Mattos et al. has showed a significant association of varices ($p<0.05$) with platelet count, spleen diameter, MELD score, platelet count/spleen diameter ratio and APRI on univariate analysis.[9] Tafarel and his coauthors revealed a significant association of varices with MELD score, APRI and decreased platelet count.[10] In another study by Giannini et al platelet count, spleen diameter and platelet count/spleen diameter ratio differed significantly among patients with and without varices.[11]

On performing multivariate analysis in our study population, it was observed that only two variables namely portal vein size and spleen diameter were found to be independent predictors of esophageal varices with a significant association. The present study showed a mean portal vein size of 14mm, those with varices revealed a mean portal vein size of 14.48 $\pm$ 1.08 while it was 13.30 $\pm$ 0.32 in those without varices. Mean spleen diameter came out to be 144.5 mm. patients with varices showed a mean spleen diameter of 155.62±19.2 while it was 122.24±13.5 mm in those without varices. Kumar and coworkers, found that portal vein diameter of >13 mm and spleen diameter of >140 mm are indicators of varices. Similarly Tarzamini et al. observed values of mean portal vein size of 13.5mm.[12] It also revealed spleen diameter of more than 157 mm as an independent predictor of varices. Splenomegaly as a predictive tool has been shown by Chalasani and coworkers and Sudha Rain et al.[13,14]

Platelet count /spleen diameter ratio has been validated as the independent predictor for varices in many studies, but our study failed to show similar results. One explanation is that majority of those studies have been performed on hepatitis B and C related cirrhotic patients whereas alcohol related cirrhotics have not shown similar sensitivity and specificity related to this ratio. The present study had no patient of hepatitis B or C related cirrhosis or portal hypertension. It is also observed that there were inconsistencies seen in meta-analysis of these studies, resulting in a low overall grade of evidence. Moreover most of these studies were done on cirrhotics, contrary to the present study which had taken portal hypertension as the inclusion criteria which is scientifically a better marker for decompensation, thus further increasing the probability of finding more accurate and predictive variables for varices. Inability of platelet count to spleen diameter ratio as an independent predictor or as an effective screening test for varices is supported by the study of Chawla et al.[15] The present study however failed to draw association between two groups of patients as regards with platelet count, MELD, INR, platelet count to spleen diameter ratio and APRI on multivariate analysis. The likely explanation is that development of esophageal varices depends mainly on increased hepatic resistance related to liver fibrosis. Indeed portal hypertension is a

consequence of the development of septal fibrosis establishing porto-caval anastomosis and arterialization and capillarization of sinusoids because of reduction of portal flow and formation of feeding vessels deriving from hepatic artery.

CONCLUSION

Noninvasive prediction for varices is the need of the hour in view of increasing patient overload, when a major chunk of cirrhotics do not show any evidence of varices. Our study, thus, concludes that portal vein size and spleen diameter which is indirect indicators of portal hemodynamics can be used effectively as a screening test without subjecting patients to EGD.

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