A study of platelet count/ spleen diameter ratio as a predictor of esophageal varices in patients of cirrhosis

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Abstract

Background: Todays guidelines are clear that there are no substitute markers to determine the presence and size of esophageal varices, and endoscopy is still the only valid method to investigate varices. **Objective:** To validate the PC/SD ratio as a predictor of the presence and absence of esophageal varices in patients with chronic hepatopathy. **Methodology:** This study is an analytical cross-sectional validation study of a diagnostic test. The study was done in cases diagnosed of having hepatic cirrhosis by histology or physical, biochemical, and imaging examinations compatible with the disease and treatment from February 1, 2013 to December 31, 2014. Various hematological, biochemical and radiological work up was done. **Results:** Of the total cases, 29(70.7%) had PC/SD ratio more than 909 and only 12(29.3%) had less than 909. The sensitivity of PC/SD ratio of 909 in predicting varix is 89.66% and specificity was 75%. Thus it can be considered a good and reliable tool for predicting varices. **Conclusion:** The use of platelet count/ splenic diameter ratio in cirrhotic patients for screening and follow up for esophageal varices can substantially reduce the cost of health care and discomfort for patients as well as reduce burden of endoscopy unit.

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Introduction

Portal hypertension is the principal complication of hepatic cirrhosis [1]. More than 80% of patients with cirrhosis will develop esophageal varices at some point, and 30% of these patients will have at least one bleeding episode because of rupture of a varix [2]. Most first bleeding episodes happen during the first year after the detection of the varices, with a 5%-10% mortality attributed to the initial hemorrhage [3]. For this reason, identifying the presence of esophageal varices is a fundamental part of the diagnostic work-up in patients with cirrhosis, and it is also a prognostic marker of the illness. The first crucial preventive step is the identification of those patients with bleeding risk and selection for prophylactic treatment. Today's guidelines are clear that there are no substitute markers to determine the presence and size of esophageal varices, and endoscopy is still the only valid method to investigate varices [4]. However, access to endoscopy and other resources is limited in some countries. At any

given time, a variable proportion of patients will not have varices, and the reported prevalence of esophageal varices is 24%-80% [5]. The use of noninvasive methods to predict the presence of esophageal varices would help restrict endoscopic studies to those with a high probability of having varices. Until a few years ago, little information was available on this subject; however, a recent consensus on the definitions, methodology, and therapeutic strategies in portal hypertension [6] recommended that all patients with cirrhosis should be assessed with endoscopy to verify the presence of varices. Recent studies [7-11] have emphasized the use of noninvasive methods to identify patients with the intention of avoiding endoscopy in low-risk cases. The fact that distinct predictors of the presence of varices have been identified in different studies probably reflects differences between the study populations and spectrum of the disease and this makes it difficult to develop a widely applicable predictive model. Giannini et al[12] proposed the use of the platelet count (PC)/spleen diameter (SD) ratio as a noninvasive tool for predicting the presence of varices.

The use of the PC/ SD ratio for the noninvasive assessment of varices seems to meet strict methodological criteria and is based on pathophysiological criteria. The diagnostic precision of this parameter was validated using endoscopic diagnosis in a follow-up of patients free of esophageal varices [13]. The preliminary results obtained by other authors have demonstrated that the diagnostic accuracy of the PC/SD ratio is maintained in patient subgroups with different hepatic disease etiologies and when applying different methodologies[14], suggesting the universality of the diagnostic method. However, few studies have confirmed the results of these earlier studies in the Indian population. Thus, different predictive values may be needed to indicate the presence of esophageal varices. The objective of our study was to validate the PC/SD ratio as a predictor of the presence and absence of esophageal varices in patients with chronic hepatopathy.

Materials and Methods

This study was an analytical cross-sectional validation study of a diagnostic test. Patients were included from the Department of Medicine, tertiary care center in central India. The inclusion criteria were a diagnosis of hepatic cirrhosis by histology or physical, biochemical, and imaging examinations compatible with the disease and treatment from February 1, 2013 to December 31, 2014. Both men and women with a diagnosis of hepatic cirrhosis of any etiology were included. The exclusion criteria were hepatocellular carcinoma, use of medications for the primary prophylaxis of variceal bleeding, history of esophageal variceal bleeding, alcohol consumption within the admission and a history of ligation, sclerotherapy, and/or portal hypertension surgery. Once the patients were included in the study, written informed consent was taken then a complete medical history was taken, and biochemical parameters were measured. All patients underwent routine blood tests- complete blood count including platelet count using MINDRAY BC3000 PLUS fully automated analyzer machine. The biochemical workup included Liver function tests- total serum bilirubin, aspartate aminotransferase, alaninie aminotransferase, serum albumin and prothrombin activity were done using BIOSYSTEM A@% fully automated analyzer machine.

The antibodies to HBsAg and HCV were also done using the ELISA method. All patients were classified according to their Child-Pugh grading. Ultrasound of the abdomen was done in all patients to measure the maximum spleen bipolar diameter and to look for signs of portal hypertension (splenomegaly, ascites, portal vein diameter) and to confirm the diagnosis of cirrhosis. Using ultrasound, cirrhosis is suggested by decrease size of liver, Change in echogenecity, the caudate lobe is enlarged relative to the right lobe, regeneration nodule may be seen as focal lesion, liver size can be assessed and the irregular nodular surface seen. The development of spontaneous shunts can be demonstrated by angiography or by noninvasive techniques, such as Doppler US. The machine used was GE VOlUSON S6. An upper gastrointestinal endoscopy was performed in all patients after overnight fasting using the FUJINON 201 H-SERIES video endoscope. All patients were given spray of 2% Xylocaine in oral cavity for local anesthesia. Then they were asked to lie down in the left lateral position, a mouth gag was placed between the teeth so as to prevent biting following which the endoscopy was gently introduced into the esophagus down to the stomach and examined for presence of esophageal varices by an experienced gastroenterologist. The grading of varices was done according to CONN'S grading system[15]. The radiologist and endoscopist were blinded to the findings of endoscopy and sonography respectively. The platelet count to spleen diameter ratio was calculated for all the patients. The platelet count, spleen diameter and platelet count to spleen diameter ratio were compared between the two groups of patients with and without EVs.

Unvariate analysis for determining the association of various clinical laboratory and ultrasonographic variables with presence of varices was performed using student 't' test for continuous variable. The P value of <0.05 were considered statistically significant. For the purpose of this study, patients were classified into one of two groups, those with varices and those without varices. Sensitivity, specificity, Positive predictive value and negative predictive value were computed and reported for PC/SD ratio. ROC curve was applied to determine the cut-off values with best sensitivity and specificity for PC/SD ratio.

Result

Out of 41 cirrhotic patients, there were 34 male patients and 7 female patients hence male predominance was noted. 58.5% of the patients were consuming alcohol. Among 41 patients 20 (48.8%) were HBsAg positive, 2 (4.9%) were HCV positive and 19 patients were negative for any viral marker. Of the total cases, 29(70.7%) had PC/SD ratio more

than 909 and only 12(29.3%) had less than 909. Almost all nearly 97.6% of the cases had ascites. And only 9.8% cases had encephalopathy at the time of presentation. Maximum, 29(70.7%) of cases had esophageal varices. Table no. 1 shows the grading of Varices. Among 29 cases of varices, 26(82.9%) were male while only 3(17.1%) were females. Chi-square test did not showed any significance between alcohol use and presence of varices (chi-square = 0.509, df=1 , P= 0.475). Similarly, no association was noted between viral marker status and presence of varices varices (chi-square = 0.500, df=1 , P= 0.779). Univariate analysis to show association was also found to be non-significant for presence of ascites or encephalopathy with presence of vaices and similarly no association was noted between gender and grade of varices. Table no. 2 shows that there was a significant association between alcohol consumption status and grade of varices. There was significant association between INR and variceal status but no association was found between other variables such as age, Sr. Bilrubin, SGOT, SGPT, Sr. albumin. **Table no. 1** Distribution of Platelet count, Spleen Diameter, SAAG, Child Pugh score, HB according to varix. There is a significant correlation of platelet count with the presence or absence of varices at the cut off point 909 according to our study, a significant linear correlation is also seen between increased bipolar spleenic diameter and presence of varices. The other parameters such as SAAG, Child Pugh Score and Haemoglobin show no correlation with the presence of varices. Similarly no association was noted between portal vein diameter and presence of varices (t = 1.13, P = 0.265). The sensitivity of PC/SD ratio of 909 in predicting varix is 89.66% and specificity was 75%. Thus it can be considered a good and reliable tool for predicting varices **Table no.2**. ROC curve for PC/SD ratio of 909 as cutoff- area under the curve is 0.823(0.664-0.983).

Table No 1: Distribution of Platelet count, Spleen Diameter, SAAG, Child pugh score HB according toVARIX

	VARIX	N	Mean	Std Deviation	T value	p value
Platelet Count (n/mm3)	Absent	12	143916.6667	49763.91232	5.808	<0.0001
	Present	29	69448.2759	31154.66739		
Spleen Diameter	Absent	12	113.7083	20.26468	3.888	<0.0001
	Present	29	152.6897	32.04807		
SAAG	Absent	12	1.5050	0.52015	0.331	0.742
	Present	29	1.5648	0.52905		
Child Pugh Score	Absent	12	7.5000	1.08711	1.091	0.282
	Present	29	7.8621	0.91512		
Haemoglobin	Absent	12	9.5750	1.73474	1.178	0.246
	Present	29	8.8207	1.91374		

Table No.-2: Distribution of PC/SD ratio according to varix.

Ratio	Varix		Total
	Absent	**Present**	**Total**
<909	9(75%)	3(25%)	12
>=909	3(10.3%)	26(89.7%)	29
Total	12(29.3%)	29(70.7%)	41

Discussion

Out of 41 patient, 29 (70.7%) had presence of esophageal varices and 12 (29.3%) had no varices. It has been reported earlier that at the time of diagnosing any patient with liver cirrhosis, esophageal varices are present in approximately 40% of patients with early disease and in approximately 60% of those with decompensated disease. [16,17]. In a study by Cherian et al [18] which consisted of 229 patients 77.7% patients had varices. Study by Baig et al [19] on 150 patients revealed that 106 had varices accounting for 70%. Similar studies by Abu El Makeram [20] revealed varices in 74.9%, Taferal et al [21] concluded varices in 57%, angone et al [22] in 35.6% and Barrera et al18 in 37.5%. Present study

showed similar proportion of varices as many of studies mentioned earlier. The prevalence of varices is higher in decompensated that in compensated cirrhosis [23]; this might be the reason of high incidence of varices in present study. However, there was no significant association found between ascites and grade of varices in present study.

Out of 47 patients, 3 (7.3%) had Grade 1 varices, 20 (48.8 %) had Grade 2 varices and 6 (14.6%) had Grade 3 varices whereas none had Grade 4 varices while only 12 (29.3%) did not have any varices. The reason for less number of grade 3 and no case with grade 4 is probably that we have excluded the patients with present or past h/o upper GI bleeding. There was no significant association found between hepatic encephalopathy and varices. There was a significant association found between alcoholism and grades of varices, maximum patients who were chronic alcoholic had grade 2 or grade 3 varices. There was no significant association found between portal vein diameter and varices. We found significant linear association between INR and grade of varices. At the same time, we did not find any association between other parameters such as age, Sr. bilirubin, SGOT, SGPT or Sr. albumin and grade of varices. There is a significant association of platelet count with the presence or absence of varices, a significant linear association is also seen between increased bipolar spleenic diameter and presence of varices. The other parameters such as SAAG, Child Pugh score and haemoglobin showed no association with presence of varices. Several Studies [5, 7,9,14,15,17,18,19] have shown that platelet count and spleen diameter correlate well with the presence of EVs. However, in patients with chronic liver disease, the presence of a decreased platelet count may depend on several factors other than portal hypertension, such as shortened mean platelet lifespan, decreased thrombopoietin production or myelotoxic effects of alcohol or hepatitis viruses [24]. On the other hand, the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbances that are mainly related to portal hypertension. With this in mind, Giannini et al attempted to devise a new parameter that might be more consistent with the noninvasive diagnosis of EVs in cirrhotic patients. The parameter connects thrombocytopenia to splenomegaly to introduce a variable that takes into consideration the decreased platelet count most likely attributed to hypersplenism caused by portal hypertension [24].

Using the Giannini criteria [13], out of 41 patients, 29 (70.7%) had a PC/SD ratio more than 909 (10.7%) and only 12 (29.3%) had ratio less than 909. Using the PC/SD ratio of ≤909 in predicting varix, the present study showed the sensitivity of 89.66%, specificity was 75% , PPV of 89.66% and NPV of 75% (Accuracy = 85.37 %, Kappa Value = 0.647, p Value <0.05). These results are much less than the original study with 100% sensitivity and 77% specificity.

Considering the PC/SD ratio cut off 909 as suggested by Giannini et al [13] (which yielded 100% sensitivity and 93% specificity) present study yielded a sensitivity are carried out with below.

Study	PC/SD RATIO	Sensitivity	Specificity	PPV	NPV
Baig et al[19]	909	80%	89%	95.4%	95.1%
Giannini et al[13]	909	100%	93%	96%	100%
Sarangapani et al [25]	909	88.5%	83%	83.3%	90.5%
Present study	909	89%	75%	89.66%	75%

Chawla S et al [26] did a systematic review and meta-analysis of 8 studies which included a total of 1275 patients. Meta-analysis yielded a pooled sensitivity of 89% [95% confidence interval (CI 87.92%; I2 statistic 92.9%] and a pooled specificity of 74% (95% CI 70.78%; I2 statistic 94.5%). They concluded that the test characteristics of PC/SD ratio of 909 may not be adequate to completely replace UGIE as a noninvasive screening tool for esophageal varices, given the low grade of evidence. However, it may be potentially useful as part of a prediction rule incorporating other clinical characteristics or varying PC/SD cutoffs. When compared with other noninvasive predictor tools, the PC/SD ratio is elegant, simple, and inexpensive. With some minor modifications, it may become a helpful tool to limit the number of endoscopies to be performed in patients for primary prophylaxis of variceal bleeding in portal hypertension.

In present study deriving from the above ROC curve the PC/SD ratio with the 100% sensitivity, the ratio came out to be 376.8 only with specificity of 44.8%. Currently, there are only a few randomized-controlled trials in the published literature that examine the efficacy of the PC/SD ratio for diagnosis of esophageal varices. Apart from being noninvasive,

the PC/SD ratio is a relatively inexpensive test as platelet counts and abdominal ultrasounds would be obtained on all cirrhotic patients routinely as part of their clinical workup.

Some limitations of the present study -
- There were relatively small no. of cases;
- Majority of patients already had ascites at the time of study;
- There is possibility of some confounding factors for low platelet count eg. low vitamin 812 level.

We need to study further with large no. of cases addressing these issues and whether it may be worth considering separate PC/SD cut off values for compensated and non-compensated cirrhotics.

Conclusion

The use of platelet count/ spleenic diameter ratio in cirrhotic patients for screening and follow up for esophageal varices can substantially reduce the cost of health care and discomfort for patients as well as reduce burden of endoscopy unit.

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