STUDY ON PLATELET COUNT TO SPLENIC DIAMETER RATIO A NON-INVASIVE TOOL IN PREDICTING THE PRESENCE OF OESOPHAGEAL VARICES

Srinivas V. Shenoy¹, Kiran VH², Dinesha³

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ABSTRACT: BACKGROUND: Cirrhosis of liver is one of the most commonly encountered diseases in our clinical practice. Portal hypertension and its complications mainly the oesophageal varices are responsible for most of the morbidity and mortality associated with cirrhosis. Though endoscopy has remained the investigation of choice both in the diagnosis and management of oesophageal varices, the economic burden continues to be a deterrent to its further expansion. Platelet count/splenic diameter ratio (PC/SD ratio) has been proposed as a screening tool for detection of oesophageal varices. However there has been no uniformity in the results obtained thus far. Our aim was to validate this parameter as a reliable non-invasive marker for oesophageal varices. **METHODOLOGY:** Our study was a cross-sectional observational study conducted in the Kasturba Medical College (KMC) group of hospitals Mangalore, where 60 cirrhosis of liver patients underwent clinical, laboratory and imaging studies including an upper gastrointestinal endoscopy. Stable patients without an active diagnosed variceal bleed were included in the study and patients previously treated for varices or having other diseases contributing to thrombocytopenia were excluded. **RESULTS:** Platelet count/Splenic diameter ratio, platelet count, bipolar splenic diameter, Child's score, Model for End stage Liver Disease (MELD) score were all found to be statistically significant using the Univariate and Multivariate analyses by Chi square test, Mann-Whitney U test, student t test. Receiver operating characteristic (ROC) curves were drawn for each of these parameters to find the parameter with the best sensitivity and specificity. "C index" equivalent to area under ROC (AUROC) curve gave the best sensitivity and specificity to the PC/SD ratio with "c-index" value of 0.969. In this study a cut off of 967 was got which gave the best positive predictive value of 93.8 % and negative predictive value of 89.1% which is lower than the mentioned studies. The sensitivity and specificity was 92% and 91% respectively for the same cut-off value. **CONCLUSION:** PC/SD ratio is a simple, inexpensive, easily reproducible, non-invasive marker for oesophageal varices that maybe used in a resource depleted setting for predicting the presence of varices.

KEYWORDS: PC/SD ratio Oesophageal Varices.

INTRODUCTION: Portal Hypertension and its sequelae mainly Oesophageal Varices (EV) is one of the most important causes of morbidity and mortality in patients with cirrhosis of liver.⁽¹⁾ The estimated incidence of EV in patients with cirrhosis of liver is between 40% to 80%. Nearly 30% of the patients with EV will bleed within 1 year at the time of diagnosis.⁽²⁾ The mortality being around 20%-35% for variceal bleeding depending on the underlying severity of liver disease.⁽³⁾ Hence detection of EV in patients with cirrhosis of liver becomes paramount for decreasing the morbidity and mortality. As per the latest Baveno V consensus workshop held in 2010 by eminent gastroenterologists it has been reiterated that all patients with cirrhosis of liver undergo screening for the presence of oesophageal varices at the time of diagnosis.⁽⁴⁾

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As far as the diagnosis of EV, endoscopy has remained the investigation of choice and periodic endoscopies have been recommended for monitoring of varices.⁽⁴⁾ These guidelines though based on sound scientific principles and research, put an enormous load on the medical services economically.

To this burden can be added the mental agony of patients having to undergo repeated endoscopy which may render them non-compliant and unwilling for further follow up which might be catastrophic in the long run.

To overcome this shortcoming associated with endoscopy, there was a need to develop non-invasive modalities to detect the presence of oesophageal varices. Certain biochemical, clinical and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the risk of bleeding from varices. Identification of non-invasive predictors of oesophageal varices will enable us to carry out upper gastrointestinal (GI) endoscopy in selected groups of patients, thus avoiding unnecessary intervention and at the same time not missing the patients at risk of bleeding. Among the non-invasive modalities, the ratio of platelet count and bipolar splenic diameter has shown promising results in terms of its accuracy in predicting the presence of oesophageal varices in many studies.^(1,5,6)

The above studies were mainly conducted among the western population and a few studies were also done in the Asian population.^(7,8) An attempt was made here to study the spectrum of patients with cirrhosis liver and the non-invasive predictors for oesophageal varices (EV) with special focus on the platelet count and splenic diameter ratio (PC/SD ratio).

MATERIALS AND METHODS: The study was a cross-sectional observational study done in the Kasturba Medical College group of hospitals, Mangalore, which is a tertiary care center. The study was carried out between October 2012 to April 2014. The study population consisted of patients diagnosed with chronic liver disease. A sample size of 60 was calculated by results obtained from previous studies^(5,7) for statistical significance.

The inclusion criteria were based on a combination of clinical, laboratory, ultrasound criteria for chronic liver disease. Patients who had been diagnosed active variceal bleed, which had been previously treated for varices either through banding or surgery, were excluded from the study. Other diseases or conditions associated with thrombocytopenia like malaria, immune thrombocytopenic purpura (ITP) also were part of the exclusion criteria.

The information collected for each patient included: Age, Gender, Etiology of Cirrhosis, clinical features (Common), biochemical parameters (Aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, serum albumin, serum creatinine, platelet count, presence and degree of ascites and encephalopathy assessed according to Child- Pugh criteria.⁽⁹⁾ In addition Model for Endstage Liver Disease (MELD) Score was also calculated for all patients.

All patients underwent an abdominal ultrasonography to assess for evidence of chronic liver disease.⁽¹⁰⁾ In addition the bipolar splenic diameter, portal vein diameter, presence of ascites was also included in the evaluation. The patients also underwent an upper gastrointestinal endoscopy by a single gastroenterologist. The presence or absence of EV was recorded. Both the ultrasonologists and the gastroenterologists were blinded to the results. Once the endoscopy and ultrasonography was done for the patients, the PC/SD ratio was calculated for analysis.

The study conformed to the ethical guidelines of the declaration of Helsinki and was carried out after clearance from the Institutional ethics committee at KMC Mangalore. An informed consent was taken from all patients during the study enrolment.

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Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean $\pm$ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance was assessed at 5% level of significance. Student t test (Two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis). Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Receiver operating characteristic (ROC) curve was applied to find out the cut-offs to each of the variables under the study to find out the best sensitivity and specificity value to predict the presence or absence of varices.

The validity of the model was measured by concordance statistics (Equivalent to the area under the ROC curve). A model with a c-index above 0.7 is considered fair, while a c-index between 0.8 and 0.9 is good and a c-value greater than 0.9 indicates excellent diagnostic accuracy. Significant figures were considered as below.

Suggestive significance (P value: $0.05 < P < 0.10$), moderately significant (P value: $0.01 < P \leq 0.05$) & strongly significant (P value: $P \leq 0.01$)

Statistical software's like SPSS 15.0 were used for the statistical analysis and Microsoft Word and Excel were used to generate graphs and tables.

RESULTS: A total of 60 patients were included in the study out of which 56 were males (93%) and 4 were females. The mean age was around 50 years. The age distribution of patients was uniform (Table 1). Various etiologies of cirrhosis in the study included alcohol abuse (n=46), hepatitis B (n=2), hepatitis C (n=1), autoimmune (n=1), cryptogenic (n=7), Wilson's disease (n=1) and combined alcohol+hepatitis B (n=2) (Table 2).

Among the 60 cirrhosis patients who were part of the study, 16 belonged to Child- Pugh class A (26.7%), 32 were class B (53.3%) and 12 were class C (20%). 35 patients in total had oesophageal varices (58.3). The grading of varices was not done since the purpose of the study was to screen patients for presence of any grade of varices. The platelet count, PC/SD ratio, child score and MELD score were significantly different in the patients with and without varices (Tables 3-6).

The ROC curve was applied to determine the cut-off values with the best sensitivities and specificities for all variables. A cut-off value of 967 was obtained for platelet count to spleen diameter ratio, which gave a sensitivity of 92% and a specificity of 91%. The area under the ROC curve was 0.969 (95% CI 0.933 to 1.005), indicating excellent diagnostic accuracy (Table 7, Fig 1).

Age	Frequency	Percent
31-40	16	26.7
41-50	16	26.7
51-60	16	26.7
>60	12	20.0
Total	60	100.0

Table 1: Age distribution

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Etiology	Frequency	Percentage
Alcohol	46	76.66
Wilson's	1	1.66
Autoimmune	1	1.66
Cryptogenic	7	11.66
Hepatitis B	2	3.33
Hepatitis C	1	1.66
Alcohol + Hepatitis B	2	3.33
Total	60	100

Table 2: Showing frequency of various etiologies for cirrhosis

Platelet count to Oesophageal Varices:

Oesophageal Varices	N	Mini-mum	Maxi-mum	Mean	Standard Deviation	Median	P value
YES	35	55000	249000	93714.29	40416.63	84000.00	HS
NO	25	94000	366000	228640.00	84649.21	224000.00	< 0.001

Table 3: Correlation between Platelet counts to Oesophageal varices

PC/SD RATIO:

Oesophageal Varices	N	Mini-mum	Maxi-mum	Mean	STD. Deviation	Median	P-value
YES	35	338	1556	654.29	257.228	606.45	HS
NO	25	764	3100	1895.99	743.055	1991.00	<0.001

Table 4: Correlation between Platelet count/Splenic diameter ratio and oesophageal varices

According to the student t-test, Platelet count/Splenic diameter ratio was significantly associated with oesophageal varices (p-value < 0.001)

CHILD'S SCORE:

Oesophageal Varices	N	Mini-mum	Maxi-mum	Mean	STD. Deviation	Median	P- value
YES	35	6	13	8.86	1.896	9.00	HS
NO	25	5	10	6.56	1.356	6.00	<0.001

Table 5: Co-relation between Child's score and EVs (oesophageal varices)

The mean Child's Score in patients with oesophageal varices was 8.86 and those patients without varices were 6.56 and this association was statistically significant.

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MELD SCORE:

Oesophageal Varices	N	Minimum	Maximum	Mean	STD. deviation	Median	P-value
YES	35	8	34	17.69	5.815	16.00	HS
NO	25	7	20	12.16	3.210	12.00	< 0.001

Table 6: Co-relation between MELD score and Oesophageal varices

Platelet count/Splenic diameter ratio (PC/SD ratio):

Area under the curve

Test result variable(s): Platelet count/splenic diameter ratio

Area	STD. Error	p-value	Asymptotic 95% Confidence Interval	
.969	.018	<0.001	.933	1.005

Table 7: AUROC for PC/SD ratio

Fig. 1: ROC curve for PC/SD ratio

According to this ROC curve a value of 967 gave the best sensitivity and specificity of 92% and 91% respectively.

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DISCUSSION: Oesophageal varices continue to be one of the most important causes for hospitalization of the patients with chronic liver disease most often with life threatening haemorrhage. Hence detection of oesophageal varices has become a cornerstone in the management of all patients with chronic liver disease. Oesophago-gastro-duodenoscopy or in simple terms an Upper GI Endoscopy has become the 'Gold Standard' in the diagnosis and management of patients with oesophageal varices. The current recommendations for endoscopy as per the periodic Baveno Consensus meetings are to screen for varices at the time of diagnosis of the chronic liver disease.⁽⁴⁾

In case there are no varices at the time of the diagnosis the patient has to undergo follow up endoscopy every 2-3 years and in case of small varices the patient needs to undergo follow up endoscopy at least once a year.

Multivariate analysis of the various parameters mentioned above revealed a highly significant association of platelet count, bipolar splenic diameter, Platelet count/splenic diameter ratio, Child's score and MELD score. Hence Receiver Operating Characteristics curves (ROC) were constructed to find the parameter with the best association. Area under Curve (AUC) or 'c-index' was used for statistical significance. All the above parameters showed statistical significance however the best parameter with a 'c-index' value of 0.969 was the platelet count/splenic diameter ratio.

The platelet count/ spleen diameter ratio was deemed to be the appropriate parameter to be used as splenomegaly is implicated in thrombocytopenia of cirrhosis with spleen size being inversely co-related with platelet count. The use of this ratio normalizes platelet count to splenic sequestration since platelet count alone may be misleading and cannot be solely attributed to portal hypertension. 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 life- time, decreased thrombopoietin production or myelotoxic effects of alcohol or hepatitis viruses.⁽¹¹⁾ 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.

Giannini et al study of 145 patients with cirrhosis found that the negative predictive value of platelet count/spleen diameter ratio 909 was 100%. Agha et al.⁽¹²⁾ Studied 114 patients with compensated HCV related cirrhotics, 909 cut-off showed negative predictive value 100% and a positive predictive value of 93.8% for the diagnosis of EV. Baig et al. reported a cut-off value of 1014, which gave positive and negative predictive values of 95.4% and 95.1%, respectively. In this study a cut off of 967 was got which gave the best positive predictive value of 93.8% and negative predictive value of 89.1% which is lower than the mentioned studies.

Chawla S et al did the first systematic review and meta-analysis examining the test characteristics of the PC/SD ratio of 909 for noninvasively predicting oesophageal varices. Their meta-analyses yielded a pooled sensitivity of 89% and a pooled specificity of 74%. The overall grade of evidence was low, suggesting that these results may not be reliable for other patient settings.⁽¹³⁾ In particular, cirrhosis secondary to alcohol would seem to have more false-positive results because of the thrombocytopenia from other etiologies including marrow suppression from alcohol and malnutrition (Vitamin B12 deficiency). In addition, alcohol is associated with lower thrombopoietin levels and increased antibody-mediated platelet destruction. This was also demonstrated by Sarangapani et al study, in which the prevalence of cirrhosis secondary to alcohol was over 50% and the specificity remained at 83%.⁽¹⁴⁾

Child's Score though showed statistical significance, however did not give an acceptable cut-off. The best sensitivity of 77% was got at score between 7 to 8 which is not at all acceptable for a

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screening parameter. MELD score gave a best sensitivity of 85% with specificity of 56%. Earlier studies did not evaluate these prognostic indices as probable screening tools though most studies mentioned above showed statistical significance in the univariate and multivariate analyses. However in view of low sensitivities and specificities for the cut off values obtained, these two prognostic

CONCLUSION: PC/SD ratio is a simple, inexpensive, easily reproducible, non-invasive marker for esophageal varices that maybe used in a resource depleted setting for predicting the presence of varices. In a rural setting, where facilities for endoscopy may not be available, a careful watch on the PC/SD ratio by the physician may help him decide when to refer the patient for endoscopy rather than having to send every patient which may not be feasible in view of limited resources.

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AUTHORS:

1. Srinivas V. Shenoy
2. Kiran VH.
3. Dinesha

PARTICULARS OF CONTRIBUTORS:

1. Junior Resident, Department of Internal Medicine, KMC Mangalore.
2. Junior Resident, Department of Internal Medicine, KMC Mangalore.
3. Professor, Department of Internal Medicine, KMC Mangalore.

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Dr. Kiran VH,
S/o. Venkataramana S,
Sneha Nilaya,
1st Cross, Sharavathi Nagar,
Shimoga-577202.
E-mail: vajrabahu2886@gmail.com

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