



PLATELET COUNT AND SPLEEN DIAMETER RATIO FOR NON INVASIVE DIAGNOSIS OF ESOPHAGEAL VARICES

General Medicine

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ABSTRACT

BACKGROUND: Portal Hypertension and its consequences mainly, Esophageal Varices (EVs) is one of the most important causes of morbidity and mortality in patients with cirrhosis of liver. Upper GI endoscopy is the investigation of choice for diagnosis of EVs and periodic endoscopies have been recommended for monitoring of varices. There is a need for non-invasive parameters to detect the presence of EVs. Identification of non-invasive predictors of EVs will help us to carry out EGD in selected groups of patients. Unnecessary endoscopies can be avoided and at the same time, patients who require endoscopy can be referred to a higher center, where facilities for endoscopy are available. Among the non-invasive modalities, the platelet count and bipolar spleen diameter ratio has shown promising results in terms of its accuracy in predicting the presence of Esophageal Varices in many studies. **MATERIALS AND METHODS:** Patients with chronic liver disease diagnosed using clinical, Laboratory and ultrasound parameters were assessed using esophagogastroduodenoscopy for the presence or absence of esophageal varices. USG abdomen was done to assess for bipolar splenic diameter and the presence or absence of EVs was correlated with the platelet count/ splenic diameter ratio, CHILD SCORE, MELD score, Platelet count alone and splenic diameter alone. Platelet count/SD ratio of 909 based on previous studies was correlated with the presence or absence of varices. Statistical analysis was done using IBM SPSS software version 20.0 and variables showing statistically significant correlations with presence of varices were used for plotting ROC curves to assess the cut of points which could be used for non invasive prediction of varices. **RESULTS:** The PC/SD ratio cut off (909), based on previous studies for non invasive diagnosis of Esophageal Varices gave sensitivity and specificity of 97.9% and 91.7% respectively, in our study, which was statistically significant (P value <0.001). The positive predictive value and negative predictive value of the PC/SD ratio (909) was 96.5% and 94.8% respectively and the accuracy of the test was 96%. ROC curve for Platelet count and Splenic diameter ratio area under the curve is 97.8% with P value < 0.001 and cutoff value 895.02 with sensitivity 96.6% and specificity 96.5%. The Positive predictive value and negative predictive value of PC/SD ratio of 895 was found to be 98.6% and 91.8% respectively and the accuracy of the test 96.5%. ROC curve for Child score in our study, area under the curve 71% with a significant P value < 0.001, and cut-off value obtained for Child score was 8.50 with sensitivity 64.8% and specificity 63.8 %. ROC curve for MELD score revealed area under the curve was 74.3% with P value as < 0.001, and the cut-off value was 15.5 with sensitivity 67.6 % and specificity 67.2%. ROC curve for Platelet count in our study, the area under the curve was 94.5% with P value as < 0.001, and the cut-off value was 108500 with sensitivity and specificity of 89.7% and 89.4% respectively. The ROC curve for Spleen diameter in our study revealed that the area under the curve was 86.8% with P value as < 0.001, and the cutoff value was 121 with sensitivity and specificity of 78.9% and 81.0% respectively. **CONCLUSION:** Among the variables studied for non-invasive diagnosis of Esophageal varices, the Platelet count / Spleen diameter ratio had the best sensitivity and specificity for diagnosing EVs. In view of low sensitivities and specificities for the cut off values obtained for Child score, MELD score, platelet count and spleen diameter, these indices may not be useful as PC/SD ratio in the non-invasive prediction of EV's. The Platelet count / Spleenic diameter ratio may be proposed as a safe parameter for diagnosing Esophageal Varices in Chronic Liver disease noninvasively, where resources are limited and endoscopy facilities are not available, to select the patients with probable Esophageal Varices who can be referred to higher centres

KEYWORDS

Cirrhosis, Platelet count splenic diameter ratio, esophageal varices, CHILD score, MELD score

INTRODUCTION

Chronic liver disease (CLD) is defined when duration of illness is more than 6 months. It generally progresses to cirrhosis, often over 20 to 40 years. Portal hypertension is a common complication of cirrhosis, can result in the development of collaterals to bypass the increased resistance to flow within the portal vein to return blood to systemic circulation, which in turn can result elevated pressures within the portal vein, leading to portal hypertension.

Portal Hypertension and its consequences mainly, Esophageal Varices (EVs) is one of the most important causes of morbidity and mortality in patients with cirrhosis of liver¹. The estimated incidence of Esophageal Varices in patients with cirrhosis of liver is around 40% to 80%. Nearly, 10-30% of all cases of upper gastro-intestinal bleeding are secondary to Varices². Based on the underlying severity of Liver disease, mortality rate was around 20% - 35% for variceal bleeding³. Hence, detection of presence of EV in patients with cirrhosis of liver is important for decreasing the morbidity and mortality in patients with cirrhosis of liver.

As per the Baveno V consensus workshop patients with cirrhosis of liver should undergo screening for the presence of EVs at the time of diagnosis⁴.

Upper GI endoscopy is the investigation of choice for diagnosis of EVs

and periodic endoscopies have been recommended for monitoring of varices⁴. These guidelines, though based on scientific principles and research, put an enormous pressure on the medical services economically. Patients have to undergo repeated endoscopy which may make them, non-compliant for follow up.

There is a need for non-invasive parameters to detect the presence of EVs. There are multiple studies which show that few clinical, biochemical and ultrasonographic parameters alone or together have good predictive power for non-invasively detecting the presence of Esophageal Varices. Identification of non-invasive predictors of EVs will help us to carry out EGD in selected groups of patients. Unnecessary endoscopies can be avoided and at the same time, patients who require endoscopy can be referred to a higher center, where facilities for endoscopy are available. Among the non-invasive modalities, the platelet count and bipolar spleen diameter ratio has shown promising results in terms of its accuracy in predicting the presence of Esophageal Varices in many studies^{1,5,6}.

Studies were mainly conducted among the western population and a few studies were also done in the Asian population^{6,7,8}. An attempt was made here to study the spectrum of patients with cirrhosis liver and the non-invasive predictors for EVs with focus on the platelet count and spleen diameter ratio (PC/SD ratio) in a South-Indian population in a tertiary care center.

Rationale behind this study is to avoid unnecessary investigations, to empathise on cost benefit of empirical treatment, decrease number patients being administered avoidable treatment and increasing number properly screened and treated patients. In a rural setting, where facilities for endoscopy may not be available- a non-invasive method will help clinician to decide when to refer patient for endoscopy.

Primary Objective:

To validate whether Platelet count / Spleen diameter ratio can be used as a non-invasive tool in the prediction of Esophageal Varices in patients with cirrhosis of liver.

Secondary Objectives:

1. To assess whether severity of liver disease calculated through Child Pugh's score and MELD score can predict the presence of Esophageal Varices.
2. To assess whether Platelet count, Spleen diameter can independently predict the presence of Esophageal Varices.

MATERIALS AND METHODS

Study setting and study design

Patients with chronic liver disease admitted to the Department of General medicine and Gastromedicine in a tertiary care hospital in South India.

It was a prospective cross sectional observational study design.

Sample size and type of sampling

Based on sensitivity, specificity and accuracy of the platelet count and spleen diameter ratio, with respect to endoscopy (with a cutoff point, ratio 909), reported in earlier publications (Reference- American Journal of Gastroenterology ISSN:0002-9270, National journal of medical research ISSN: 2249 4995) and with 95% confidence and 20% allowable error, minimum sample size comes to <5. However we have included 200 cases in this study. This will give the estimate 99% confidence and only <5% error.

Study period

18 months from October 2015 to April 2017

STUDY patients

INCLUSION CRITERIA

1. All patients included in the study were patients with cirrhosis of liver. Cirrhosis was diagnosed based on clinical, laboratory and imaging criteria.

Clinically –atleast one sign of liver cell failure (jaundice, parotid swelling, loss of axillary/pubic hair, palmar erythema, spider naevi, dupuyten's contracture, gynaecomastia, testicular atrophy)

Laboratory investigations –reversal of Albumin; Globulin ratio and raised prothrombin time

Imaging – Ultrasound evidence for cirrhosis

Liver edge (blunted), liver surface (irregular), and liver parenchyma (coarse echotexture)⁹.

Patients fulfilling all the previous 3 criteria – clinical + laboratory + radiological were included.

Informed consent was obtained from all the patients

Institutional Ethics committee provided the ethical clearance for the study

EXCLUSION CRITERIA

1. Patients who had been previously treated for Esophageal Varices including band ligation, sclerotherapy and TIPS.
2. Patients having co-existing conditions producing low platelet count such as malaria, dengue, ITP etc.
3. Patients on drugs that were known to cause thrombocytopenia were also excluded.
4. Patients with diagnosed active variceal bleed were excluded.

Data collection Methods

The information collected for each patient included age, gender, etiology of cirrhosis, clinical features, biochemical parameters (Aspartate aminotransferase [AST], Alanine aminotransferase [ALT],

total bilirubin, serum albumin, serum creatinine, platelet count, presence and degree of ascites and encephalopathy. In addition, Child score and MELD score was calculated for all patients.

All patients underwent an abdominal ultrasonography to assess for evidence of chronic liver disease and presence of ascites, bipolar splenic diameter was also included in the evaluation. The patients also underwent an Esophagogastro -duodenoscopy to look for presence or absence of Esophageal Varices. Platelet count was measured in (N/mm^3) and maximum spleen diameter was determined and bipolar splenic diameter was expressed in millimeter(mm). Platelet count and spleen diameter ratio [$(N/mm^3)/mm$] was calculated in all patients and its diagnostic accuracy was compared with presence or absence of Esophageal Varices

STATISTICAL ANALYSIS

1. Validity parameters such as sensitivity, specificity, accuracy, predictive values of positives and negatives of Platelet count and Spleen diameter ratio with respect to endoscopy were computed
2. Based on the data, ROC analysis was done to find out an ideal cut off point with maximum possible sensitivity and specificity.

METHODS OF STATISTICAL ANALYSIS

Statistical analysis was done using IBM SPSS version 20.0 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are either given in Mean $\pm$ SD, and for categorical variables as percentage. To compare the mean difference of numerical variables between groups, independent two sample 't' test was applied for parametric data and mann whitney u test for non parametric data. To find out the association between two categorical variables, chi-square test was applied. ROC curve was used to find out the cutoff value of non-invasive variables for diagnosis of Esophageal Varices, to compare the outcome of two different methods, McNemars test was used with sensitivity, Specificity, Predictive Value Positive, Predictive value Negative and Accuracy. A P-value < 0.05 was considered as statistically significant. Microsoft Word and Excel were used to generate graphs and tables.

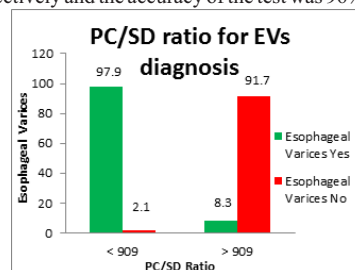
RESULTS:

1. Platelet count / Spleen diameter ratio of 909 for non invasive diagnosis of Esophageal Varices

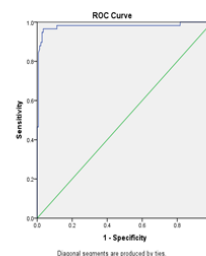
Esophageal varices	PC/SD Ratio		P Value	Sensitivity (%)	Specificity (%)	Accuracy (%)
	Yes < 909 n (%)	No > 909 n (%)				
No	3 (2.1)	55 (91.7)	< 0.001	97.9	91.7	96
Yes	137 (97.9)	5 (8.3)				

Original table 1

The PC/SD ratio cut off (909), based on previous studies for non invasive diagnosis of Esophageal Varices gave sensitivity and specificity of 97.9% and 91.7% respectively, in our study, which is statistically significant (P value < 0.001). The positive predictive value and negative predictive value of the PC/SD ratio (909) was 96.5% and 94.8% respectively and the accuracy of the test was 96%.



2. Receiver operating characteristic curve for PC/SD ratio



Original figure 2: ROC curve for Platelet count and Splenic diameter ratio area under the curve is 97.8% with P value < 0.001 and cutoff value 895.02 with sensitivity 96.6% and specificity 96.5%. The Positive predictive value and negative predictive value of PC/SD ratio of 895 was found to be 98.6% and 91.8% respectively and the accuracy of the test 96.5%.

3. Age distribution of patients

Age category	Frequency	Percentage
21-30	4	2.0
31-40	16	8.0
41-50	53	26.5
51-60	57	28.5
> 60	70	35.0

Table2

4. Comparison of mean age among groups

Variable	Esophageal varices						P-value
	No			Yes			
	N	Mean	SD	n	Mean	SD	
Age	58	58.59	13.0	142	53.6	10.67	0.011

Original table3

5. Gender distribution

Gender	Frequency	Percentage
Female	19	9.5
Male	181	90.5

Original table4

6. Distribution of Esophageal Varices

Esophageal varices	Frequency (n=200)	Percentage
No	58	29.0
Yes	142	71.0

Original table5

7. Distribution of patients based on Etiology

Etiology	Frequency	Percentage
ALCOHOL	144	72.0
AUTOIMMUNE	3	1.5
CRYPTOGENIC	14	7.0
CYSTIC FIBROSIS	1	0.5
DRUG	5	2.5
HEMOCHROMATOSIS	2	1.0
HEP B	9	4.5
HEP C	7	3.5
NASH	13	6.5
WILSON	2	1.0

Original table6

8. Distribution of patients according to Child's classification

CHILD	Frequency	Percentage
A	49	24.5
B	59	29.5
C	92	46.0

Original table7

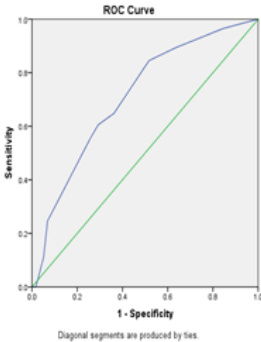
9. Association of Esophageal Varices with Child's classification

CHILD	Esophageal varices				P Value
	No		Yes		
	N	(%)	n	(%)	
A	28	57.1	21	42.9	< 0.001
B	16	27.1	43	72.9	
C	14	15.2	78	84.8	

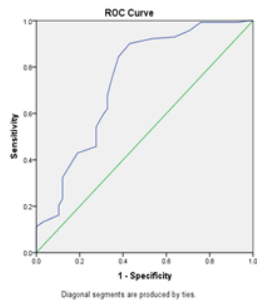
Original table8

10. Receiver operating characteristic curve for Child's score

Original figure 3: According to ROC curve for Child score in our study, the area under the curve is 71% with P value < 0.001, and the cut-off value is 8.5 with sensitivity and specificity of 64.8% and 63.8% respectively

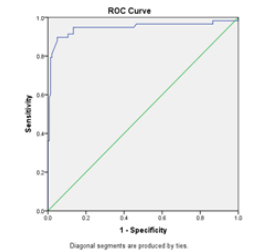


11. Receiver operating characteristic curve for MELD score



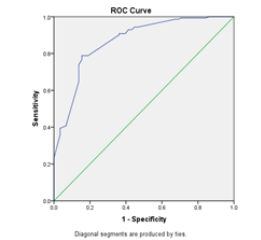
Original figure 4: According to ROC curve for MELD score in our study, the area under the curve is 74.3% with P value as < 0.001, and the cut-off value is 15.5, with sensitivity and specificity of 67.6% and 67.2% respectively

12. Receiver operating characteristic curve for platelet count



Original figure 5: According to ROC curve for Platelet count in our study, the area under the curve is 94.5% with P value as < 0.001, and the cut-off value is 108500 with sensitivity and specificity of 89.7% and 89.4% respectively.

13. Receiver operating characteristic curve for Spleen diameter



Original figure 6: According to ROC curve for Spleen diameter in our study, the area under the curve is 86.8% with P value as < 0.001 and the cutoff value is 121 with sensitivity and specificity of 78.9% and 81.0% respectively

14. Statistical analysis of clinical presentation variables in association with Esophageal Varices

A) Association of sex with Esophageal Varices					
Sex	Esophageal varices				P value
	No		Yes		
	N	%	n	%	
Male	47	26.0	134	74.0	<0.05
Female	11	57.9	8	42.1	

Original table9

B) Association of abdominal distension with Esophageal Varices

Abdominal distension	Esophageal varices				P value
	No		Yes		
	n	%	n	%	
No	39	47.0	44	53	<0.001
Yes	19	16.2	98	83.8	

Original table10

C) Distribution of various etiologies with Esophageal Varices

Etiology	Esophageal varices			
	No		Yes	
	n	%	n	%
ALCOHOL	39	27.1	105	72.9
AUTOIMMUNE	2	66.7	1	33.3
CRYPTOGENIC	6	42.9	8	57.1
CYSTIC	0	0.0	1	100.0
DRUG	2	50.0	2	50.0
HEMOCHROMATOSIS	0	0.0	2	100.0
HEP B	3	33.33	6	66.66
HEP C	0	0.0	7	100.0
LITHIUM	1	100.0	0	0.0
NASH	5	38.5	8	61.5
WILSON	0	0.00	2	100.0

Original table11

15. Comparison of Esophageal Varices with main variables

Variables	Esophageal varices	n	Mean	SD	P Value
Platelet	No	58	180820.69	77826.42	< 0.001
	Yes	142	73212.68	25082.31	
AST	No	58	70.69	55.21	0.575
	Yes	142	71.22	64.93	
ALT	No	58	43.40	57.07	0.927
	Yes	142	38.11	31.14	
Total bilirubin	No	58	3.45	4.87	0.005
	Yes	142	4.88	4.65	
Albumin	No	58	2.97	0.68	0.016
	Yes	142	2.67	0.52	
INR	No	58	1.42	0.47	< 0.001
	Yes	142	1.93	0.91	
Creatinine	No	58	1.07	0.31	< 0.001
	Yes	142	1.39	0.71	
Spleen diameter	No	58	109.68	19.30	< 0.001
	Yes	142	133.289	14.91	
PC/SD ratio	No	58	1667.60	672.74	< 0.001
	Yes	142	552.30	204.13	
MELD score	No	58	13.43	6.173	< 0.001
	Yes	142	19.85	6.750	
Child score	No	58	7.88	2.583	<0.001
	Yes	142	9.77	2.277	

Original table12

DISCUSSION

Esophageal varices is an important cause for morbidity of the patients with CLD. Detection of EVs has become essential in the management of patients with CLD.

Upper gastrointestinal endoscopy is the 'Gold Standard' in the diagnosis and management of patients with EVs. In our study an attempt was made to describe the clinical and laboratory parameters of CLD patients and to link it to the presence of EVs focussing especially on the parameters in our study namely PC/SD ratio, platelet count, bipolar spleen diameter, Child's score and MELD score.

An attempt was made to include patients in the study who were representative of the population of cirrhotics seen in clinical practice and also to avoid biases by selection of particular subgroups of patients.

Platelet count / Spleen diameter ratio, Child's score and MELD score Multivariate analysis of the various variables mentioned above revealed a highly significant association of platelet count, bipolar

spleen diameter, Platelet count / Spleen diameter ratio, Child's score and MELD score. Hence, Receiver operating characteristics curve was constructed to find the variable with the best association. Area under curve was used for statistical significance. Area under curve for platelet count was 0.945, spleen diameter was 0.868, PC/SD was 0.978, Child score and MELD score was 0.710 and 0.743 respectively. All the above mentioned variables were found to be statistically significant (P value <0.001).

The cut off value for Platelet count / Splenic diameter in our study was found to be 895 with a sensitivity and specificity of 96.6 and 96.5% respectively. The positive predictive value and negative predictive value of the Platelet count / Spleen diameter ratio are 98.6 and 91.8% respectively. The accuracy of the test was found to be The Platelet count / Spleen diameter ratio of 909 based on previous studies^{15,10}, for non-invasive diagnosis of Esophageal varices gave sensitivity of 97.9% and specificity of 91.7% in our study, which is statistically significant (P value <0.001). The positive predictive value and negative predictive value of the PC/SD ratio (909) is 96.5% and 94.8% respectively and the accuracy of the test was 96%.

The Platelet count/ Spleen diameter ratio was the variable with the best association for non-invasive diagnosis of Esophageal varices, which is statistically significant (P value- <0.001). Giannini et al¹, in a study of 145 patients with cirrhosis found that the negative predictive value of Platelet count / Spleen diameter ratio 909 was 100%. Giannini et al⁵, showed that the Platelet count / Spleen diameter ratio had 86% diagnostic accuracy for EVs; 909 cut-off had 91.5% sensitivity, 67% specificity, 76.6% positive predictive value and 87% negative predictive value for the diagnosis of EVs. Jayesh Sharma and group¹⁰ showed that Platelet count/ Spleen diameter ratio of 909 showed sensitivity and specificity of 98.6% and 96% respectively for detection of EVs with positive and negative predictive value of 98.6% and 96% respectively. In our study a cut off value of 895 was obtained which gave the best positive predictive value and negative predictive value of 98.6% and 91.8% respectively.

ROC curve for Child score in our study, area under the curve 71% with a significant P value < 0.001, and cut-off value obtained for Child score was 8.50 with sensitivity 64.8% and specificity 63.8 %. The positive and negative predictive value for a cut-off of 8.50 for Child score was found to be 42.5% and 81.4% respectively. ROC curve for MELD score revealed area under the curve was 74.3% with P value as < 0.001, and the cut-off value was 15.5 with sensitivity 67.6 % and specificity 67.2%. The positive predictive value and negative predictive value for MELD score of 15.5 was found to be 45.9% and 83.5% respectively.

In view of low sensitivities and specificities for Child score and MELD score for the cut off values obtained, these cannot be recommended in the non-invasive diagnosis of Esophageal Varices.

According to ROC curve for Platelet count in our study, the area under the curve is 94.5% with P value as < 0.001, and the cut-off value is 108500 with sensitivity and specificity of 89.7% and 89.4% respectively. The ROC curve for Spleen diameter in our study revealed that the area under the curve is 86.8% with P value as < 0.001, and the cutoff value is 121 with sensitivity and specificity of 78.9% and 81.0% respectively.

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 for Child score, MELD score, platelet count and spleen diameter, these indices may not be useful as PC/SD ratio in the non-invasive prediction of Evs.

CONCLUSION

Among the variables studied for non-invasive diagnosis of Esophageal varices, the Platelet count / Spleen diameter ratio had the best sensitivity and specificity for diagnosing Evs.

The Platelet count / Splenic diameter ratio may be proposed as a safe parameter for diagnosing Esophageal Varices in Chronic Liver disease noninvasively, where resources are limited and endoscopy facilities are not available, to select the patients with probable Esophageal Varices who can be referred to higher centres However, more studies are required in a larger population of Cirrhotics with various etiologies

of Chronic Liver disease for validation of the ratio of Platelet count / Spleen diameter ratio and to determine a cut-off value that can be safely recommended for the non-invasive diagnosis of Esophageal Varices.

Limitations

The main etiology of cirrhosis in our study was alcohol; the study needs to be carried out on patients having cirrhosis secondary to other causes, to validate if it can be used as a non-invasive parameter in all the cases of Chronic Liver disease. Inter-observer variability in measurement of bipolar Spleen diameter.

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