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Predictive Value of Platelet Count to Spleen Diameter Ratio for Oesophageal Varices

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ABSTRACT

BACKGROUND AND AIM Oesophageal variceal bleeding is a frequently occurring complication in patients with end stage liver disease and cirrhosis with very high mortality rates. The diagnosis and management of oesophageal varices is dependent on repeated upper gastrointestinal endoscopy which is invasive in nature. However, it presents a problem in terms of non-compliance by patients and its invasive nature. Hence, in this study we explored the use of "ratio of platelet count to spleen diameter" to predict oesophageal varices in patients with cirrhosis as it is a non-invasive parameter and would result in better compliance. Although such a parameter cannot negate the importance of upper gastrointestinal endoscopies but may be used as an adjuvant to ascertain adequate interval for monitoring thereby ensuring optimal utilization of resources.

METHODS: This study was conducted in a tertiary care hospital in Delhi between August 2018 to 2019 and we computed the ratio of platelet count to spleen diameter in all patients to predict oesophageal varices in cirrhotic patients. It was carried out on 81 patients. The diagnosis of liver cirrhosis was made on the basis of clinical evidence of decompensation or varices and/or radiological evidence of nodularity of liver and collaterals and/or fibroscan values suggestive of cirrhosis. Platelet count was recorded and spleen diameter was measured and the ratio was then calculated. In order to confirm oesophageal varices in all these patients, an upper gastrointestinal endoscopy was done as a standard test.

RESULTS: Results showed predominance of male participants at 72.8% (n=59). Overall, the incidence of oesophageal varices was 69.1%. In 38.3% participants, alcoholic liver disease was the cause of cirrhosis. The cut off ratio of ≤975 was present in 65.4% patients and a total 69.1% patients had varices on endoscopy. Thus, the ratio of <975 showed good accuracy in picking up the presence of oesophageal varices which was confirmed on endoscopy. The sensitivity (94.6%), specificity (84%), positive predictive value (93%) and negative predictive value (87.5%) of the ratio were found to be high in predicting oesophageal varices with high Area under the curve (0.96, 95%CI=0.93-0.99).

CONCLUSION: The platelet count to spleen diameter ratio of 975 had high sensitivity (94.6%) and specificity (84%) as well as good positive and negative predictive values of 93% and 87.5 % respectively for predicting oesophageal varices. Based on our study results, the ratio was found to be a good marker to predict the probability of having oesophageal varices among end stage liver disease

patients and can help in categorising high risk patients and thereby prevent unnecessary invasive endoscopies in low risk individuals.

KEYWORDS: platelet count, spleen diameter, oesophageal varices

INTRODUCTION

Liver cirrhosis is an emerging public health problem. There was a 46% increase in chronic liver disease mortality in the world between 1980-2013 [1]. Portal HTN is a complication of cirrhosis which leads to 2 main complications: ascites and variceal haemorrhage. Around 60-80% of patients with cirrhosis can present with oesophageal varices and of these, 20-40% can have varices associated haemorrhage [2,3]. Presently instead of using the term non alcoholic fatty liver disease, we are using the term 'metabolic dysfunction associated fatty liver disease' (MAFLD). The term MAFLD is more holistic in usage as it represents all types of metabolic abnormalities [4]. The incidence and prevalence of MAFLD is also rising globally which would further increase the burden of liver cirrhosis and its complications like oesophageal varices in the future. In this respect, use of non-invasive markers to predict varices will help reduce investigation burden and invasive endoscopies.

Bleeding associated with varices has a high mortality of upto 50% and recurrent bleeding is often witnessed in liver cirrhosis patients [3]. Therefore, current recommendation is to perform endoscopic screening (gold standard test) for all patients diagnosed with end stage liver disease and cirrhosis. This should be performed at the time of presentation itself. If initial endoscopy shows no varices, it is repeated at 2-3 years intervals and in smaller varices, at 1-2 years intervals to evaluate progression of varices [5,6]. However the practise of endoscopic screening increases burden on medical resources (by increasing public cost) and could be hampered by lack of compliance by patients for the screening process because of their invasive nature and its availability in resource limited settings is also questionable. Hence various studies have been done to identify non-invasive parameters to predict oesophageal varices in cirrhosis in order to reduce the patient's financial burden and decrease the frequency of endoscopies. However very few studies have been done in developing countries in this context. We therefore did this study to find a non-invasive parameter that can predict oesophageal varices with high sensitivity and specificity and thereby help in reducing unnecessary endoscopies, especially in liver cirrhosis patients who are at low risk for varices and associated bleeding [7].

Most of the studies done in the past concluded that various markers that were associated with portal hypertension such as splenomegaly and decreased platelet count were predictors of oesophageal varices in chronic liver disease. Thrombocytopenia (low platelet count) is usually an initial clue to the progression of cirrhosis. But in cirrhosis various factors other than just portal hypertension are known to have a bearing on platelet count. These include reduced lifespan of platelets due to rapid destruction and bone marrow suppressant effects of various hepatitis viruses as well as alcohol [8]. Splenomegaly in cirrhosis itself as a complication is linked to portal hypertension [9]. Therefore, we cannot rely solely on the use of platelet count to look for oesophageal varices in cirrhotic patients. Hence in this study rather than using platelet count alone, we used the ratio of platelet count to spleen diameter as a more reliable marker for prediction of oesophageal varices in cirrhosis. [10]. Moreover, this parameter does not have any involvement or use of Child Pugh classification. This can be advantageous as we can use the PC/SD ratio even in patients who do not show any signs of decompensation of liver disease. Rescreening for oesophageal varices is important in patients with no varices on initial endoscopy because during the

course of liver disease these patients can develop small varices which can predispose them to the risk of developing larger varices at a later stage. Thus, the PC/SD ratio being non-invasive with lower cost, easily reproducible and available would provide a better option for follow up of cirrhotic patients with improved patient compliance compared to endoscopy.

METHODS

The study population consisted of patients aged 30-80 years who attended the Medicine OPD or admitted in wards of a tertiary care hospital in Delhi between August 2018 to 2019 and diagnosed with liver cirrhosis based on clinical evidence of decompensation or varices and/or radiological evidence of nodules in liver and collaterals and/or Fibroscan values suggestive of cirrhosis. It was a cross-sectional study and a total of 81 patients were included. We excluded patients with active or past history of gastrointestinal bleed, patients with history of variceal ligation/sclerosant therapy, patients who underwent trans jugular intra hepatic portosystemic shunt surgery. Patients with hepatic encephalopathy, acute febrile illness/tropical splenomegaly/chronic malaria, chronic renal failure, portal/splenic vein thrombosis, non-cirrhotic portal fibrosis/ haematological malignancies/connective tissue disorders were also excluded. We obtained a written informed consent from all patients in the study. All selected patients underwent a protocol-based evaluation that included details of jaundice, alcohol intake, blood transfusions, sexual contact etc. A thorough examination was done to evaluate the patients for signs of decompensated liver disease like jaundice, hepatic encephalopathy, ascites and splenomegaly. Following investigations were done: Complete blood count including platelet count was done by using ADVIA 2120i (Siemens) automated haematology analyser. Prothrombin time (PT) and international normalised ratio (INR) was done using ACL TOP 300 CTS Haemostasis Testing System. Liver function tests were done using ADVIA 1800 (Siemens, random axis autoanalyzer). Anti-HCV antibodies were tested by Rapid Assay Elisa Membrane (using 4th generation HCV TRI-DOT). HBsAg was tested by Rapid Assay Elisa Membrane (VIRUCHECK). Ultrasonography of abdomen (USG) was done to diagnose liver cirrhosis(hypoechoic nodules in liver parenchyma and round edges [11]), ascites and spleen diameter was calculated by measuring the craniocaudal length of the spleen in millimetres (mm). The USG machine used was EPIQ7G (Philips). Splenomegaly was defined as craniocaudal length >120mm. Upper GI endoscopy was done for detection of oesophageal varices as it is the standard investigation for confirming varices. Endoscopies were performed using an OLYMPUS, EVIS EXERA III, CV-190 gastrointestinal videoscope (Olympus, Tokyo, Japan). For the purpose of study patients were divided into those with oesophageal varices and those without varices. Fibroscan was performed using Fibroscan machine (Fibroscan model 502, Echosens, France) and was done by single investigator. It was used to document liver cirrhosis in patients as the sensitivity of most individual signs of cirrhosis on ultrasound is low.

Normal Values Of The Parametrs Used As Per Our Laboratory Standards Were :

Platelet count: 150-410 x 103/mm3; serum bilirubin: 0.2-1.2 mg/dl; serum albumin: 3.5-5.5 mg/dl; mean normal prothrombin time (PT): 10.8

The ratio of platelet count to spleen diameter was measured for all patients and a cut off value best suited to predict oesophageal varices was arrives at. Upper gastrointestinal endoscopy was performed for detection of oesophageal varices as a gold standard test in all patients.

Statistical analysis

The results were projected in the form of frequencies, percentages and mean ± SD (standard deviation).

Chi-square test was used to compare the categorical/dichotomous variables. The Unpaired t-test was used to compare continuous variables between two strata. One-way analysis of variance with Tukey's post hoc tests was used to compare continuous variables among strata. The ROC curve analysis was carried out to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The AUC with 95% confidence interval (CI) was calculated. The p-value<0.05 was considered significant. All analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

The study consisted of 81 patients of either gender. In Table-1 we can see the distribution of cases according to different ages and gender. Majority of patients were males (72.8%, n=59). The mean age of patients was 54.89±9.35 years.

Table-2 shows distribution of causes of liver cirrhosis. Alcoholic liver disease was the main cause (38.3%; n=31) followed by non alcoholic fatty liver disease (now referred to as MASLD) (23.5%; n=19), Hepatitis C (13.6%; n=11), Hepatitis B (12.3%; n=10), Cryptogenic cirrhosis (8.6%; n=7), Autoimmune hepatitis (2.5%; n=2) and Haemochromatosis (1.2%; n=1). In Table-3 the values of platelet count to spleen diameter ratio are used to differentiate patients with oesophageal varices from those without varices(based on endoscopy). 65.4%(n=57) patients had a cut off ratio of <975 and a total 69.1%(n=56) patients had varices on endoscopy. Hence the ratio had high sensitivity to identify patients with oesophageal varices. The ratio >975 was found in 25.9%(n=24) of patients and 30.1%(n=25) of total patients had no oesophageal varices on endoscopy; hence the specificity of the ratio in prediction of varices was also good. The sensitivity (94.6%), specificity (84%), positive predictive value (93%) and negative predictive value (87.5%) of the PC/SD ratio were found to be high in predicting oesophageal varices with high Area under the curve (AUC- Figure-1) (0.96, 95%CI=0.93-0.99).

Table-4 shows the comparison of mean PC/SD ratio in patients with and without oesophageal varices. The mean ratio was significantly (p=0.0001) lower among patients in whom oesophageal varices was present (731.81±214.16) than absent (1248.17±314.77). Similar observation was found among patients whose PC/SD ratio was ≤975. Table-5 shows the comparison of Fibroscan values with Platelet count/spleen diameter ratio. Fibroscan values were significantly (p=0.0001) higher among patients with platelet count/spleen diameter ratio ≤975 (38.95±19.99) than >975 (19.46±13.15).

In Table-6 the patients were divided into 2 groups (those with ratio >975 and those with ratio <975) and the various parameters were compared amongst these two groups. There was significant (p<0.01) difference in all the studied parameters between platelet count/spleen diameter ratio ≤975 and >975. Mean values of Serum bilirubin, PT, INR and spleen diameter were significantly higher in patients with ratio < 975(n=57) than those with ratio >975(n=24). Mean values of serum albumin, platelet counts and platelet count/spleen diameter ratio were found to be much lower in patients with ratio <975.

Table 1 Distribution Of Cases According To Age And Gender

Age in years	Male		Female		Total	
	No.	%	No.	%	No.	%
<40	5	71.4	2	28.6	7	8.6
40-50	16	80.0	4	20.0	20	24.7

51-60	22	68.8	10	31.2	32	39.5
>60	16	72.7	6	27.3	22	27.2
Total	59	72.8	22	27.2	81	100.0
Mean±SD (Range)	54.71±9.61 (33-72)		55.36±8.81 (35-68)		54.89±9.35 (33-72)	

SD – Standard Deviation

Table 2 Distribution of cases according to age and gender

Causes of liver cirrhosis	No. (n=81)	%
Alcoholic liver disease	31	38.3
Autoimmune hepatitis	2	2.5
Cryptogenic cirrhosis	7	8.6
Haemochromatosis	1	1.2
Hepatitis B	10	12.3
Hepatitis C	11	13.6
Non alcoholic fatty liver disease (now called MASLD)	19	23.5

Figure 1 ROC curve showing sensitivity and specificity of PC/SD ratio in differentiating patients with oesophageal and without oesophageal varices

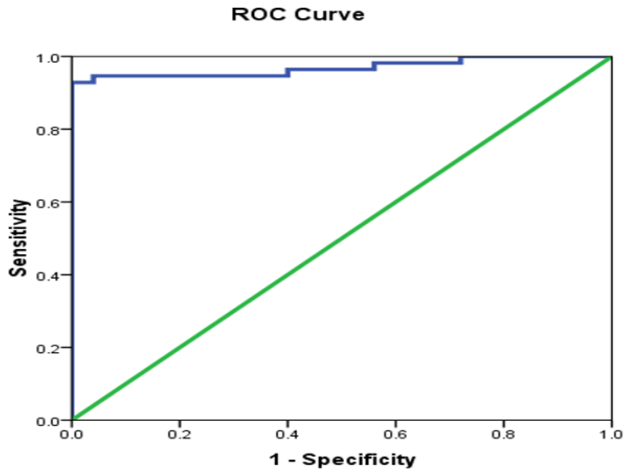

Table 3 Diagnostic values of PC/SD ratio in differentiating patients with and without oesophageal varices

Platelet count/spleen diameter ratio	Oesophageal varices (On upper GI endoscopy)				Total	
	Present		Absent			
	No.	%	No.	%	No.	%
≤975	53	65.4	4	4.9	57	70.4

>975	3	3.7	21	25.9	24	29.6
Total	56	69.1	25	30.9	81	100.0
Diagnostic value, % (95%CI)						
Sensitivity	94.6 (88.7-100.5)					
Specificity	84.0 (69.6-98.4)					
PPV (positive predictive value)	93.0 (86.4-99.6)					
NPV (negative predictive value)	87.5 (74.3-100.7)					
AUC (95%CI)	0.96 (0.93-0.99)					

CI – Confidence interval, AUC- Area under curve

Table 4 Comparison of mean PC/SD ratio in differentiating patients with and without varices (on UGI endoscopy)

PC/SD ratio	Mean PC/SD ratio values in patients with and without varices (On Upper GI Endoscopy)		p-value[1]
	Present	Absent	
≤975	704.56±184.07	957.75±9.05	0.009
>975	1213.20±114.07	1303.49±314.33	0.63
Total	731.81±214.16	1248.17±314.77	0.0001

Table 5 Compariosn of Fibroscan Values with PC/SD Ratio

PC/SD ratio	Fibroscan values (Mean±SD)	p-value
≤975	38.95±19.99	0.0001
>975	19.46±13.15	
Total	33.17±20.24	

Table 6 Comparison of mean values of various parameters with Platelet count/spleen diameter ratio cut off

Parameters	Platelet count/spleen diameter ratio cut off (Mean±SD)		p-value
	≤975	>975	
Serum bilirubin (mg/dl)	3.53±1.14	1.61±0.61	0.004
Serum albumin (g/dl)	2.74±0.38	3.19±0.24	0.0001
Prothrombin time (seconds)	18.90±6.64	14.58±1.57	0.002
INR	1.73±0.52	1.34±0.13	0.001
Platelet count (n/mm^3)	92070.18±24457.59	145541.67±29132.35	0.0001
Spleen diameter (mm)	131.77±14.70	113.42±8.95	0.0001
Ratio (n/mm)	722.33±189.62	1292.20±296.62	0.0001

DISCUSSION

Oesophageal variceal bleeding has a major contribution in overall mortality in cirrhotic patients. Therefore in order to reduce mortality in cirrhotic patients and to improve the overall quality of life it is imperative to prevent variceal bleeding [12]. The reference standard test for diagnosing oesophageal varices is oesophagogastroduodenoscopy which is invasive. On their 1st endoscopy visit, around 70% patients are detected with oesophageal varices and close to 30% have large varices that have high risk of bleeding requiring primary prophylaxis [13]. As the overall prevalence of larger varices is low, therefore it may not be justified to subject all cirrhotic patients to endoscopic surveillance as it is invasive. Moreover, due to the global rise in the incidence of liver cirrhosis, a greater number of people would be needing these endoscopic screening services in the future. [14]. The global incidence and prevalence of MASLD, which is the most prevalent cause of chronic liver disease are also steadily rising [15]. Therefore, the need of the hour is to explore parameters which are non-invasive and can help in predicting varices in cirrhosis patients as well as reduce medical costs for the patients.

Most studies done in the past to explore various other markers which are non invasive in nature to predict varices in liver cirrhosis patients focussed on patients with decompensated cirrhosis and very few took into account patients with compensated cirrhosis [10]. Therefore, in this study we also included patients with compensated cirrhosis to avoid bias caused by selection of particular subgroup of patients. In our study, only simple, easily available and reproducible parameters were taken like platelet count and spleen diameter using ultrasonography. The emphasis in our study was on identifying presence/absence of oesophageal varices rather than concentrating on large varices alone as doing so would miss an important subgroup of patients in need of medical surveillance [10].

In our study, the total number of male patients were 72.8%(n=59) and female patients were 27.2%(n=22). Our study showed no significant difference in the incidence of oesophageal varices between males and females, hence oesophageal varices were present equally in both genders. Similar findings were observed in a study by Giannini et al [10] in which incidence of oesophageal varices in males and females was 60% and 64.2% respectively and the difference was insignificant. Hence the occurrence of oesophageal varices in cirrhosis is not found to be influenced by gender.

The mean age of patients in our study was 54.89±9.35 years. In our study alcoholic liver disease was the main cause of cirrhosis (38.3%;n=31) followed by MASLD (23.5%;n=19), Hepatitis C (13.6%;n=11), Hepatitis B (12.3%;n=10), cryptogenic cirrhosis (8.6%;n=7), autoimmune hepatitis (2.5%;n=2) and haemochromatosis (1.2%;n=1). These findings were compared with a multi centric study in Indian population done by Partha S Mukherjee et al [1]. Their study showed that alcohol was the most common cause of cirrhosis similar to our study which can be explained by a surge in alcohol intake due to effects of urbanisation and westernised lifestyle in our country [16]. In their study the next most common causes were hepatitis B and C followed by NAFLD whereas in our study MASLD was the 2nd common cause followed by viral hepatitis. This could be because their study was multi centric across various regions of India and was representative of the etiological variations of cirrhosis across India while ours was done in a single hospital and the sample size was relatively smaller. Also, the incidence of diabetes and MASLD has been increasing in our population which can explain their increasing contribution to cirrhosis.

The main aim of our study was to calculate PC/SD ratio to predict oesophageal varices in liver cirrhosis for which the ROC curve was used to determine the cut-off value to find the ratio with highest sensitivity and specificity and we obtained a cut-off value of 975 for PC/SD ratio. The PC/SD cut off

ratio of 975 in our study was found to have a high sensitivity (94.6%), specificity (88.6%), negative predictive value (87.5%) and a positive predictive value of 93% in predicting oesophageal varices. The area under the ROC curve was found to be 0.942 indicating excellent diagnostic accuracy of the ratio in differentiating between patients with and without varices. Similar results were found in a study by Albreedy AM [17] who found that for prediction of oesophageal varices, PC/SD ratio of ≤979.9 had area under curve 0.922 with sensitivity 100% although it had low specificity of 30%. Another study done by Mossie GY et al [18] found a cut off PC/SD ratio of < 1119 for predicting oesophageal varices. Their ratio had a sensitivity of 86.32% and specificity of 70% and in their study the area under the curve was 0.835 (95%CI: 0.736-0.934, P < 0.001). A study was done by Schwarzenberger E [19] retrospectively analysed 137 patients with liver cirrhosis. In their study the cut off PC/SD ratio was 909 and it had a positive predictive value of 74% and a negative predictive value of 73% to check for the presence of oesophageal varices. They however concluded that this ratio is not sufficiently accurate enough to predict oesophageal varices and that it cannot replace endoscopy.

After viewing multiple previous studies we noted that there was a difference in the numerical value of PC/SD ratio between our study and previous studies. This difference could be due to difference in racial characteristics and indicates that it is important to determine a cut off for the ratio in a specific population.

Our study showed that the PC/SD ratio value was less among patients in whom varices was present (731.81±214.16) than absent (1248.17±314.77). Similar observation was found among the patients whose PC/SD ratio was ≤975. This finding was similar to a study by Waqas Wahid Baig et al [20] in which the ratio among patients with and without oesophageal varices was 702 and 1300 respectively and the difference was significant. Since we used Fibroscan in our study to assess liver stiffness, we correlated Fibroscan values in patients with ratio ≤ 975(n=57) and > 975(n=24) and found that values were significantly (p=0.0001) higher among patients whose PC/SD ratio was ≤975 (38.95±19.99) than >975 (19.46±13.15). Study by Mehmood Gillani et al [21] compared liver stiffness values with Child Pugh classes and found that mean liver stiffness value in Child Pugh A was 24.71±10.74, in Child Pugh B was 33.32 ± 13.6 and in Child Pugh C was 52.38 ± 18.67 kPa. This observation correlated that values increased with increasing decompensation of the disease. He also showed that mean fibroscan values in patients with no oesophageal varices (15.5 ± 2.14) compared to patients with varices (36.18 ± 6.76) were lower. Jamil Z [22] evaluated the role of 4 different non-invasive variables (platelet count, portal vein diameter, splenic diameter, and ratio of platelet count to splenic diameter PC/SD ratio) in a study done in 150 cirrhotic patients. The sensitivity, specificity, positive and negative predictive values of each variable were obtained and and area under the ROC curve was studied. Their study concluded that out of all the variables, PC/SD ratio was found to be most accurate marker for oesophageal varices (p<0.0001). In their study the cut off ratio came out to be ≤1077.42 and it had a sensitivity of 88.75% and specificity of 81.43% in prediction of varices in cirrosis.

In our study we found that the mean values of serum albumin (2.74±0.38) and platelet count (92070.18±24457.59) were significantly lower in the group with PC/SD ratio ≤975(n= 57) compared to the group with ratio >975 (n=24) (albumin-3.19±0.24, platelet count- 145541.67±29132.35, PC/SD ratio-1292.20±296.62). Values of serum bilirubin (3.53±1.14), PT (18.90±6.64), INR (1.73±0.52), spleen diameter (131.77±14.70) on the other hand were significantly higher in the group with ratio ≤ 975. Similar results were observed in a study by Barrera F et al (23) who found that a PC/SD cut off ratio of <830.8 was useful for predicting oesophageal varices with a sensitivity of 76.9%, specificity of 74.2%

and a negative predictive value of 77.8%. They found that the mean serum bilirubin levels(p=0.005) and spleen diameter values(p=0.0001) were higher in patients with oesophageal varices who had lower PC/SD ratio.

Our study was carried out on a small sample size, so more studies with larger sample sizes would be needed to ensure generalisability of results. Moreover, factors like varying duration of chronic liver disease of subjects may act as a confounding factor in the study.

CONCLUSION:

PC/SD cut off ratio of <975 can be used as a good parameter to predict oesophageal varices in liver cirrhosis patients with a high positive predictive value of 93%, high sensitivity of 94.6%, specificity of 84% and a negative predictive value of 87.5 %. It is a useful, non-invasive, easily accessible and cost effective tool for predicting oesophageal varices in liver cirrhosis patients in resource limited settings and in patients who are non compliant to upper gastrointestinal endoscopy.

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