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A study on non endoscopic predictors of esophageal varices and portal hypertension in chronic liver disease

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ABSTRACT

Portal hypertension is associated with liver cirrhosis and esophageal varices is a common complication. Cirrhotic liver increases resistance to the passage of blood and thereby increased splanchnic blood flow secondary to vasodilation. Prevalence of portal hypertension varies from 50-60% in patients with liver cirrhosis. The first episode of variceal bleeding causes mortality, which ranges from 40-70%. All cirrhotic patients should be screened for the oesophageal varices according to Baveno III consensus conference on portal hypertension and recommendation for endoscopy is at 2-3 years intervals in patients without varices and at 1-2 years interval in patients with small varices in order to evaluate the development of variceal progression. But this is questionable as endoscopy is an invasive procedure and also cost-effective. Only 9-36% of patients with cirrhosis were found to have varices on screening endoscopy. Non-invasive assessment of variceal bleeding with good predictivity includes biochemical, clinical and ultrasonographic parameters. Thus unnecessary intervention is avoided and at the same time, the patients at risk of bleeding are also not missed. This study emphasizes the need for an annual ultrasonogram examination as a part of a surveillance program for screening of oesophageal varices in patients of chronic liver disease.

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INTRODUCTION

Cirrhosis of the liver is a histopathologically described irreversible condition presenting with various clinical features & complications. Removal of underlying cause reverses the fibrosis, as seen in chronic hepatitis C, hemochromatosis and alcohol liver disease. The term "cirrhosis" was coined by Lannec in 1826, with the meaning of orange color in greek as because of the yellowish-tan color of the cirrhotic liver. The three morphological characteristics of cirrhotic liver are Bridging fibrous septa, Parenchymal nodules, Architectural disruption of the liver (Friedman, gastroenterology 134). Alcoholism, auto immune hepatitis, chronic viral hepatitis, biliary cirrhosis, non-alcoholic steatohepatitis, inherited metabolic liver disease like hemochromatosis, Wilson's disease, cystic fibrosis and cryptogenic cirrhosis are the various etiologies of cirrhosis (Lebrec *et al.*, 1980). Liver cirrhosis causes portal hypertension. Portal hypertension is the consequence of an increase in the splanchnic blood flow secondary to vasodilation and increased resistance to the passage of blood through the cirrhotic liver (Gupta *et al.*, 1997). Log-

ical classification of portal hypertension is based on the site of increased resistance to portal flow. Five main groups can be delineated according to presinusoidal, sinusoidal, or post sinusoidal block. Presinusoidal and post sinusoidal portal hypertension can be further subdivided into intra-or extrahepatic causes. Liver cirrhosis is the leading cause of portal hypertension in the West, although the differential diagnosis is extensive (Boyer *et al.*, 1977). Porto-systemic collaterals may develop when the portal pressure reaches a critical value., A corrected portal pressure of 10 to 12mm Hg appears to be necessary for the development of oesophageal varices in alcoholic cirrhosis (Garcia-Tsao *et al.*, 1985).

A consequence of portal hypertension are haemetemesis as a result of esophageal varices, splenomegaly, Caput medusa (Burroughs *et al.*, 1986). The incidence of variceal bleed is 5-15% per year (Sánchez-Roig *et al.*, 1994). Hypersplenism may occur in the absence of splenomegaly. In the absence of other factors that affect the platelet count (alcohol, medications), thrombocytopenia, between 50,000 and 125,000 platelets/nm3, is an indicator of portal hypertension in cirrhosis (Groszmann, 1984). The prognosis of liver disease was assessed by the Child Turcotte pugh classification and helps in predicting the survival rates (Violi *et al.*, 1994). Meld score is used to prioritize the patients for liver transplantation (Kajiwara *et al.*, 1995). A major cause of death in patients with cirrhosis is gastrointestinal hemorrhage, most often as a result of the portal hypertensive state. The 1- year bleeding rate of unselected patients with cirrhosis, without a history of hemorrhage, ranges from 6% to 76% and depends on endoscopic features as well as the degree of hepatic decompensation (Graham and Smith, 1981). Mortality for the first variceal hemorrhage ranges from 10% to 65% (Burroughs *et al.*, 1986; Cales *et al.*, 1990) and the majority of deaths occur within the first 6 weeks following the bleeding episode (Calès *et al.*, 1990). For early detection and evaluation of progression of esophageal varices and portal hypertensive gastropathy, repeated screening endoscopy at certain intervals was suggested. However, that approach had its limitations because of the invasiveness of the procedure and also the cost-effectiveness. In one study, it was found that empiric β-blocker therapy for the primary prophylaxis of variceal hemorrhage is a cost-effective measure, as the use of screening endoscopy to guide therapy adds significant cost with an only marginal increase in effectiveness Spiegel *et al.* (2003). So the identification of clinical features that can accurately predict large esophageal varices and help identify patients at greater risk is quite attractive (Ong, 1999). This study was undertaken to identify and evaluate non-invasive parameters as predictors of esophageal varices and portal hypertensive gastropathy in cirrhotic patients.

MATERIALS AND METHODS

This is a Prospective observational study carried out in 60 patients at the Department of General Medicine, Saveetha Medical College and Hospital, Chennai to identify the clinical, biochemical, hematological and ultrasonographic parameters associated with the presence of oesophageal varices in patients with chronic liver disease without any previous evidence of GI bleeding and to assess the ability of these parameters as non-invasive tools to predict the presence of oesophageal varices and finally to identify candidates for surveillance endoscopy based on the presence of these parameters.

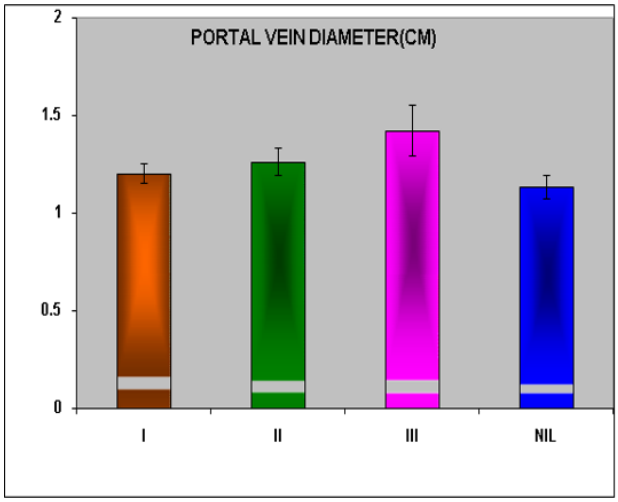

Figure 1: Portal vein diameter

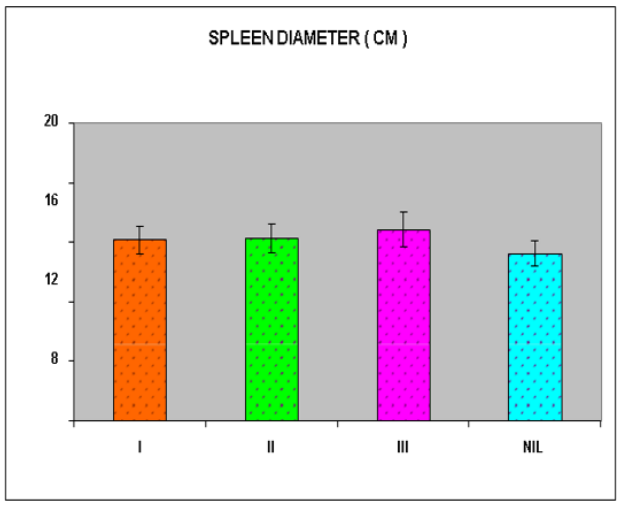

Figure 2: Splenic diameter

Cirrhotic liver patients without any past history

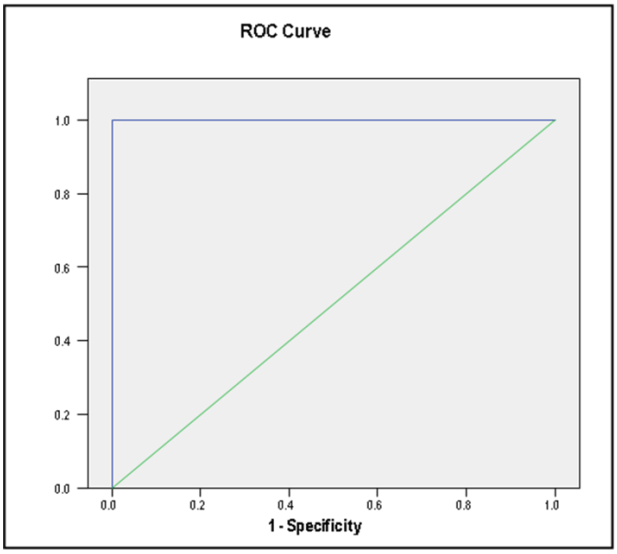

Figure 3: Platelet Count ROC Curve

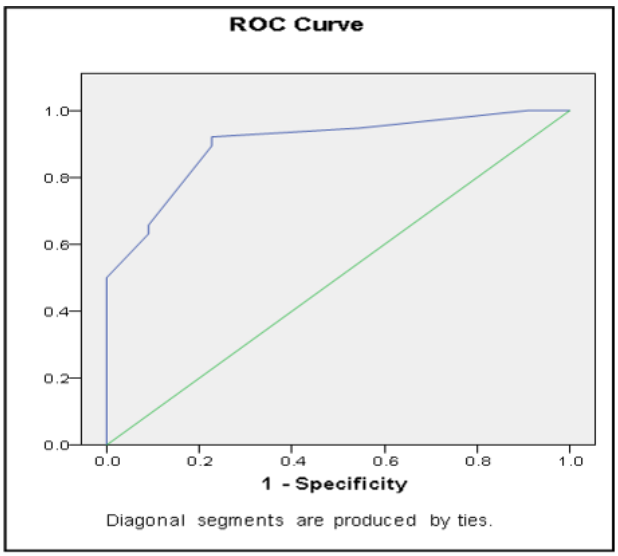

Figure 4: Portal Vein Diameter ROC Curve

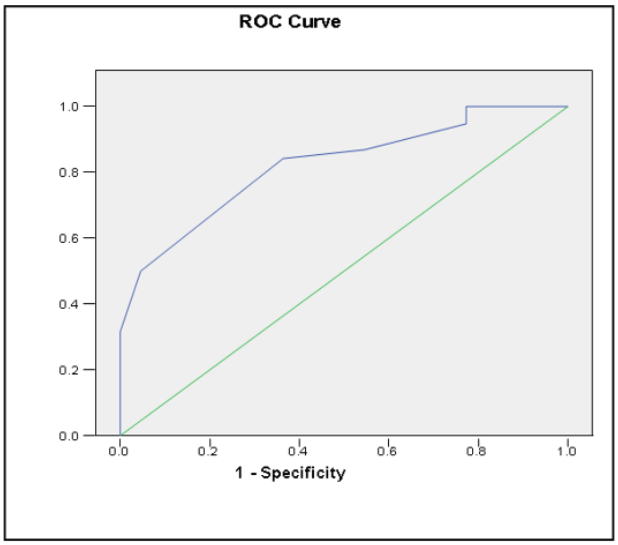

Figure 5: Spleen Diameter ROC Curve

of upper (or) lower gastrointestinal bleed were included in the study. Combination of physical findings like Gynaecomastia, Ascites, splenomegaly (etc.), impaired liver function tests, deranged clotting profile and irregular liver surface with coarse echoes (or)shrunken liver and ratio of the transverse caudate lobe to transverse right lobe width >0.65 on ultrasonographic examination.

Patients those who are with a present or previous history of bleeding, on previous/current treatment with Beta-blockers, on diuretics (or) anti-platelet drugs, who had undergone sclerosis (or) band ligation of oesophageal varices, TIPSS (or) surgery for portal hypertension, who were on active alcohol abuse (less than six months abstinence) and serum albumin <1.5 gm are excluded from the study. All the study participants were subjected to a detailed history, clinical examination and blood investigations. Clinical examination of the study population was concentrated on the physical findings in cirrhotic patients, and special emphasis was on the presence of a palpable spleen. Routine blood investigations like Blood urea, sugar, serum creatinine and serum electrolytes were taken along with blood for hepatitis serology and liver function tests. Platelet count was estimated using an automated analyzer (Sysmex KX-21). Prothrombin time was also estimated for all the patients. Patients were classified into a child's grade A/B/C as per child-pugh criteria. In addition, all the patients were subjected to ultrasonographic examination to assess the liver size, structure and the size of the portal vein, and size of the spleen. A 3.5MHZ transducer was used for the USG study.

An upper GI endoscopy was done in all patients to evaluate for the presence of and the degree of oesophageal varices as small and large varices based on the following findings. Varices that flatten with insufflation or minimally protruding into the oesophageal lumen and which protrude into the oesophageal lumen and touch each other (or) fill at least 50% of the oesophageal lumen are considered as small and large one respectively.

Statistical analysis was performed using SPSS 20.0. Results were expressed as mean $\pm$ S.D. Qualitative data were tabulated in frequencies and percentages. Quantitative data were given in mean and standard deviation. Association between qualitative data like sex, Childs grade, Ascites, palpable spleen and grade of varices were analyzed using the Pearson chi-squared test. Association between quantitative data like Serum bilirubin, Prothrombin time, platelet count, spleen size, portal vein diameter and variceal grading were analyzed using one-way anal-

ysis of variance (ANOVA) F-test and student t-test. All tests were 2 tailed and a 'P' value of <0.05 was considered to be significant. 'P-value <0.001 was considered to be highly significant. Using the ROC curve, the threshold of different variables for the best compromise sensitivity specificity was determined.

RESULTS AND DISCUSSION

The total number of patients in the current study was 60. There were 58 males and 2 females. The Male: Female ratio was 1:0.034 Males formed 96.7% and females 3.3 % of the study, respectively.

Table 1 shows the mean portal vein diameter in patients with no varices on endoscopy was 1.134 cm compared to 1.203 with grade I varices, 1.264 with grade II varices and 1.429 with grade III varices. The mean portal vein diameter of 60 patients is 1.238.

Figure 1 shows the mean portal vein diameter among patients with various grades of varices suggesting mean portal vein diameter increases with the severity of varices. Mean portal vein diameter is maximum in grade 3 varices.

Table 2 shows the mean splenic diameter in patients with no varices was 11.25 cms compared with 12.167 cm in patients with grade I varices, 12.278 cm in grade II and 12.864 cms in patients with grade III varices. The mean splenic diameter of 60 patients is 11.992.

Figure 2 shows the mean spleen diameter among patients with various grades of varices suggesting spleen diameter increases with the severity of varices. Mean splenic diameter is maximum in grade 3 varices.

Table 3 depicts that the mean platelet count was 1.51 lakhs per mm^3 in patients with no varices compared to a mean value of 97,000 in grade I varices, 86,527 in grade II and 86,227 in patients with grade III varices. The mean platelet count of 60 patients is 1,11,650.

Out of 6 patients with minimal ascites, 2 patients had grade I varices(3.3%). Out of 24 patients with moderate ascites, 7 had grade I varices(11.7%), 16 had grade II varices(26.7%),1 had grade III varices(1.7%). Out of 12 patients with tense ascites,2 had grade II varices(3.3%), 10 had grade III varices(16.7%).

The mean total bilirubin was 1.723 in patients with no varices compared to a mean of 2.078 in grade I varices,3.461 in grade II varices and 6.218 in grade II varices patients. The ANOVA-F test showed statistical significance($p<0.003$).

The mean prothrombin time(PT) was 12.14 s in patients with no varices compared to 15 s in grade I varices,15.94 s in grade II and 17.09 s in grade III varices patients. The ANOVA-F test showed statistical significance($p<0.0001$).

On univariate analysis, a significant correlation was noted between the presence of varices - Ascites, Splenic diameter, Total serum bilirubin, Prothrombin time, Platelet count and Portal vein diameter.

Table 4 shows that the platelet count <1,11,500 cells per mm3 had a sensitivity and specificity of 100% and 86.4%%, respectively, in predicting varices. Portal vein diameter >1.19 cm had a sensitivity of 89.5% and a specificity of 77.3% for the prediction of varices. Spleen diameter >11.5 cm had a sensitivity of 84.2% and a specificity of 63.6% for the prediction of oesophageal varices.

The sensitivity and specificity of each of the above parameters was then determined using the ROC curve.

Figure 3 depicts that the area under the curve was maximum for platelet count <1,11,500 cells per mm^3.

Figure 4 depicts that the area under the curve was maximum for portal vein diameter >1.19 cm.

Figure 5 depicts that the area under the curve was maximum for spleen diameter >11.5cm.

Based on the above observations, a platelet count of <1,11,500 cells per mm3, portal vein diameter >1.19cm and spleen diameter >11.5 cm were found to have significant predictive value for the presence of oesophageal varices.

The present study showed lesser values of sensitivity, specificity, positive and negative predictive values with lesser area under the curve (<0.7) for other parameters including Prothrombin time(PT), Total bilirubin(TBR).

Non-invasive prediction of oesophageal varices in patients suffering from cirrhosis, with no history of upper GI bleed is essential as the number of patients undergoing screening for the presence of oesophageal varices are likely to increase in the near future, as a result of the growing pool of patients with chronic liver disease.

Most of the studies have clearly revealed that a platelet count less than $88x10^3$/mL is associated with large varices an endoscopy. In the present study, platelet count of <1,11,500 cells per mm^3 showed significant association with the presence of oesophageal varices.

A very few studies have detailed the portal vein size to be a predictor of large varices. The portal vein

Table 1: Mean Portal Vein Diameter

Grade of varices	Number	Mean	STD Deviation	Lower Bound (95% CI)	Upper Bound (95% CI)
NIL	22	1.134	0.0643	1.106	1.163
I	9	1.203	0.0589	1.158	1.249
II	18	1.264	0.0752	1.227	1.302
III	11	1.429	0.1364	1.337	1.521
TOTAL	60	1.238	0.1340	1.203	1.272

Table 2: Mean Splenic Diameter

Grade of varices	Number	Mean	STD Deviation	Lower Bound (95% CI)	Upper Bound (95%CI)
NIL	22	11.25	0.8128	10.89	11.610
I	9	12.167	0.9354	11.448	12.886
II	18	12.278	0.9428	11.809	12.747
III	11	12.864	1.1638	12.082	13.646
TOTAL	60	11.992	1.1027	11.707	12.277

Table 3: Mean Platelet Count

Grade of varices	Number	Mean	STD Deviation	Lower Bound (95% CI)	Upper Bound (95% CI)
NIL	22	150909.09	36946.434	134527.96	167290.22
I	9	97000.00	3201.562	94539.06	99460.94
II	18	86527.78	9603.113	81752.26	91303.29
III	11	86227.27	11066.534	78792.67	93661.87
TOTAL	60	111650.00	38145.495	101795.97	121504.03

Table 4: Predictive values for the presence of esophageal varices using various parameters

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Area (ROC)
PORTAL VEIN DIAMETER(>1.19CM)	89.5	77.3	87.2	80.9	0.9
SPLEEN DIAMETER(>11.5CM)	84.2	63.6	80.0	70.0	0.821
PLATELET COUNT(<1,11,500 CELLS PER MM ^{3})	100.0	86.4	92.7	99.0	1.0

Table 5: Platelet count in various studies

Name of study	Year of study	Platelet Count (CELLS/ MM^3)
PRESENT STUDY	2015- 16	<1,11,500
Chalasani *et al.* (1999)	1999	<88,000
Schepis *et al.* (2001)	2001	<1,00,000
Zaman *et al.* (1999)	1999	<88,000
Sarwar *et al.* (2005)	2003- 04	<88,000

Table 6: Portal vein diameter in various studies

Name of study	Year of study	Portal Vein Diameter
PRESENT STUDY	2015- 16	>1.19 CM
Schepis *et al.* (2001)	2001	>1.3 CM
Sarwar *et al.* (2005)	2003- 04	>1.1 CM

Table 7: Spleen diameter in various studies

Name of study	Year of study	Spleen diameter
PRESENT STUDY	2015- 16	>11.5 CM
Chalasani *et al.* (1999)	1999	>11.5 CM

size predicting oesophageal varices in our study was very similar to that observed in the study by Sarwar *et al.* (2005); Chalasani *et al.* (1999) 42 found that in addition to a platelet count <88x10^3/mL, splenomegaly was independently associated with the presence of large varices. Platelet count <1,11,500 cells per mm^3 had a significant correlation with oesophageal varices with sensitivity and specificity of 100% and 86.4%, respectively. Portal vein diameter >1.19 cm had a significant correlation with oesophageal varices with sensitivity and specificity of 89.5% and 77.3%, respectively. Width of portal vein on ultrasonographic examination is an indirect indicator of portal pressure, which is responsible for the development of varices. Spleen diameter >11.5 cm had a significant correlation with oesophageal varices with sensitivity and specificity of 84.2% and 63.6%, respectively.

Table 5 Shows platelet count in various studies predicting esophageal varices.

In present study, Platelet count <1,11,500 cells per mm3 had significant correlation with Oesophageal varices with sensitivity and specificity of 100% and 86.4%, respectively.

Table 6 Shows portal vein diameter in various studies predicting esophageal varices.

In the present study, Portal vein diameter >1.19 cm had a significant correlation with oesophageal varices with sensitivity and specificity of 89.5% and 77.3%, respectively. Other studies also reports nearly the same as in the present study.

Table 7 Shows spleen diameter in other study predicting esophageal varices.

In the present study, Spleen diameter >11.5 cm had a significant correlation with oesophageal varices with sensitivity and specificity of 84.2% and 63.6%, respectively. The supporting study also reveals the same.

CONCLUSION

Sixty patients with a chronic liver disease without any previous history of upper GI bleed were studied to identify non-invasive parameters which could predict the presence of oesophageal varices. The following parameters were studied: Portal Vein diameter, Platelet count, Splenic diameter, Total Bilirubin, Prothrombin time. Of the above parameters, Portal vein diameter, Splenic diameter and Platelet count showed a significant correlation in the form of sensitivity, specificity and maximum area under the ROC curve(>0.8).

The present study showed lesser values of sensitivity, specificity, positive and negative predictive values with lesser area under the curve (<0.7) for other parameters including Prothrombin time, Total bilirubin. Platelet count <1,11,500 cells per mm3, Portal vein diameter >1.19 cm and Spleen diameter>11.5 cm are independently associated with the presence of oesophageal varices. Chronic liver disease patients with no past history of upper GI bleed should have surveillance endoscopy if any of these parameters were identified. The use of these parameters would avoid unnecessary invasive procedures in patients without a significant risk of missing oesophageal varices. This study emphasizes the need for an annual ultrasound examination as a part of a surveillance program for screening oesophageal varices in chronic liver disease patients.

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