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Correlation Between P2/MS Index and Portal Hypertension in Cirrhosis: A Prospective Study

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KEYWORDS

Portal Hypertension, cirrhosis, liver, esophageal varices, PHT

ABSTRACT:

Background- Portal hypertension is a progressive complication of liver cirrhosis and it is the cause of high morbidity and mortality. Prevalence of esophageal varices inpatients with portal hypertension was 60-80% and incidence increasing by 5% per year with risk of bleeding by 25% -35%. Mortality rate in these patients is 20%-35% despite early diagnosis and treatment of variceal haemorrhage. Recently many studies have been conducted to use non-invasive methods to detect oesophageal varices in patient with cirrhosis of liver. One such method is P2/MS INDEX (Platelet count)^2/ [monocyte fraction (%) - segmented neutrophil fraction (%)] of patients with cirrhosis of liver. P2/MS INDEX is a simple, accurate and non- invasive test for detecting varices in cirrhosis of patients.

Methodology- The study was conducted on 50 patients admitted with a diagnosis of cirrhosis of liver at general medicine and medical Gastroenterology wards of Saveetha Medical college, over the period of two years. Data was collected from all the patients who underwent detailed clinical evaluation, appropriate blood investigations, radiological studies (ultrasound with Doppler) and upper G.I endoscopy.

Results- Out of 50 patients, majority 18(36%) were in the age group 41-50. 27(54%) were Cirrhosis without PHT & 23(46%) were Cirrhosis with PHT. In patients with portal hypertensionthe median P^2/MS index was 35 whereas in patients without portal hypertensionthe median P^2/MS index was 114 which was statistically significant (p- value<0.001). Grade I varices in 7 patients with median P^2/MS Index of 43, Grade II varices in 16 patients with median P^2/MS Index of 35, Grade III varices in 8 patients with median P^2/MS Index of 23.

Conclusion- Esophageal varices are more likely to be present in patients with a low p2/ms score, which has emerged as a strong predictor of the existence ofesophageal varices in cirrhosis patients.

Introduction

Portal hypertension is a chronic consequence of liver cirrhosis that is associated with a high rate of morbidity and mortality. Cirrhosis patients with gastroesophageal varices account for around half of all cases. The treatment of cirrhotic patients with varices varies depending on the severity of the varices and whether or not there is acute variceal bleeding.[1] Cirrhotic patients acquire varices at an annual rate of 8%, and having a portal-hepatic venous pressure gradient (HVPG) greater than 10 mmHg is HVPG is the strongest predictor of their development in those who do not have varicesat the time of initial endoscopic screening. [2,3] Variceal haemorrhage occurs at a rate of 5% to 15% each year, with the size of the varices being the most relevant predictor, with the highest risk haemorrhage happening in patients with big varices.[4] The esophagogastroduodenoscopy is the gold standard for

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diagnosing varices (EGD).

Cirrhosis patients should have endoscopic screening for varices at the time of diagnosis.[5-6] Because the frequency of medium/large varices is estimated to be between 15% and 25%[1], the majority of individuals who undergo screening EGD either do not have varices or have varices that do not require preventative treatment. As a result, numerous models have been developed to predict the presence of high-risk varices using non-invasive methods, which has piqued researchers' curiosity. Several studies have looked at non-invasive markers of esophageal varices in cirrhosis patients, such as platelet count, spleen size, Fibro test, portal vein diameter, and transient elastography.[7,8] P2/MS, a simple noninvasive test developed by Lee and colleagues [9] in a study of individuals with virus-related chronic liver disease, was recently recommended (CLD). (Platelet count)^2/ [monocyte fraction (%) - segmented neutrophil fraction (%)] was the formula they employed. P2/MS, on the other hand, has been limited external validation of its diagnostic accuracy and cut-off values for detecting esophageal varices.[10] For individuals with liver cirrhosis, an EV diagnosis is essential to identify those who will benefit from variceal bleeding primary prophylaxis. The gold standard test for such diagnosis is currently esophago-gastro-duodenoscopy (EGD). EGD, on the other hand, is limited by its invasiveness and high expense. If proven to have appropriate specificity and sensitivity, a simple non-invasive, widely available, and inexpensive test would be ideal.

As a result, the above study was conducted to find the correlation between P2/MS index and Portal Hypertension in Cirrhosis.

Materials and Methods

Study place- The study was conducted at the General Medicine and Medical Gastroenterology wards of Saveetha Medical College from August 2019 to August 2021.

Study design- Prospective analytical study.

Inclusion criteria- Patients with cirrhosis of the liver, ready to give written informed consent for participation.

Exclusion criteria- Individuals presenting with previous variceal bleeding, those on β-blocker therapy or endoscopic treatments (band ligation or sclerotherapy), Portal vein thrombosis, underwent previous surgery for portal hypertension or transjugular intrahepatic porto systemic shunt stent placement, having Hepatocelluar carcinoma and unwilling to give written consent.

Sample size- 50 patients diagnosed with cirrhosis of liver.

Data analysis- Data was entered in MS - EXCEL and statistical analysis done by SPSS 23 software.

Ethical consideration- Ethical clearance was obtained from the Institutional Ethical Committee before starting the study.

The patient's demographic and clinical information was collected using a proforma that was previously created. All of the patients underwent a thorough clinical examination, relevant investigations, imaging examinations (ultrasound with Doppler), and upper gastrointestinal endoscopy. A full blood count test was performed on 50 liver cirrhosis patients whohad no previous variceal haemorrhage and were not on beta blocker prophylaxis. The platelet count, monocyte fraction, and neutrophil fraction were used to produce the P2/MS index. Esophago-gastro-duodenoscopy was used to look for esophageal varices.The predictive value, specificity, and sensitivity were computed.

Results

Table 1: Age distribution of the Study Population

Age Groups(in years)	No (%)
>60	7(14.0)
30-40	11(22.0)
41-50	18(36.0)
51-60	14(28.0)
Total	50 (100.0)

Out of 50 patients 18(36%) were in the age group 41-50, 14(28%) in the age group of 51-60, 11(22%) in the age group of 30-40, and 7(14%) belonged to the age group above 60.

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Table 2: Distribution Patients with portal hypertension & without portal hypertension

Diagnosis	No (%)
Cirrhosis without PHT	27(54.0)
cirrhosis with PHT	23(46.0)
Total	50 (100.0)

Out of 50 patients 27(54%) were Cirrhosis without PHT &23(46%)were Cirrhosis with PHT.

Table 3: OGD findings of the Patients

OGD findings	No (%)
Normal Study	19 (38.0)
Oesophageal varcies grade 1	7 (14.0)
Oesophageal varcies grade 2	16 (32.0)
Oesophageal varcies grade 3	8 (16.0)
Total	50 (100.0)

Out of 50 patients Ogd findings were normal in 19 patients (38%),Grade II Oesophageal varices in 16 patients (32%), Grade III Oesophageal varcies in 8 patients (16%),Grade I Oesophageal varcies in 7 patients (14%).

Table 4: Diagnosis

	Diagnosis	
	Cirrhosis with PHT (n=23)	**Cirrhosis without PHT (n=27)**
	Median (IQR)	Median (IQR)
P^2/MS Index	35.0 (58.58,29.33)	114.0 (127.69,80.01)
p-value	**<0.001(significant)**	

In patients with portal hypertension, the median P^2/MS index was 35 where as in patients without portal hypertension the median P^2/MS index was 114 which are statistical significant (p-value<0.001).

Table 5: OGD Findings

	OGD Findings			
	Normal(n=19)	Oesophageal varcies grade I(n=7)	Oesophageal varcies gradeII (n=16)	Oesophageal varcies gradeIII (n=8)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
P^2/MS Index	137.0 (160.79,124.37)	43.0 (53.43,38.85)	35.0 (40.51,31.74)	23.0 (34.98,16.27)
p-value	**<0.001 (significant)**			

Out of 50 patients OGD findings were normal in 19 with median P^2/MS index of 137, grade I varices in 7 patients with median P^2/MS Index of 43, Grade II varices in 16 patients with median P^2/MS Index of 35,Grade III varices in 8 patients with median P^2/MS Index of 23, Which are statistical significant (p-value<0.001).

Table 6: Area under the ROC curve

Area under the ROC curve 0.905										
P^2/MS Index	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**PPV**	**95% CI**	**NPV**	**95%CI**	**+LR**	**-LR**
36.5	88.43	58.0 –100.0%	55.32	41.8 –95.5%	66.34	44.6 –88.1%	88.43		4.3	0.4
31.5	91.7	40.1 –98.6%	56.32	60.5 –98.3%	83.2	43.7 –99.5%	86.67	64.0– 98.5	9.7	1.8
>27	83.2	40.1 –98.6%	57.65	72.3 –99.6%	63.15		89.23	66.1– 99.8		1.7

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DISCUSSION

Oesophageal varices are found in almost half of all cirrhotic patients at the time of diagnosis, and they are more common in Child-Pugh class C patients than Child-Pugh class A patients (85 percent versus 40 percent)[3,11]. Denovo varices arise at a rate of 5% per year, with a higher rate in people who continue to drink alcohol or who have decreasing liver function [3]. Large varices with a diameter of more than 5 mm pose the greatest riskof bleeding, which is influenced by the severity of liver disease as measured by the Child-Pugh score and the presence of red wale markings on varices at endoscopy. According to reports from the 1940's to the 1980's, variceal haemorrhage has a dismal prognosis, with fatality rates ranging from 30 to 60% [12,13,14], but studies suggest that the situation has improved in recent decades [15]. Carbonell et al. found that in hospital mortality from variceal bleeding fell from 42.6 percent to 14.5 percent between 1980 and 2000, and that this was linked to lower rebleeding and bacterial infection rates. Although improved endoscopic and radiographic procedures, as well as new pharmacologic therapy, have reduced mortality following a bleeding episode, a 20–30% mortality rate indicates that bleeding from oesophageal varices remains a substantial clinical concern. Early detection of varices before the first bleed is critical, as studies of primary prophylaxis have shown that the risk of variceal haemorrhage can be decreased by 50% to 15% for large oesophageal varices**.**

As a result, current guidelines recommend that all cirrhotic patients be screened for varices at diagnosis, with follow-up every 2-3 years for patients without varices (depending on the severity of the liver disease) and every 1-2 years for patients with small varices to assess for varice enlargement and the need for prophylactic treatment.

In 100 cirrhotic patients Cales et al. discovered that the inter-observer agreement for the size of oesophageal varices and the presence of red signals was good, with kappa values of 0.59 and 0.60, respectively. Bendtsen et al., on the other hand, discovered significant heterogeneity in inter-observer agreement on the diagnosis and grading of oesophageal varices between 22 endoscopists, as well as a wide range of kappa values.

As GM-CSF encourages the formation of these cells more aggressively than lymphocytes, the proportion of neutrophils and monocytes may increase [12]. P2/MS provides a number of clinical advantages in addition to its great pathophysiological diagnostic value. In a study of 213 individuals with compensated cirrhosis and portal hypertension but no varices, Qamar et al. [11] found that the median platelet countat the time of varices onset was 91,000. They concluded that platelet count is an insufficient noninvasive marker for predicting the presence of oesophageal varices (AUROC curve 0.63) since no platelet count accurately indicated the presence of oesophageal varices (AUROC curve 0.63). The platelet count has been coupled with other variables in an attempt to improve its predictive value.

In above study, out of 50 patients, OGD results were normal in 19 cases with a median p2/ms index of 137, grade I varices in 7 cases with a median p2/ms index of 43, grade II varices in 16 cases with a median p2/ms index of 35, and grade III varices in 8 cases with a median p2/ms index of 23. The median p2/ms index in patients with portal hypertension was 35, while the median p2/ms index in patients without portal hypertension was 114. OGD results were normal in 19 of 50 cirrhosis patients, with a median p2/ms index of 137.In this study. HREV could be ruled out if the P2/MS cut-off value was more than 31.5, with a negative predictive value [NPV] of 86.6 percent. P2/MS demonstrated a high likelihood of consistently identifying individuals with HREV [0.897] in a prior study conducted by M.A. Amin et al [10], with results somewhat lower than those reported in the other study by Beom Kyung et al. [0.941][11]. With the exception of our novel test variable, P2/MS out performed all other variables in predicting HREV. We proposed a single cut-off point for HREV detection, which differs slightly from those proposed by Beom Kyung et al. who used two cut-off values since patients could fall somewhere in the middle. HREV could be ruled out if the P2/MS cut-off value was more than 28.85, with a negative predictive value [NPV] of 86.3 percent.

Patients may be able to avoid needless endoscopy if this number is used. These patients have a low risk of bleeding, thus routine monitoring with this formula may be sufficient. Unlike earlier trials, ours focused on predicting the existence of HREV rather than varices of any size, with the goal of identifying patients who would benefit from prophylactic endoscopic ligation.

Kim et al. found similar results when they looked at the validity of P2/MS in predicting esophageal varices in 318

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individuals with hepatitis B (HBV)-related cirrhosis. They discovered that P2/MS<11 reliably identified 83 patients as having HEV (94 percent positive predictive value), while P2/MS greater than 25 reliably identified 179 patients as not having HEV (94.4 percent negative predictive value).

In total, P2/MS accurately predicted the presence of HEV in 262 individuals (82.4 percent) in their study. Patients with P2/MS <11 should be considered for appropriate preventative treatments, whereas those with P2/MS>25 should safely go for endoscopy, according to the researchers.

In another study by Topal et al., 412 patients with HBV-related cirrhosis evaluated and when the cut-off value of P2/MS was selected as 11, they obtained apositive predictive value of 93.80 percent [95 percent CI (80.20-98.70)]. Whenthe cut-off value for P2/MS was set to >25, they got a negative predictive valueof 94.30 percent [95 percent CI (86.20-98.20 percent)]

In another study, 475 patients with HBV-related cirrhosis were followed for four years prospectively. EV haemorrhage was shown to be considerably more common in subgroup 1: P2/MS 9 than in subgroup 2: P2/MS9 (p = 0.029). P2/MS was found to be a significant predictor of EV haemorrhage (p = 0.04). As a result, the authors suggested that different preventative therapies for the subgroup with a P2/MS 9 be considered. When compared to other non-invasive scores in detecting the presence of EV, P2/MS in our study had the high area under the curve (AUROC) with a significant difference (AUROC= 0.907, 95 percent CI 0.940 - 0.998, p 0.001). P2/MS AUROC area under the curve for P2/MS was [0.897, 95% confidence interval (CI) 0.841 - 0.953] which showed values better than those of AAR[0.511, 95% CI 0.405 - 0.618; P = 0.828], API [0.757, 95% CI 0.669 - 0.845; P =0.000], SPRI [0.767, 95% CI 0.684 - 0.850; P = 0.000], ASPRI [0.771, 95% C0.688 - 0.853; P =.000] and APRI [0.697, 95% CI 0.605 - 0.788; P = 0.000] all of which were significantly lower than that of P2/MS, according to Amin, M et al [11].

Conclusion

Esophageal varices are more likely to be present in patients with a low P2/MS score, which has emerged as a strong predictor of the existence ofesophageal varices in cirrhosis patients. When compared to patients without portal hypertension, the P2/MS score was low in patients with portal hypertension.

Limitations of the Study

Since it was a cross-sectional investigation, and the diagnosticsignificance of sequential P2MS measurement in predicting later high risk oesophageal Varices development should be investigated further in a longitudinal study. Finally, because there is no noninvasive diagnostic method that can distinguish between chronic hepatitis and cirrhosis with 100% accuracy, some individuals with cirrhosis may have been excluded from the study.

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