Original Article

Utility of P²MS Index in Predicting Esophageal Varices in Patients with Hepatitis C Associated Chronic Liver Disease in Pakistani Population

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ABSTRACT

Background: Screening for esophageal varices (EVs) in patients with chronic liver disease is critical for identifying those needing primary prophylaxis against variceal bleeding. The gold standard for EV screening is endoscopy, an invasive and costly procedure often avoided by patients. This necessitates the need for non-invasive predictive tools for the presence of EVs and high-risk varices (HRVs). The P²MS index, a relatively new model, has shown promise in this regard.

Objective: This study aimed to evaluate the effectiveness of the P²MS index, alongside APRI and FIB-4 scores, in predicting the presence of EVs and HRVs in patients with hepatitis C-related chronic liver disease.

Methods: Conducted at the Sindh Institute of Urology and Transplantation's Hepato-Gastroenterology department, this cross-sectional study involved 375 participants aged 18-50 years, recently diagnosed with liver cirrhosis due to hepatitis C. Excluding those with varied medical backgrounds, the study used non-probability consecutive sampling. Diagnostic procedures included esophagogastroduodenoscopy (EGD) and complete blood count. P²MS index, APRI, and FIB-4 scores were calculated for each participant. Data analysis was performed using SPSS version 25.0, focusing on the Area Under the Receiver Operating Curve (AUROC) to assess diagnostic accuracy.

Results: In our population, the P²MS index at a cutoff of <10.7 showed a specificity of 93.22% and sensitivity of 87.88% for predicting the presence of EVs, with a PPV and diagnostic accuracy exceeding 90%. For HRVs, a cutoff of <5.4 demonstrated an excellent NPV, alongside good sensitivity, specificity, and diagnostic accuracy. Compared to APRI and FIB-4, the P²MS index had the highest AUROC for predicting the presence of EVs (0.92, 95% CI 0.89-0.95, p<0.001). For HRVs, it was comparable to APRI (AUROC=0.88, 95% CI 0.85-0.92, p<0.01) and superior to FIB-4.

Conclusion: The P²MS index is an effective non-invasive tool for screening EVs in patients with hepatitis C-related chronic liver disease, demonstrating high accuracy for predicting the presence of EVs. However, its efficacy in predicting HRVs is comparable to other non-invasive indices and warrants further validation.

Keywords: Esophageal Varices, High-Risk Varices, Chronic Liver Disease, Hepatitis C, P²MS Index, Non-Invasive Prediction, Screening.

INTRODUCTION

Esophageal varices (EVs), a significant complication of liver cirrhosis caused by portal hypertension, are abnormally dilated, tortuous submucosal veins in the esophagus that emerge primarily in patients with liver fibrosis due to increased portal venous pressure (1, 2). These varices pose a severe risk, as their rupture can lead to fatal bleeding, a complication seen in liver cirrhosis. Approximately 6-8% of patients succumb to uncontrolled bleeding, and within six weeks of a variceal hemorrhage, the mortality rate stands at 25-30%. For those who survive an initial bleed without intervention, there is a 60-70% likelihood of rebleeding and a 40-50% mortality risk within two years (3). The prevalence of EVs correlates with the progression of liver disease, as indicated by the Child-Turcotte Pugh (CTP) classification. Kovac et al. noted an increased incidence of EVs in patients advancing from CTP class A to C, with a marked increase from 43% in CTP A patients to 76% in CTP C patients. Alongside this, there is a yearly 10% risk of small varices developing

into larger ones, and a higher annual bleeding risk from large varices at 15%, compared to 5% for small varices (4). Globally, hepatitis C (HCV) infection affects about 2.5% of the population, equivalent to 177.5 million individuals (5). In Pakistan, the prevalence of HCV infection ranges from approximately 4.8% to 6%, based on various studies (6). A literature review identified genotype 3a as the most prevalent HCV genotype in Pakistan, constituting 58% of cases, followed by genotypes 3b, 2a, 1a, and 1b (6).

Esophago-gastro-duodenoscopy (EGD) is the preferred method for screening esophageal varices (7). According to BAVENO VI guidelines, every patient diagnosed with cirrhosis should undergo an upper gastrointestinal endoscopy (8). However, EGD is costly, resource-intensive, and invasive, causing considerable discomfort to patients. Consequently, recent studies have focused on non-invasive predictors of esophageal varices. These studies emphasize the significance of laboratory and ultrasonographic data in predicting the presence of EVs, including indices such as the platelet count (PC), fibrosis-4-index (FIB-4), aspartate-aminotransferase-to-platelet-ratio index (APRI), and the aspartate-aminotransferase-to-alanine-aminotransferase ratio (AAR) (9–12). However, the diagnostic accuracy of these markers varies, and currently, their use in predicting esophageal varices is not recommended.

One notable marker is the P2MS index, calculated using components of a complete blood count, a test conducted routinely in patients. This index has not only proven useful in detecting the presence of EVs but also in grading them (13). Shabana SS et al. in an Egyptian study found that a P2MS index below 15.57 could detect esophageal varices with a high sensitivity and specificity. Furthermore, they noted an exceptional sensitivity in identifying high-risk varices (HRVs) at a cutoff value below 10.12 (13). Similarly, in a Korean study focusing on hepatitis B (HBV)-related cirrhosis, Kim BK et al. validated the P2MS index's efficacy, suggesting that individuals with a P2MS index above 25 could avoid endoscopy (14). In Turkey, Topal F et al. also affirmed the predictive value of the P2MS index in HBV-related variceal bleeding, with significant positive and negative predictive values at specific cutoff points (15).

Given the high prevalence of hepatitis C in certain populations, our study aimed to determine the utility of the P2MS index in predicting EVs in patients with Hepatitis C-related chronic liver disease (CLD). This research is pivotal in our context, as it can aid in identifying patients requiring endoscopic screening for EVs and predict HRVs, potentially alleviating the burden on patients and healthcare systems. Our primary objective was to evaluate the effectiveness of the P2MS index in predicting esophageal varices and high-risk varices in patients with hepatitis C-associated CLD.

MATERIAL AND METHODS

This cross-sectional study was conducted to evaluate the efficacy of the P2MS index, APRI, and FIB-4 scores in predicting the presence of esophageal varices (EVs) and high-risk EVs (HRVs) in patients diagnosed with chronic liver disease (CLD) due to hepatitis C. The research took place at the Hepato-Gastroenterology department of the Sindh Institute of Urology and Transplantation (SIUT), where the study received approval from the institution's Ethical Review Committee (ERC-SIUT). Spanning from January 1, 2022, to December 21, 2022, the study employed a non-probability consecutive sampling method.

Participants selected for the study were between the ages of 18 and 50 and had been recently diagnosed with liver cirrhosis attributed to hepatitis C. Patients presenting with a diverse range of medical histories were excluded. Diagnostic procedures for each participant included standard laboratory tests such as esophagogastroduodenoscopy (EGD) and a complete blood count. On EGD, esophageal varices were characterized as abnormally large, coiled, or convoluted dilated veins within the esophagus. HRVs were identified and classified into two grades: Grade 2, showing a beading appearance, and Grade 3, characterized by large, sinuous varices with a tumefactive appearance running obliquely. Liver cirrhosis was diagnosed using abdominal ultrasonography, with the criteria including altered hepatic echo texture, irregular liver borders, a spleen size exceeding 12 cm, and a portal vein diameter greater than 12 mm.

The P2MS index was calculated using the formula: [Platelet count (x10^9/L)]^2 / [monocyte fraction (%) X segmented neutrophil fraction (%)] (13). The APRI score was determined by: [(AST/ULN)/Platelet count x 10^9/L] x 100 (16). The FIB-4 score was calculated as follows: Age (years) x AST (U/L) / [PLT (x 10^9/L) x sqrt(ALT (U/L))] (17).

For the analysis of the collected data, the study employed SPSS version 25.0. The diagnostic accuracy of the predictors was evaluated using the Area Under the Receiver Operating Curve (AUROC), with a focus on identifying the optimal cutoff values. The statistical significance of the predictive capabilities of the indicators was determined with a significance level set at $p < 0.05$. This comprehensive approach ensured a robust assessment of the potential of the P2MS index, APRI, and FIB-4 scores in predicting EVs and HRVs in patients with hepatitis C-related CLD.

RESULTS

In this study, we closely examined the baseline characteristics of 375 participants to evaluate the predictive value of the P2MS index, APRI, and FIB-4 scores for esophageal varices (EVs) and high-risk esophageal varices (HRVs) in patients with chronic liver disease associated with hepatitis C. The study population predominantly consisted of males (62.4%) and individuals classified under the

Child Turcotte Pugh Score A (67.5%). Esophageal varices were present in 52.8% of the patients, while 25.3% had high-risk varices. The mean age of participants was 44.5 years, with standard deviations indicating a wide age range. Laboratory findings showed a mean hemoglobin level of 11.1 g/dL, a total leucocyte count of 5.4x10^9/L, and a platelet count averaging at 93.1x10^9/L. The segmented neutrophil and monocyte fractions were 75.2% and 10% respectively. The mean values for total bilirubin, AST, ALT, and serum albumin were also reported, with the P2MS Index, APRI, and FIB-4 scores calculated for each participant (Table 1).

A further analysis of the baseline variables in relation to the presence of esophageal varices revealed significant associations. Among the patients with EVs, a higher proportion were male (75.5%), and they had a lower average age compared to those without varices. Significant differences were observed in hemoglobin levels, total leucocyte count, platelet count, segmented neutrophil and monocyte fractions, total bilirubin, AST, ALT, serum albumin levels, and the international normalized ratio (INR). Notably, the mean P2MS Index, APRI, and FIB-4 scores were markedly different between those with and without EVs, suggesting a strong association of these indices with the presence of varices (Table 2).

Table 1 Baseline Characteristics of the population included in the study (N-375)

Study Population		N (%)
Gender	Male	234(62.4)
	Female	141(37.6)
Child Turcotte Pugh Score	A	253(67.5)
	B	122(32.5)
Esophageal varices (EVs)	Present	198(52.8)
	Absent	177(47.2)
High Risk Varices (HRVs)	Present	95(25.3)
	Absent	280(74.7)
Mean age (years±S.D)		44.5±12.9
Hemoglobin (g/dL)		11.1±2.03
Total Leucocyte Count (x109/L)		5.4±2.8
Platelet Count (x109/L)		93.1±46.8
Segmented neutrophil fraction (%)		75.2±4.8
Segmented monocyte fraction (%)		10±4.1
Total Bilirubin (mg/dl)		1.2±0.75
Aspartate Transaminase (AST)(IU/L)		56±46
Alanine Transaminase (ALT)(IU/L)		43±30
Serum Albumin(g/dl)		3.4+0.6
P²MS Index		18.5+19.7
APRI		2.9 +3.8
FIB-4		6.2+7.4

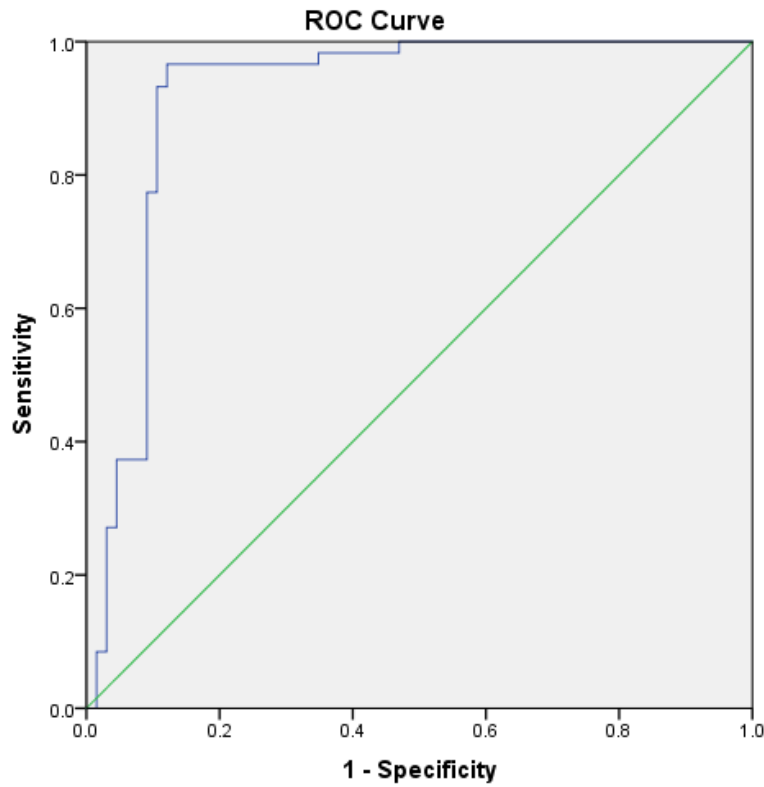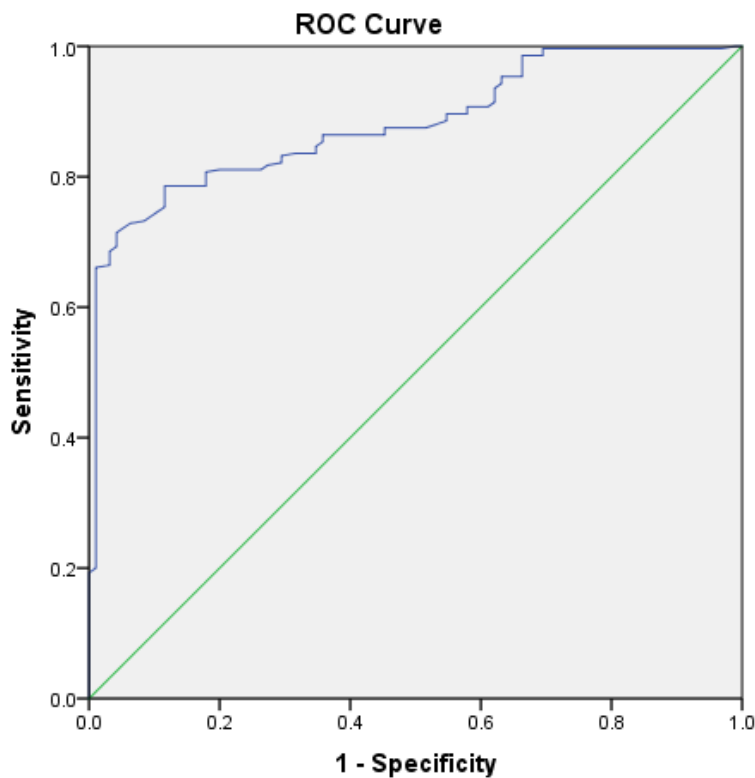Legend: CTP: Child Turcotte Pugh; APRI: aspartate aminotransferase to platelet ratio index; FIB-4: Fibrosis score-4

Figure 1 Area under the receiver operating curve for P2MS index in predicting the presence of esophageal varices is 0.914(p-value <0.001)

Figure 2 Area under the receiver operating curve for P2MS index in predicting High Risk esophageal varices (HRVs) is 0.88(p-value <0.001)

Table 2 Performance P2MS index in predicting the presence of esophageal varices(EVs) and also in identifying high risk EVs(HRVs)

EVendo score	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Diagnostic Accuracy
For Presence if EVs Cut off <10.7	87.88%	93.32%	93.55%	87.30%	90.40%
For identifying HRVs Cutoff <5.4	80%	81.1%	58.2%	92.28%	80.8%

Table 3 Comparison of P2MS index with APRI and FIB-4 in predicting the esophageal varices and high risk varices

Model	Presence of Esophageal varices			Presence of High risk Esophageal varices		
	AUROC	95%CI	p-value	AUROC	95%CI	p-value
P2MS	0.92	0.89- 0.95		0.88	0.85- 0.92	
APRI	0.88	0.85- 0.91	<0.001	0.874	0.83-0.90	0.12
FIB-4	0.90	0.88-0.937	<0.001	0.859	0.822-0.97	<0.001

Legend: APRI: aspartate aminotransferase to platelet ratio index; FIB-4:Fibrosis score-4

The diagnostic accuracy of the P2MS index was substantiated through the Area Under the Receiver Operating Curve (AUROC). For predicting the presence of esophageal varices, the AUROC was 0.914 with a statistically significant p-value, indicating a high predictive value (Figure 1). Similarly, the AUROC for predicting high-risk esophageal varices using the P2MS index was 0.88, again showing significant predictive capability (Figure 2).

In terms of the performance of the P2MS index, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated for different cutoff values. For the presence of EVs at a cutoff of <10.7, the index showed a sensitivity of 87.88%, a specificity of 93.32%, a PPV of 93.55%, an NPV of 87.30%, and an overall diagnostic accuracy of 90.40%. When predicting high-risk varices at a cutoff of <5.4, the sensitivity was 80%, specificity 81.1%, PPV 58.2%, NPV 92.28%, and diagnostic accuracy 80.8% (Table 3).

Comparing the P2MS index with APRI and FIB-4 in predicting the presence of esophageal varices and high-risk varices, the P2MS index demonstrated superior performance. The AUROC values for P2MS were consistently higher compared to APRI and FIB-4 for both EVs and HRVs. Specifically, the AUROC for P2MS in predicting EVs was 0.92 and for HRVs was 0.88, indicating a higher predictive accuracy compared to the other indices (Table 4). These findings underscore the potential of the P2MS index as a reliable tool for predicting esophageal varices in patients with hepatitis C-related chronic liver disease.

DISCUSSION

In the context of our study, the primary objective was to determine the efficacy of the P2MS index as a non-invasive predictor for the presence and severity of esophageal varices (EVs) in patients with chronic liver disease. The screening for EVs is crucial to identify patients requiring primary prophylaxis to prevent variceal bleeding, with endoscopy being the gold standard. However, the invasive nature and high cost of endoscopy often lead to patient aversion, underlining the need for non-invasive predictive tools.

Our findings suggest that the P2MS index holds significant promise in this regard. Previous studies, like those conducted by Shabana SS et al. in an Egyptian population (13) and Kim BK et al. in a Korean setting (14, 20), have similarly highlighted the P2MS index's effectiveness in predicting both the presence of EVs and high-risk varices (HRVs). In these studies, the P2MS index demonstrated excellent sensitivity and specificity at various cutoff values, affirming its potential as a useful tool in different populations.

In our study, the P2MS index showed a specificity of 93.22% and a sensitivity of 87.88% at a cutoff of <10.7 for predicting EVs. For HRVs, a cutoff of <5.4 yielded an impressive negative predictive value along with good sensitivity, specificity, and diagnostic accuracy. This performance was superior compared to APRI and FIB-4, especially in predicting the presence of EVs, as indicated by the highest AUROC values (p<0.001). However, in the prediction of HRVs, while the P2MS index outperformed FIB-4, it was comparable to APRI, suggesting that it may not be as robust in this aspect.

The study's strength lies in its comprehensive evaluation of the P2MS index, offering valuable insights into its applicability in a Pakistani population with distinct demographic characteristics. However, there are certain limitations to consider. The sample size was relatively small, potentially impacting the index's performance, particularly in predicting HRVs. Furthermore, the study did not

compare the P2MS index's diagnostic accuracy with other existing non-invasive models, which could have provided a more holistic understanding of its relative effectiveness.

CONCLUSION

In conclusion, our study underscores the P2MS index as a potentially effective tool for esophageal variceal screening in patients with chronic liver disease. While it demonstrated superior accuracy over other non-invasive indices in predicting the presence of EVs, its performance in predicting HRVs was comparable to existing tests. These findings, coupled with the ease and non-invasive nature of the P2MS index, point towards its potential utility in clinical practice. However, larger-scale studies are needed to further validate its effectiveness and to establish its role alongside other non-invasive screening methods. This research not only adds to the growing body of evidence supporting the use of non-invasive indices in the management of liver diseases but also highlights the need for continuous evaluation and refinement of these tools to enhance patient care.

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