P2/MS index for esophageal varices prediction in hepatitis C related liver cirrhosis

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Abstract: Background: Recent guidelines recommend that all cirrhotic patients without previous variceal hemorrhage should undergo endoscopic screening to detect esophageal varices (EV). Noninvasive identification of patients at highest risk for EV would limit investigation to those most likely to benefit. **Aim**: To evaluate the predictive value of P2/MS index derived from the patient's complete blood count in detecting EV in HCV related liver cirrhosis. **Patients and Methods**: 100 patients with HCV related liver cirrhosis were enrolled in the study. All patients underwent upper gastrointestinal endoscopy for detection and classification of EV as low risk or high risk (HEV). All patients had complete blood count, AST, ALT, serum albumin, total bilirubin, INR and abdominal ultrasound. P2/MS [platelet count^2 (10^9/L) /monocyte (%) x segmented neutrophil (%)] and some other previously reported non-invasive scores for EV detection (AAR, API, APRI, ASPRI, SPRI and platetlet count/spleen diameter ratio) were calculated for all subjects. **Results**: the prevalence of EV was 73% and of HEV 48%. For detection of EV, P2/MS showed a sensitivity of 98.63%, specificity of 92.59%, 97.3% positive predictive value, 96.2% negative predictive value, 13.32 positive likelihood ratio and 0.01 negative likelihood ratio at cutoff value ≤ 15.57. For detecting high risk esophageal varices (HEV), P2/MS showed a sensitivity of 95.83%, specificity of 84%, 92% positive predictive value, 91.3% negative predictive value, 5.99 positive likelihood ratio and 0.05 negative likelihood ratio at cutoff value ≤ 10.12. P2/MS had the highest AUROC compared with other scores in both detecting the presence of esophageal varices (0.987, 95% CI 0.940 - 0.998) and in HEV detection (0.930, 95% CI 0.846 - 0.977). **Conclusion**: P2/MS is a reliable simple non-invasive index for the detection and classification of EV in patients with HCV related liver cirrhosis and it is recommended that patients with P2/MS ≤ 10.12 should have screening endoscopy.

[Sherif S Shabana, Hany A Hussein, Ahmed S Abo-Halima, Sameh A Abdel-bary. **P2/MS index for esophageal varices prediction in hepatitis C related liver cirrhosis.** *J Am Sci* 2013;9(12):483-488]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 65

Key Words: HCV, cirrhosis, P2/MS, esophageal varices, noninvasive.

1.Introduction:

The prevalence of varices in patients with liver cirrhosis is approximately 60-80% and the risk of bleeding is 25-35%, while the incidence of esophageal varices (EV) increases by nearly 5% per year, with the rate of progression from small to large varices is approximately 5 to 10 % per year (1). Despite significant improvements in the early diagnosis and treatment of variceal hemorrhage, the mortality rate of first variceal hemorrhage remains high (20%-35%) (2).

The American Association for the Study of Liver Disease (AASLD) recommended that all cirrhotic patients should be screened for the presence of EV when liver cirrhosis is diagnosed (3). However, subjecting all patients with cirrhosis to screening endoscopy imposes a needless burden of stress and expense on patients and medical facilities. Moreover, as the prevalence of high-risk esophageal varices (HEV) at any point in time is approximately 15–25%, most subjects screened either do not have varices or have varices that do not require prophylactic therapy (4).

A more affordable approach for screening would be possible if patients at low or high risk of having EV could be identified from easily obtainable clinical variables (5). As liver fibrosis is related to portal hypertension and EV, an index to detect histological cirrhosis or significant fibrosis would be an effective noninvasive tool to detect the presence of EV and it could reduce the requirement for both liver biopsy and endoscopy in clinical practice (6).

Recently, a simple, accurate, and noninvasive test for hepatic fibrosis known as P2/MS was developed (6,7). It uses only simple laboratory tests, i.e., complete blood cell counts and is calculated using the following formula: [platelet count^2 (10^9/L) /monocyte (%) x segmented neutrophil (%)]. P2/MS was used in detecting esophageal varices in HBV patients (8) so validation of P2/MS within a homogenous group of patients with HCV related liver cirrhosis will be especially useful.

Aim of the study:

The aim of this study is to investigate the validity of P2/MS index in predicting the presence of esopheal varices (EV) and high risk esophageal varices (HEV) in patients with hepatitis C related

liver cirrhosis, and to compare the performance of the P2/MS index with other noninvasive tests.

2. Patients and Methods:

Patients: This study was performed in the period between October 2012 and October 2013 on 100 patients with hepatitis C related liver cirrhosis attending the gastroenterology and hepatology outpatient clinics, internal medicine department, Ain Shams University Hospital. The study was performed according to the ethical standards for human experimentation and was approved by the scientific committee of Ain Shams University. Informed consent was obtained from the selected patients after explaining the aim of the study and the nature of the investigations required. Diagnosis of HCV related liver cirrhosis was based on clinical, laboratory and radiological data.

Exclusion criteria: The exclusion criteria included the following: causes of liver cirrhosis other than HCV; previous variceal bleeding; β-blocker therapy or endoscopic treaments (band ligation or sclerotherapy); portal vein thrombosis, previous surgery for portal hypertension or transjugular intrahepatic porto-systemic shunt stent placement and hepatocelluar carcinoma.

Methods: All patients were subjected to full clinical assessment, laboratory investigations including: complete blood count, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total bilirubin, serum albumin, INR, abdominal ultrasonography and upper GIT endoscopy for detection and grading of esophageal varices.

Endoscopic evaluation

EV were classified as small (veins minimally elevated above the oesophageal mucosal surface), medium (tortuous veins occupying less than one third of the oesophageal lumen), or large (those occupying more than one-third of the oesophageal lumen). In this study, patients with HEV were defined as those with medium or large EV and those with small EV, but with red signs or decompensated cirrhosis (3, 9).

P2/MS and other noninvasive tests

For the calculation of noninvasive tests including P2/MS, laboratory data obtained on the same day as the endoscopic examination were used. Within one day following or preceding the endoscopy, all patients underwent an ultrasonographic examination of the upper abdomen, performed by the same independent experienced operator blinded to the patients' clinical and laboratory data. A spleen bipolar diameter was defined as the greatest longitudinal dimension at the level of splenic hilum on the image monitor using electronic calipers (10). The values for P2/MS and other noninvasive tests were calculated using the formulas shown in (Table 1) (11-14).

Table 1. Formulas for calculation of the non invasive predictors of esophageal varices

Test	Calculation
P2/MS	[Platelet count (10^9/L)]^2 / [monocyte fraction (%) X segmented neutrophil fraction (%)]
AAR	AST/ALT
API	Age (years): 0-30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; >70 = 5 Platelet count (109/L): > 225 = 0; 200–224 = 1; 175–199 = 2; 150–174 = 3; 125–149 = 4; o-125 = 5 AP index is the sum of the above (possible value 0–10).
APRI	[(AST/ULN)/platelet count(10^9/L)]X100
SPRI	Spleen size (cm)/platelet count (10^9/L)X100
ASPRI	Age (years): 0-30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; >70 = 5 ASPRI is the sum of age and SPRI
Platelet count/spleen diameter ratio	Platelet count per ml divided by spleen diameter in millimeters

AAR, AST/ALT ratio; API, age-platelet index; APRI, AST-to-platelet ratio index; SPRI, spleen-to-platelet ratio index; ASPRI, age–spleen-to-platelet ratio index; ULN, upper limit of normal.
N.B. AST upper limit of normal in our study was 30 U/l

Statistical Methodology:

Statistical analysis was performed using SPSS v.18.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were described as mean and standard deviation (SD) while qualitative variables were described as frequency and percentage. Receiver operating characteristic (ROC) curves were constructed and the corresponding areas under the ROC curve (AUROC) were computed for each of the noninvasive indices. The sensitivity, specificity,

positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated using the ROC curves. Cutoff points were determined as the value corresponding with the highest accuracy (maximum sensitivity and specificity) for each index. Significance level was expressed as P<0.05.

3. Results:

A total of 100 patients were included in the study. Patients (76 male patients and 24 female patients) mean age was 47.76±8.61 years with their ages ranged between 30 and 70 years old. Prevalence of EV of any degree in the study population was 73 % (73 patients). Prevalence of HEV was 48% (48 patients) (table 1).

Table 1- Study population characteristics.

Parameter	Findings
Age	47.76±8.61 years
Sex	Male 76 (76%) Female 24 (24%)
Esophageal varices	Present 73 (73%) Absent 27 (27%)
Risky esophageal varices	High risk 48 (48%) Low risk 25 (25%)
Child Pugh class	A 15 (15%) B 43 (43%) C 42 (42%)
ALT	29.15 ± 11.04 U/l
AST	37.01 ± 13.23 U/l
Hemoglobin	9.81± 2.21 gm/dl
White blood cells	4.2± 1.8 (x 10^9/l)
Platelets	88.22±57.81 (x 10^9/l)
Monocyte (%)	7.34 ± 2.34 %
Segmented neutrophil (%)	75.49±8.38 %
Spleen diameter (cm)	14.27±2.09 cm
INR	1.63 ± 0.39
Total bilirubin	4.44 ± 3.08 mg/dl
Serum albumin	2.53 ± 0.62 gm/dl

Area under the ROC curve (AUROC) for P2/MS in predicting the presence of EV of any degree was 0.987 (95% CI 0.940-0.998, *p*= 0.0001). It showed sensitivity of 98.63%, specificity of 92.59%, 97.3% positive predictive value, 96.2% negative predictive value, 13.32 positive likelihood ratio and 0.01 negative likelihood ratio at cutoff value ≤ 15.57 (Table 2, Figure1).

Area under the ROC curve (AUROC) for P2/MS in predicting the presence of HEV was 0.930 (95% CI 0.846-0.977, *p*=0.0001). P2/MS showed sensitivity of 95.83%, specificity of 84% , 92% positive predictive value, 91.3% negative predictive value, 5.99 positive likelihood ratio and 0.05 negative likelihood ratio at cutoff value ≤ 10.12 (Table 2, Figure 2).

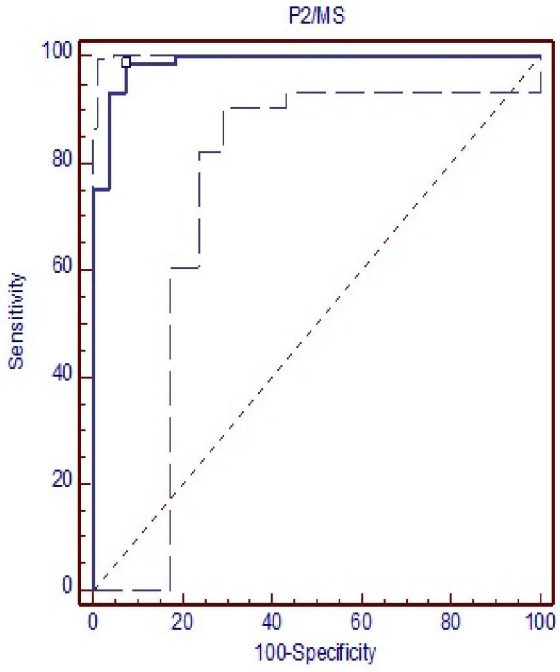

Figure 1- ROC curve for P2/MS in predicting presence of esophageal varices of any degree

Table 2- Performance of P2/MS in detection of esophageal varices and high risk esophageal varices.

Parameter	Esophageal varices	High risk esophageal varices
AUROC	0.987 (95% CI 0.940 - 0.998)	0.930 (95% CI 0.846 - 0.977)
P value	0.0001	0.0001
Cutoff point	≤ 15.57	≤ 10.12
Sensitivity	98.63 % (95% CI 92.6 - 99.8)	95.83% (95% CI 85.7 - 99.4)
Specificity	92.59 % (95% CI 75.7 - 98.9)	84 % (95% CI 63.9 - 95.4)
PPV	97.3%	92.0%
NPV	96.2%	91.3%
PLR	13.32	5.99
NLR	0.01	0.05

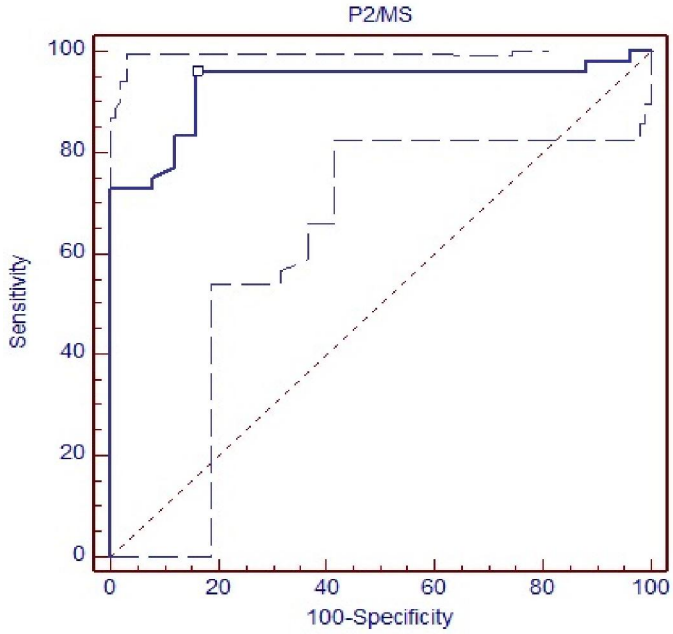

Figure 2- ROC curve for P2/MS in predicting high risk esophageal varices

Comparing the performance of the seven noninvasive indices included in the study in detecting esophageal varices presence, P2/MS had the highest area under the curve (AUROC) with significant difference when compared to other scores (p<0.001) (Table 3).Comparing the performance of the seven noninvasive indices in detecting high risk esophageal varices, P2/MS also had the highest AUROC with significant difference between it and APRI, API, AAR (p <0.001) but no significant difference were found between it and SPRI (P=0.136), ASPRI (p =0.093) and platelet count/ spleen diameter ratio (p =0.189) (Table 3).

Table 3- Comparison between P2/MS and other noninvasive indices in detecting the presence of esophageal varices and high risk esophageal varices.

Non invasive index	Esophageal varices presence			High risk esophageal varices		
	AUROC	95% CI	P value	AUROC	95% CI	P value
P2/MS	0.987	0.940 - 0.998		0.930	0.846 - 0.977	
SPRI	0.821	0.732 - 0.891	P < 0.001	0.885	0.789 - 0.948	P = 0.136
ASPRI	0.803	0.712 - 0.876	P < 0.001	0.873	0.775 - 0.940	P = 0.093
APRI	0.852	0.767 - 0.915	P < 0.001	0.715	0.597 - 0.815	P < 0.001
API	0.686	0.585 - 0.775	P < 0.001	0.531	0.410 - 0.649	P < 0.001
AAR	0.719	0.620 -0.804	P < 0.001	0.567	0.446 - 0.683	P < 0.001
Platelet count/spleen diameter ratio	0.821	0.732 - 0.891	P < 0.001	0.884	0.788 - 0.947	P = 0.189

4. Discussion

The diagnosis of EV is required for patients with liver cirrhosis to detect those who will benefit from variceal bleeding primary prophylaxis. Currently, esophago-gastro-duodenoscopy (EGD) remains the gold standard test for such diagnosis. However, EGD is limited by its invasiveness and high cost. A simple non-invasive widely available and cheap test would be ideal if proved to have sufficient specificity and sensitivity. Therefore, we aimed to study the diagnostic value of an index derived from the patients' complete blood count; namely the P2/MS ratio as a predictive tool for the presence of varices and if they are at high risk of bleeding.

The present study showed that at a cutoff value of ≤ 15.57, P2/MS ratio had a sensitivity of 98.63%, specificity of 92.59%, 97.3% positive predictive value, 96.2% negative predictive value, 13.32 positive likelihood ratio and 0.01 negative likelihood ratio in detecting the presence of esophageal varices (EV). Furthermore, P2/MS showed a sensitivity of 95.83%, specificity of 84%, 92% positive predictive value, 91.3% negative predictive value, 5.99 positive likelihood ratio and 0.05 negative likelihood ratio at cutoff value ≤ 10.12 in detecting high risk esophageal varices (HEV). Similar results were shown by Kim et al (8), who studied the validity of P2/MS in predicting esophageal varices in 318 patients with hepatitis B (HBV) related cirrhosis. They found that P2/MS<11 reliably identified 83 patients as having HEV (94 % positive predictive value), while 179 patients were reliably identified as not having HEV with P2/MS more than 25 (94.4% negative predictive value). Overall, P2/MS reliably determined the likelihood of HEV in 262 patients (82.4%) in their study. They recommended that patients with P2/MS<11 should be considered for appropriate prophylactic treatments, while those with P2/MS>25 may avoid endoscopy reliably.

In another study, 475 patients with HBV related cirrhosis were followed prospectively for 4 years. The risk of EV bleeding was significantly higher in subgroup 1: P2/MS ≥9 than in subgroup 2: P2/MS <9 (p = 0.029). A lower P2/MS was significant predictor for EV bleeding (p = 0.04). So authors recommended that different prophylactic treatments should be considered for the subgroup with a P2/MS <9 (15).

The current study revealed that P2/MS had the highest area under the curve (AUROC) when compared to other studied noninvasive scores in detecting the presence of EV with significant difference (AUROC= 0.987, 95% CI 0.940 - 0.998, p < 0.001). Kim *et al.* (8) found that in predicting EV, P2/MS AUROC (0.915, 95% CI 0.881–0.949) values were comparable to those of ASPRI (p = 0.968) and SPRI (p = 0.871), and better than those of API (p <0.001), APRI (p <0.001) and AAR (p <0.001).

Comparing the performance of the seven noninvasive indices in detecting HEV, P2/MS also had the highest AUROC (0.930, 95% CI 0.846 - 0.977) with significant difference between it and APRI, API and AAR (p <0.001) but no significant difference was found between it and SPRI (p =0.136), ASPRI (p =0.093) and platelet count/ spleen diameter ratio (p =0.189). Similarly, Kim *et al.* (8) found that an AUROC of P2/MS was 0.941 (95% CI 0.912–0.970) for HEV, comparable with those of ASPRI (p =0.317) and SPRI (p =0.324), and better than those of API (p <0.001), APRI (p <0.006) and AAR (p <0.001).

In the study by Lee *et al.* (6) on 556 patients with viral related chronic liver disease and EV prevalence of 34% (compared with 73% in our study), AUROC of P2/MS was 0.916 (95% CI 0.879-0.954) for detecting EV, and 0.905 (95% CI 0.862-0.947) for detecting HEV.

Our observations suggest that in general, P2/MS ratio is more valuable than several non-invasive tests in detecting the presence of EV. However, it is comparable to some non-invasive tests when determining the presence of HEV. Our findings also implicate that patients with P2/MS ≤ 10.12 should have screening endoscopy. However, our findings require further studies to evaluate the potential role of P2/MS as a cheap, bedside reliable index to select the group of patients who might benefit from endoscopic screening for esophageal varices.

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11/28/2013