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Is P2/MS score valuable for prediction in HBV-related variceal bleeding?

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ABSTRACT

Objective: To determine the predictive value of P2/MS in patients with chronic HBV-related cirrhosis, and to predict high-risk esophageal varices, and obtain a cut-off value. **Methods:** A total of 412 patients with HBV-related cirrhosis who were admitted to our hospital between August 2014 and August 2017 were retrospectively evaluated. A diagnosis of cirrhosis was made with standard laboratory, radiological and physical examination findings. According to these evaluations, esophageal varices were classified as small, medium and large. For all obtained data, P2/MS was calculated. Two threshold values (P2/MS<11 and P2/MS>25) were considered in predicting the presence of high-risk EVs during recording. And the optimal cut-off value of the P2/MS index was determined for high-risk esophageal varices in patients with chronic viral hepatitis B. **Results:** A total of 375 patients who met the inclusion criteria were included in the study. When the P2/MS index was compared with other noninvasive tests, the mean and median P2/MS scores were respectively 54.17 and 33.25. The P2/MS value of the patients without esophageal varices was higher than that of the patients with esophageal varices. When these results were evaluated, the higher the score, the lower the risk of varices. We obtained a positive predictive value of 93.80% [95% *CI* (80.20-98.70)] when the cut-off value of P2/MS was taken as <11, and obtained a negative predictive value of 94.30% [95% *CI* (86.20-98.20%)] when the cut-off value of P2/MS was taken as >25. **Conclusions:** We could predict the patients with high-risk esophageal varices within this group at a extremely good rate. We also compared the results of this test with other non-invasive tests and achieved successful results. We have shown that P2/MS can be used in order to optimally select patients for endoscopic screening and prevent all of the expensive and unnecessary procedures safely.

1. Introduction

Portal hypertension is one of the most serious complications of hepatic cirrhosis. It particularly causes severe problems such as ascites formation and hepatic encephalopathy. It is also one of the major causes of esophageal variceal bleeding. High portal vein pressure leads to the development of portosystemic collateral vessels. The dilation and increase in the systemic circulation cause the formation of gastroesophageal varices. Gastroesophageal varices are seen in 25%-55% of cirrhotic patients.

The portal system contains the vessels that carry blood away from

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the gastrointestinal tract, spleen, pancreas, and gallbladder. The portal vein is usually formed by the convergence of the superior mesenteric vein and the splenic vein immediately behind the head of the pancreas. It is 5-8 cm long and extends up to the porta hepatis. It divides into the right and left portal veins within the liver and then courses alongside the hepatic artery. It contributes 72% of the total oxygen supply to the liver. Normal portal venous pressure is approximately 8-10 mmHg. There are many anastomoses between the portal system and the systemic venous system. In portal hypertension, these anastomoses are opened to reduce portal venous pressure. If portal venous pressure increases, it leads to serious complications. Splenomegaly, gastroesophageal varices, portal hypertensive gastropathy, hemorrhoids, congestive jejunopathy, colonopathy, and umbilical venous collateral scan occur. The basic mechanism of portal hypertension is the impaired liver structure and venous obstruction, leading an increase in resistance to portal blood flow.

The most common causes of portal hypertension are chronic hepatitis and alcoholism. Portal vein thrombosis is not rare as previously thought. Factors such as coagulation disorders and use of oral contraceptives also increase the thrombotic tendency. Venous obstructions cause an increase in portal venous pressure. Portal hypertensive gastropathy that is characterized by the mosaic pattern of the gastric mucosa occurs in the stomach is due to portal hypertension. Venous occlusions cause splenomegaly in the later period. Ascites is one of the most frequent complications of cirrhosis. Liver function and morphology are initially normal. However, toxic substances that pass from portal to systemic circulation through the gastroesophageal collaterals can lead to hepatic encephalopathy.

Varices are evaluated and graded by endoscopic examination. Esophageal varices: stage 1$\leqslant$5 mm, straight, limited to the distal esophagus; stage 2=5-10 mm, tortuous, darker color, mid-esophagus or above; stage 3$\geqslant$10 mm, large enough to fill the lumen of the esophagus, red spots.Varices are generally prone to converge. The size of varices, the presence of red spots, the Child Pugh class C, and the diameter of the portal vein are important predictive findings for esophageal variceal bleeding.

The most serious and lethal complication of cirrhosis is variceal bleeding. Varices can be asymptomatic until the bleeding starts. After esophageal varices develop, the prognosis of the disease worsens rapidly. For this reason, all important publications in the literature emphasized that there is a need for prophylactic treatment. Periodic endoscopic screening and follow-up are also recommended for all cirrhotic patients. The prevalence of varices during periodic screening is 15%-20%. Therefore, the reason for recommending frequent, periodic screening in cirrhotic patients is to reduce mortality.

However, frequently repeated endoscopic examinations impair the quality of life of patients and pose a serious financial burden. In a patient without symptoms, there are risks during the process of preparation for endoscopy and during endoscopy procedure. Even these small probabilities can have serious consequences. For these reasons, non-endoscopic, low-cost biochemical methods are needed to predict the presence of esophageal varices. For this purpose, studies are planned all over the world. In a recent study of Lee *et al.* conducted in patients with chronic viral liver disease, they have suggested that the P2/MS test (which is a simple, non-invasive test that they have developed) can be used for this purpose[1].

P2/MS is calculated using the formula below:

Platelet count (10^9/L) (2)/(monocyte fraction % $\times$ segmented neutrophil fraction %).

However, sufficient evidence has not yet been provided for the predictive value of P2/MS. Its significance should be confirmed by performing these studies with different groups.

Therefore, this study was planned to determine the predictive value of P2/MS in patients with chronic HBV-related cirrhosis, to predict high-risk esophageal varices, and obtain a cut-off value.

2.Materials and methods

2.1. Patients and methods

Our study was conducted at Izmir Katip Çelebi University Atatürk Research and Training Hospital. A total of 412 patients with HBV-related cirrhosis who were admitted to our hospital between August 2014 and August 2017 were retrospectively evaluated. A diagnosis of cirrhosis was made with standard laboratory, radiological and physical examination findings. In some patients, cirrhosis was assessed by examining liver histopathology results. Ultrasonographic results of the patients were also examined to confirm a diagnosis of cirrhosis. Cirrhotic patients with coexisting HBV infection and alcohol use (those consumed $\geqslant$20 g/day of alcohol) were not included in the study (n=13). Moreover, patients with previous variceal bleeding (an exclusion criteria) were excluded from the study (n=13). Patients who underwent band ligation or endoscopic sclerotherapy, who were operated for portal hypertension or transjugular intrahepatic portosystemic stent (n=5), and who were diagnosed with portal vein or splenic vein thrombosis (n=1) and with hepatocellular carcinoma (n=5) were not included in the study. The study protocol was in accordance with declaration of Helsinki ethical guidelines.

The patients were selected from among those who regularly visited at periodic intervals. All patients who were included in the study underwent surveillance endoscopy every year. In addition, they were followed with ultrasound and laboratory examinations every 6 months. It was seen in the patients' medical records that the patients received antiviral therapy (nucleoside analogues such as lamivudine, adefovir, or entecavir) and propranolol therapy according to the guidelines, provided that they were clinically relevant and not contraindicated. Moreover, it was seen in the patients' medical records that suspicious bleeding conditions such as upper

gastrointestinal bleeding, hematemesis, hematochezia, or melena were shown to originate from esophageal varices by endoscope. The patients were treated in accordance with their complications.

Endoscopies and biopsies were performed by the gastroenterology clinic of our hospital. Biopsies were evaluated by pathologists in our hospital. Radiological or ultrasonographic evaluations were based on radiology reports. Our study was also based on these reports. According to these evaluations, esophageal varices (EVs) were classified as small (vessels that are more deeply located than the esophageal mucosa), medium (tortuous vessels occupying less than one third of the esophageal lumen), and large (occupying more than one third of the esophageal lumen). Patients with high-risk EV were defined as those with medium or large EV, those with small EV but with red color sign, or those with decompensated cirrhosis. Patients with low-risk EV were defined as those with small EV without red color sign. Cirrhotic patients without acute decompensation were considered to be at low-risk.

The patients' medical records were examined for the laboratory results. For all obtained data, P2/MS was calculated using the formula below:

Platelet count (10^9/L) (2)/(monocyte fraction % $\times$ segmented neutrophil fraction %)

The laboratory data including P2/MS were calculated based on blood samples taken 1 day before endoscopy or after endoscopy. In order to assess the reproducibility of segmented neutrophil fraction for P2/MS, we calculated the intraclass correlation coefficient (0.92) using blood samples taken 1 day before endoscopy.

Based on a study of Kim *et al.* conducted in patients with HBV-related cirrhosis[2], two threshold values (P2/MS<11 and P2/MS>25) were considered in predicting the presence of high-risk EVs during recording.

2.2. Statistical analysis

The main objective of our study was to examine the predictive value of P2/MS in patients at risk of esophageal variceal bleeding. The Mann-Whitney U test or Student's *t*-test was used according to their suitability in order to evaluate continuous variables and to calculate differences between groups. The *Chi*-Square test was also performed. The Receiver Operating Characteristic (ROC) curve and the Area Under the Curve (AUC) were calculated to assess the diagnostic value of P2/MS. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the ROC curves. The Kaplan-Meier method was used to examine time from beginning until the first occurrence of esophageal variceal bleeding (primary endpoint). After univariate analysis was performed using the Kaplan-Meier method, the Cox proportional-hazards model was used for multivariate analysis. In order to assess the predictive value of the model for cumulative bleeding events during follow-up, time-dependent ROC curves were generated for the first event of esophageal variceal bleeding, and the AUC was also calculated. A value of $P< 0.05$ was considered statistically significant.

3. Results

A total of 412 patients with HBV-related cirrhosis were evaluated by considering the inclusion criteria. Cirrhotic patients with coexisting HBV infection and alcohol use were not included in the study (n=13). A total of 13 patients who had esophageal variceal bleeding and received β-blocker therapy were not included in the study. Patients who underwent band ligation or endoscopic sclerotherapy, who were operated for portal hypertension or transjugular intrahepatic portosystemic stent (n=5), and who were diagnosed with portal vein or splenic vein thrombosis (n=1) and with hepatocellular carcinoma (n=5) were not included in the study. A total of 375 patients who met the inclusion criteria were included in the study.

The mean age of the patients was 50.1 years. 300 (80%) of the patients included in our study were male. A total of 183 (48.8%) patients were diagnosed with EV. Of them, 63 (16.8%) had small EV, 103 (27.5%) had medium EV, and 17 (4.5%) had large EV. The red color sign was seen in 51 (13.6%) of the patients included in the study. A total of 125 (33.3%) were generally considered risky. Of the 125 patients with high-risk EV requiring prophylactic β-blocker therapy, only 13 (3.2%) received propranolol. The median dose of propranolol was 120 mg/day (between 40 mg and 180 mg). 25 (6%) patients also had portal hypertensive gastropathy.

The median platelet count was 125 $\times 10^9$/L, the median segmented neutrophil fraction was 59.2%, and the median monocyte fraction 7.2%.

The patients were classified according to their Child-Pugh score. A total of 330 (80%) had Child-Pugh class A, 70 (21.2%) had Child-Pugh class B, and 12 (3%) had Child-Pugh class C.

A total of 246 patients were started on antiviral therapy during follow-up. The most commonly prescribed drug was lamivudine (n=140), followed by entecavir (n=76).

When the P2/MS index was compared with other noninvasive tests, the mean and median P2/MS scores were respectively 54.17 and 33.25. The P2/MS value [median 65.4, IQR (41.0-114.1)] of the patients without esophageal varices was higher than that [median 9.89, IQR (6.68-17.97), P<0.001] of the patients with esophageal varices. When these results were evaluated, the higher the score, the lower the risk of varices.

The aim of this study was to determine whether a non-invasive test such as P2/MS score was a predictor of high-risk esophageal varices and to reveal which patients would need prophylaxis. Therefore, we tried to determine the optimal cut-off value of the P2/MS index for high-risk esophageal varices in patients with chronic viral hepatitis B. In patients with chronic HBV-related cirrhosis, we obtained a positive predictive value of 94.60% when the cut-off value of P2/MS was taken as <11. Thus, it was able to identify 94.60% of the patients

with high-risk esophageal varices. We obtained a negative predictive value of 94.10% when the cut-off value of P2/MS was taken as >25. Because high-risk esophageal varices are less likely to develop in patients with P2/MS score >25 by considering the calculated cut-off values, we can predict in these patient groups that prophylactic treatment may not be applied and that endoscopic applications can be reduced.

According to the data obtained from the study, we obtained a positive predictive value of 93.80% [95% *CI* (80.20-98.70)] when the cut-off value of P2/MS was taken as <11. We obtained a negative predictive value of 94.30% [95% *CI* (86.20-98.20%)] when the cut-off value of P2/MS was taken as >25 (Table 1).

Table 1
Validation of suggested cut-off values of P2/MS for prediction of high-risk oesophageal varices using bootstrap samples.

Items	P2/MS cut-offvalues	
	11	25
NPV (%)	82.80 (73.30–90.10)	94.30 (86.20–98.20)
PPV (%)	93.80 (80.20–98.70)	77.70 (64.40–88.00)
Sensitivity (%)	65.80 (50.30–79.20)	91.30 (79.80–97.20)
Specificity (%)	97.40 (91.30–99.40)	84.50 (74.40–91.80)
PLR	27.09 (5.21–157.57)	6.55 (3.43–12.82)
NLR	0.36 (0.23–0.62)	0.10 (0.04–0.31)
Interpretation	Presence of high-risk oesophageal varices	Presence of high-risk oesophageal varices

Note: Inparentheses, 95% CI. NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

4. Discussion

The most important cause of mortality and morbidity in cirrhotic patients is esophageal variceal bleeding. For this reason, regular endoscopic examination and prophylactic treatment are absolutely recommended to determine whether or not esophageal varices develop or to show the status of existing varices. These follow-ups and treatments are especially important for those with high-risk esophageal varices and with red color sign. However, screening all cirrhotic patients also leads to unnecessary endoscopies. This causes both financial burdens and medical risks for patients. Due to frequent follow-up checks and repeated endoscopic examinations, patients do not regularly visit. Patients become lost to follow-up. Therefore, selective and low-cost noninvasive screening tools that can be well correlated with the prognosis of patients have been developed for patients with high-risk esophageal varices. Lee *et al*. and Kim *et al.* showed that P2/MS (a new simple formula based on complete blood count to predict high-risk EVs) had a good diagnostic value in their cross-sectional studies[1,2]. There are not enough current studies; however, a limited number of studies showed that it may be useful. Although P2/MS is specially designed and is a new index based on complete blood count to predict esophageal varicesin chronic viral liver disease, it has been recognized in patients with HBV-related cirrhosis. We have made a control of this study in our study.

In patients with chronic HBV-related cirrhosis, we obtained a positive predictive value of 94.60% when the cut-off value of P2/MS was taken as <11. We obtained a negative predictive value of 94.10% when the cut-off value of P2/MS was taken as >25. Because high-risk esophageal varices are less likely to develop in patients with P2/MS score >25 by considering the calculated cut-off values,we can predict in these patient groups that prophylactic treatment may not be applied and that endoscopic applications can be reduced. Prophylactic β-blocker therapy is started without performing endoscopy in all cirrhotic patients regardless of the status or size of esophageal varices. In our study, there would be no need for the initiation of prophylactic drug by evaluating esophageal varices with P2/MS score[3-5]. We do not have evidence that it does not provide benefits for a long time in patients with small EV without red color sign or decompensation. Through this study, we have provided an opportunity to determine not only those who needed to be screened by endoscopy for EVs but also those who might be suitable for prophylactic treatment.

The validity of P2/MS as a marker for the progression of portal hypertension in the development of esophageal varices can be explained in terms of the pathophysiology of chronic liver disease. As fibrosis and portal hypertension increase, the spleen grows with increased sequestration and platelet destruction. The production of thrombopoietin is reduced in hepatocytes[1,6-8]. Portal hypertension also increases the breakdown of thrombocytes, granulocytes, and red blood cells in the spleen, and a decrease in circulating granulocyte count causes a slight increase in serum[9]. Since GM-CSF stimulates the production of these cells more actively than that of lymphocytes, the proportion of neutrophils and monocytes also increases[10]. In addition to excellent diagnostic value in terms of pathophysiology, P2/MS has many clinical advantages. Unlike other non-invasive tests that require standardization and use ultrasonographic parameters such as portal vein velocity and portal vein diameter, P2/MS can be calculated at bedside or outpatient clinic because it does not require standardization. Since P2/MS parameters are obtained with a single blood test in cirrhotic patients, this economic test provides superiority over expensive tests that require special device or additional biochemical analysis. P2/MS will allow us to achieve better results than complex and expensive methods. For this reason, it is a valuable test for developing countries because it is an easy and cost-effective method.

This study has some limitations. Firstly, it is necessary to examine the long-term development of high-risk esophageal varices with cross-sectional and consecutive and then to re-evaluate the value of this score. Secondly, it would be appropriate to develop a quantitative analysis of certain parameters using hepatic venous pressure gradient measurement (an invasive but standardized method for assessing portal hypertension and related complications). Moreover, further studies should be made on not only endoscopic

data but also histological data proven by liver biopsy. On the other hand, it should be kept in mind that some of patients with advanced liver fibrosis may also have esophageal varices without cirrhosis. For this reason, it is necessary to expand the study population and to evaluate rare cases. Finally, the reproducibility test was not completed in this study. In order to obtain universally valid data, inter-center reproducibility must be verified by prospective, multi-centered studies.

In summary, we studied in a relatively large and homogeneous group with chronic HBV-related cirrhosis. We could predict the patients with high-risk esophageal varices within this group at a extremely good rate. We also compared the results of this test with other non-invasive tests and achieved successful results. We have shown that P2/MS can be used in order to optimally select patients for endoscopic screening and prevent all of the expensive and unnecessary procedures safely This study should be compared with homogeneous and larger-scale studies.

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