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Noninvasive assessment of the presence and size of esophageal varices

Neinvazivna procena postojanja i veličine varikoziteta jednjaka

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Abstract

Background/Aim. A significant number of patients with liver cirrhosis who underwent screening endoscopy do not have esophageal varices (EVs) or have EVs that do not require prophylactic therapy. Given the invasiveness of the procedure, the need to develop nonendoscopic methods in predicting the presence of EVs is reasonable. The aim of the study was to determine the significance of clinical, biochemical, and ultrasonic parameters in the prediction of EVs. **Methods**. The study included 59 patients with cirrhosis of the liver, 39 (66.1%) patients with EVs, and 20 (33.9%) patients without EVs. In the group of patients with EVs, 22 (56.4%) patients had small EVs, and 17 (46.3%) had large EVs. Clinical parameters that included Child-Pugh (CP) score, ascites, and splenomegaly were evaluated. In all participants, complete blood count, liver function tests, abdominal ultrasound, and gastroscopy were performed, and a platelet count/spleen diameter (PC/SD) ratio was calculated. **Results**. Univariate logistic regression analysis showed that independent risk factors for the occurrence of EVs were the following: CP B class [odds ratio (OR) 6.67; $p = 0.003$] and CP C class (OR 23.33; $p = 0.005$) relative to class A, ascites (OR 7.78; $p = 0.001$), spleen size (OR 1.035; $p = 0.016$), bilirubin (OR 1.065; $p = 0.007$), albumin (OR 0.794; $p = 0.001$), prothrombin time (OR 0.912; $p < 0.001$), international normalized ratio-INR (OR 231.364; $p < 0.001$), platelet count (OR 0.989; $p = 0.023$), and PC/SD ratio (OR 0.999; $p = 0.034$). In a multivariate model, it was shown that a decreased platelet count was a statistically significant risk factor for the presence of EVs (OR 0.983; $p = 0.023$). Leukopenia and the size of the right liver lobe were found to be statistically significant factors for the occurrence of large EVs. Based on the receiver operating characteristic (ROC) curve for the PC/SD ratio, the cutoff value of the test was obtained at 907 (907.11), with a negative predictive value of 76.4% for large EVs. **Conclusion.** The cutoff value of PC/SD ratio < 907 has a predictive value for the occurrence of large EVs.

Key words:
esophageal and gastric varices; liver cirrhosis; platelet count; prognosis; risk factors; spleen.

Apstrakt

Uvod/Cilj. Znatan broj bolesnika sa cirozom jetre podvrgnutih „skrining“ endoskopiji nema ezofagealne varikozitete (EV) ili ima EV za koje nije potrebna profilaktička terapija. Imajući u vidu invazivnost te procedure, razumljiva je potreba za razvojem neendoskopskih metoda za procenu prisustva EV. Cilj rada bio je da se utvrdi značaj kliničkih, biohemijskih i ultrazvučnih parametara u predviđanju EV. **Metode.** U istraživanje je bilo uključeno 59 bolesnika sa cirozom jetre, 39 (66,1%) bolesnika sa EV i 20 (33,9%) bolesnika bez EV. U grupi bolesnika sa EV 22 (56,4%) bolesnika imalo je male EV, a 17 (46,3%) bolesnika velike EV. Procenjivani su klinički parametri, koji su uključivali *Child-Pugh* (CP) klasu, prisustvo ascita i splenomegaliju. Svim ispitanicima urađeni su kompletna krvna slika, testovi funkcije jetre, ultrazvuk abdomena, gastroskopija i izračunat je odnos broja trombocita/dijametra slezine (*platelet count/spleen diameter* – PC/SD). **Rezultati.** Univarijanta logistička regresiona analiza pokazala je da su nezavisni faktori rizika od pojave EV bili: CP B klasa [*odds ratio* (OR) 6,67; $p = 0,003$] i CP C klasa (OR 23,33; $p = 0,005$) u odnosu na klasu A, prisustvo ascita (OR 7,78; $p = 0,001$), veličina slezine (OR 1,035; $p = 0,016$), bilirubin (OR 1,065; $p = 0,007$), albumin (OR 0,794; $p = 0,001$), protrombinsko vreme (OR 0,912; $p < 0,001$), *international normalized ratio*-INR (OR 231,364; $p < 0,001$), broj trombocita (OR 0,989; $p = 0,023$) i odnos PC/SD (OR 0,999; $p = 0,034$). U multivarijantnom modelu pokazalo se da je statistički značajan faktor rizika od prisustva EV bio smanjenje broja trombocita (OR 0,983; $p = 0,023$). Utvrđeno je da su statistički značajni faktori rizika od pojave velikih EV bili leukopenija i veličina desnog lobusa jetre. Na osnovu *receiver operating characteristic* (ROC) krive za odnos PC/SD, dobijena je granična (*cutoff*) vrednost testa 907 (907,11), sa negativnom prediktivnom vrednošću od 76,4% za velike EV. **Zaključak.** *Cutoff* vrednost odnosa PC/SD < 907 ima prognostički značaj za pojavu velikih EV.

Ključne reči:
jednjak i želudac, variksi; jetra, ciroza; trombociti, broj; prognoza; faktori rizika; slezina.

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Introduction

Portal hypertension (PH) is a common clinical syndrome, which is hemodynamically defined as a pathological increase in portal venous pressure. With the increase in portal venous pressure, the pressure gradient between the *inferior vena cava* and the portal vein increases as well (hepatic venous pressure gradient – HVPG), with the formation of portosystemic collaterals that divert the portal bloodstream to the systemic circulation, bypassing the liver. The normal HVPG value is 1–5 mmHg. PH is the result of an increase in resistance or blood flow in the portal vein. Any process that disrupts blood flow at any level of the portal venous system can cause PH. Liver cirrhosis (LC) causes more than 90% of cases of PH in Western countries [1–5].

Patients with LC go through two different stages of the disease, through compensated and decompensated cirrhosis. Depending on the pressure level at the level of the portal system, patients with PH and LC may be divided into patients with mild or subclinical PH (HVPG gradient > 5 mmHg, < 10 mmHg) and patients with clinically significant PH (CSPH), defined by an increase in HVPG ≥ 10 mmHg. Above this critical threshold, patients are at increased risk of developing clinical decompensation of the disease and complications, gastroesophageal varices (GEVs), ascites, variceal bleeding (VB), and encephalopathy [6, 7]. GEVs are the most relevant portosystemic collaterals because VB caused by wall rupture of the varix is the most common complication of LC with a fatal outcome. GEVs are present in 50% of patients with LC. The most significant predictor of esophageal varices (EVs) occurrence in patients who had no EVs at initial endoscopy is an increase in HVPG above 10 mmHg. Patients with HVPG over 12 mmHg, especially over 16 mmHg, are at increased risk of bleeding from EVs and have an increased mortality rate. Bleeding from GEVs is the cause of more than 70% of gastrointestinal bleeding events in patients with PH. An increase in HVPG over 20 mmHg is the most significant risk factor for early rebleeding (within one week of initial bleeding) (83% vs. 29%), treatment failure (64% vs. 20%), and one-year mortality compared to the period when HVPG is lower. The risk of variceal hemorrhage is 5% to 15% *per* year. It is important to understand that every patient with HVPG higher than 12 mmHg does not bleed from varices. Other important prognostic indicators of the risk of VB are the Child-Turcotte-Pugh score, the size of varices, and the presence of red signs on varices, such as hematocystic spots and blue-colored varices [1, 8–12].

The only reference method of quantifying the severity of PH is measuring the gradient of hepatic venous pressure. All portal pressure measurement methods are invasive. An indirect, less invasive method measures the "wedged" hepatic venous pressure (WHVP) by balloon catheterization of the hepatic vein. Despite its accuracy, this method, due to its invasiveness and limited availability in hospitals, has led to the development of noninvasive diagnostic tests and procedures of varying sensitivity [6, 13, 14].

The next "gold standard" in evaluating PH is the upper gastrointestinal endoscopy for the detection of GEVs, which is essential in the treatment of VB. Annually, 7%–8% of patients with compensated LC develop EVs, and in 8–12% of patients, progression from small to large EV is recorded. Given the dynamics of HVPG over time, accompanied by clinical worsening of the disease, patients with LC should undergo endoscopy at the time of diagnosis as well as periodic endoscopies [1, 13, 15, 16].

Patients repeatedly undergo an uncomfortable, invasive procedure with associated risks, although half of the patients do not have recognizable varices even ten years after the diagnosis of LC [17]. Today, significant efforts are being made to detect noninvasive tests that would identify patients with LC and low risk of the presence of varices.

Studies have shown that serum hepatic insufficiency markers such as hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia, and stratification of patients based on Child-Pugh (CP) correlate with clinically significant PH and presence/degree of varicosity. Patients with CP class B and C have a three-fold higher risk of developing varices compared to patients with CP class A, including the presence of large varices [18].

By integrating two parameters, platelet count and craniocaudal spleen diameter measured by ultrasound, a new pathophysiologically important parameter was obtained that can be easily calculated and used in clinical practice as the EVs screening method. Given that spleen diameter and platelet count measurements are part of the routine treatment of patients with LC, the costs would be lowered, while patients would be spared the inconvenience of exposure to endoscopy [19].

The aim of our research was to identify the clinical, biohumoral, and ultrasonographic predictors of the presence and size of EVs in patients with LC.

Methods

Retrospective research was conducted at the Clinic for Gastroenterology and Hepatology of the University Clinical Center Niš. Serbia. This study was approved by the Ethics Committee of this institution.

The study included 59 patients over 18 years of age diagnosed with LC of different etiology, using adequate immunoassays and determining antibodies for hepatitis B and C viruses. Patients who had consumed more than 50 g of alcohol *per* day for at least five years were diagnosed with alcoholic cirrhosis of the liver. In cases where the etiologic factor of the disease was not detected, LC was classified as cryptogenic. In the study, there were no patients with hereditary or metabolic liver diseases.

Patients with bleeding from EVs at the time of examination, patients who had previously bled and had sclerosis of EVs or band ligatures, and patients with already diagnosed hepatocellular carcinoma were not included in the study.

Physical examination evaluated the presence of ascites, splenomegaly, hepatomegaly, spider angioma, and hepatic encephalopathy.

In laboratory blood analyses, complete blood count was performed; the values of aspartate aminotransferase (AST), al-

anine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total and direct bilirubin, urea, creatinine, proteins, albumins, prothrombin time, and international normalized ratio (INR) were obtained.

An ultrasound examination of the abdomen was performed during the morning hours using an ultrasound probe of 3.5 MHz, which was preceded by fasting the night before the examination.

The position, shape, contours, and echostructure of the liver parenchyma were evaluated, and the size of the right lobe in the medioclavicular line expressed in mm was measured. The size of the spleen was determined by measuring its largest longitudinal diameter expressed in mm. The presence of ascites was assessed. Using the platelet count and maximum longitudinal spleen diameter (PC/SD) ratio for each patient was calculated [19, 20].

The assessment of liver function was performed using the CP classification. The classification includes two clinical parameters (ascites size and degree of hepatic encephalopathy) and four biochemical parameters (serum bilirubin and albumin levels and plasma levels of prothrombin time and INR). For each indicator, values are numerically individually classified into one of the categories, and each category brings a possible sum of points of 1–3. The total sum of points, which ranges from 5–15 depending on the values of the aforementioned parameters, classifies patients into three categories: A, B, or C. The patient belongs to Group A if the total number of points is 1–6, Group B if the score is from 7–9, and Group C if the score is greater than 9 [21].

Proximal video-endoscopy was performed in the endoscopy room of the Clinic for Gastroenterology and Hepatology of the University Clinical Center Niš. During the endoscopic examination, the presence and size of EVs, the presence of gastric varices, portal hypertensive gastropathy (PHG), and endoscopic signs indicating a risk of bleeding (cherry red spots) were assessed. The size of EVs during endoscopy was classified into three degrees: Grade 1 EVs – minimally penetrate the esophageal lumen and can be flattened by air insufflation but do not disappear; Grade 2 EVs – occupy less than 50% of the esophageal lumen; Grade 3 EVs – occupy more than half of the lumen, being confluent within the esophageal circumference [22].

Grade 1 EVs are considered "small" EVs, whereas grade 2 and 3 EVs are considered "large". For the purposes of this study, patients were divided into a group of patients without EVs and a group of patients with EVs. The group of patients with EVs was further divided into a group with "small" EVs and a group with "large" EVs.

Statistical analysis

Data are given as arithmetic mean and standard deviation and as numbers (percentages) of categorical data. The comparison of continuous variables between the two groups was performed using the *t*-test and Mann-Whitney *U* test. Categorical data were analyzed using the Chi-squared (χ^2) test. The testing of potential risk factors for the presence and size of EVs was performed by logistic regression analysis. GGT was excluded from the multivariate model due to multicollinearity. The discriminant ability of the PC/SD ratio was assessed by the receiver operating characteristic (ROC) curve. The hypothesis was tested with a significance threshold of $p < 0.05$. Statistical data analysis was performed in the program package R.

Results

Results related to the occurrence of esophageal varices

The study included 59 patients with LC, 39 (66.1%) patients with EVs, and 20 (33.9%) patients without EVs. The mean age of the patients with and without EVs was 60.28 ± 8.73 years and 57.10 ± 10.69 years, respectively. The groups were matched for age and gender ($p = 0.259$, $p = 0.972$). The male gender prevailed in both groups, with 69.2% in the group with EVs, i.e., 65.0% in the group without EVs.

Table 1

Clinical characteristics related to the presence of esophageal varices (EVs)

Parameters	With EVs	Without EVs	p^1
Etiology			
alcoholic	25 (64.1)	9 (45.0)	0.337
cryptogenic	8 (20.5)	3 (15.0)	
primary biliary cirrhosis	2 (5.1)	2 (10.0)	
hepatitis B virus	1 (2.6)	2 (10.0)	
hepatitis C virus	3 (7.7)	3 (15.0)	
autoimmune	0 (0.0)	1 (5.0)	
Child-Pugh class			
A	9 (23.1)	15 (75.0)	< 0.001
B	16 (41.0)	4 (20.0)	
C	14 (35.9)	1 (5.0)	
Encephalopathy	13 (33.3)	3 (15.0)	0.234
Cherry red spots	2 (5.1)	0 (0.0)	0.544
Portal hypertensive gastropathy	29 (74.4)	6 (30.0)	0.003
Spider angioma	8 (20.5)	3 (15.0)	0.872
Ascites	30 (76.9)	6 (30.0)	0.001
large	19 (63.3)	4 (66.7)	1.000
small	11 (36.7)	2 (33.3)	

All values are expressed as numbers (percentages). [1] Chi-squared test.

In the group of patients with EVs, 25 (64.1%) had alcoholic cirrhosis of the liver, 8 (20.5%) had cryptogenic LC, 3 (7.7%) had hepatitis C virus LC, 2 (5.1%) had primary biliary cirrhosis, and 1 had hepatitis B virus LC. Alcohol LC was also the most prevalent in the group of patients without EVs, in 9 (45%) patients. It was found that there was no statistically significant difference in the etiology of LC with reference to the presence of EVs ($p = 0.337$) (Table 1).

In the group of patients with EVs, 16 were in CP class B, 14 were in CP class C, and 9 patients were in CP class A. In the group of patients without EVs, 15 were in CP class A, 4 were in CP class B, and 1 was in CP class C. In the group of patients with EVs, CP class B (41.0%) and C (35.9%) dominated, while CP class A was dominant in the group without EVs (75.0%). There was a statistically significant difference in the frequency of different classes in relation to the presence of EVs ($p < 0.001$) (Table 1). In the group of patients with EVs, 30 had ascites diagnosed by ultrasound. In the group of patients without EVs, in most of them, ascites was not diagnosed with ultrasound. The frequency of ascites was statistically significantly larger in patients with EVs compared to patients without EVs (76.9% vs. 30.0%; $p = 0.001$). Thirteen patients with EVs had hepatic encephalopathy, while in the group without EVs, only three patients had this diagnosis. Spider angioma was found in eight patients with EVs and in three patients without EVs. The frequency of encephalopathy ($p = 0.234$) and spider angioma ($p = 0.872$) was nonsignificantly different compared to the presence of EVs (Table 1).

A comparison of routine laboratory and ultrasound parameters showed that AST, ALT, ALP, and GGT values were nonsignificantly different compared to the presence of EVs ($p = 0.737$, $p = 0.592$, $p = 0.361$, $p = 0.313$, respectively). Bilirubin values were statistically significantly higher in patients with EVs ($p = 0.001$). Albumin values were statistically significantly lower in patients with EVs ($p < 0.001$). Prothrombin time and platelet count were statistically significantly lower in patients with EVs ($p < 0.001$ and $p = 0.023$, respectively). INR values were statistically significantly higher in patients with EVs ($p < 0.001$). Leukocyte count did not differ statistically significantly in relation to the study groups ($p = 0.255$). PC/SD ratio values were statistically significantly lower in patients with EVs ($p = 0.025$). The size of the spleen was statistically significantly larger in patients with EVs compared to those who did not develop them ($p = 0.017$) (Table 2).

Univariate logistic regression analysis showed that independent risk factors for EVs were: PHG [odds ratio (OR) 6.77; $p = 0.002$], CP B class (OR 6.667; $p = 0.003$) and CP C class (OR 23.333; $p = 0.005$) relative to class A, ascites (OR 7.778; $p = 0.001$), spleen size (OR 1.035; $p = 0.016$), bilirubin values (OR 1.065; $p = 0.007$), albumin (OR 0.794; $p = 0.001$), prothrombin time (OR 0.912; $p < 0.001$), INR (OR 231.364; $p = 0.001$), platelet count (OR 0.989; $p = 0.023$), and PC/SD ratio (OR 0.999; $p = 0.034$). In a multivariate model, it was shown that a decrease in platelet count was a statistically significant risk factor for the presence of EVs. A decrease in platelet count by one unit led to a statistically significant 2% increase in the risk of EVs (OR 0.983; $p = 0.023$) (Table 3).

Based on the ROC curve for PC/SD ratio, the limit value of the test was obtained: 1,013 (1,013.82). The area under the ROC curve was 0.687 (0.540–0.833), ($p = 0.025$) (Figure 1). For the calculated parameters, the following values were obtained: sensitivity of 84.6%, specificity of 46.7%, positive predictive value of 56.4%, negative predictive value of 78.9%, and diagnostic efficiency of 63.8%.

Table 2

Biochemical and ultrasound parameters related to the presence of esophageal varices (EVs)

Parameters	Reference range (units)	With EVs	Without EVs	p[1]
AST	10–31 (U/L)	77.37 ± 58.27	78.05 ± 47.11	0.737
ALT	10–35 (U/L)	34.37 ± 18.23	40.9 ± 28.55	0.592
ALP	30–120 (U/L)	125.21 ± 56.74	164.18 ± 187.63	0.361
GGT	0–38 (U/L)	252.68 ± 381.28	261.41 ± 318.75	0.313
Bilirubin	5–20 (μmol/L)	45.69 ± 34.68	20.88 ± 13.16	0.001
Albumin	35–42 (g/L)	31.56 ± 4.62	37.81 ± 5.87	< 0.001[2]
Urea	2.5–7.5 (μmol/L)	5.49 ± 2.94	5.69 ± 2.52	0.642
Creatinine	53–115 (μmol/L)	81.05 ± 18.58	80.19 ± 17.79	0.823[2]
Prothrombin time	75–120 (%)	51.33 ± 12.32	80.71 ± 26.09	< 0.001
INR	0.8–1.2	1.54 ± 0.24	1.25 ± 0.28	< 0.001
Platelets	120–380 (× 10^9/L)	141.74 ± 59.04	183.6 ± 67.36	0.023
Leukocytes	4.0–9.0 (× 10^9/L)	7.07 ± 2.94	6.12 ± 1.81	0.255
PC/SD ratio	/	1,017.21 ± 484.42	1,320.54 ± 451.22	0.025
Right liver lobe	/	168.69 ± 26.16	165.25 ± 22.44	0.601[2]
Spleen	/	145.35 ± 20.43	129.90 ± 23.32	0.017[2]

AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alanine phosphatase; GGT – gamma-glutamyl transpeptidase; INR – international normalized ratio; PC/SD – platelet count/spleen diameter.

All values are expressed as arithmetic mean ± standard deviation.

[1] Mann-Whitney *U* test; [2] *t*-test.

Table 3

Risk factors for the presence of esophageal varices – logistic regression analysis

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Gender	1.212	0.386–3.800	0.742			
Age	1.036	0.978–1.098	0.225			
PHG	6.77	2.046–22.384	0.002			
Child-Pugh class						
A		RG			RG	0.710
B	6.667	1.690–26.298	0.191	3.546	0.533–23.600	0.191
C	23.333	2.610–208.616	0.230	5.730	0.331–99.336	0.230
Spider angioma	1.462	0.342–6.252	0.608			
Ascites	7.778	2.314–26.141	0.001	6.731	0.668–67.852	0.106
Right lobe	1.006	0.984–1.028	0.612			
Spleen	1.035	1.006–1.064	0.016	1.013	0.978–1.049	0.475
AST	1.000	0.990–1.010	0.964			
ALT	0.987	0.964–1.011	0.292			
ALP	0.997	0.993–1.002	0.256			
GGT	1.000	0.998–..001	0.929			
Bilirubin	1.065	1.018–1.114	0.007			
Albumin	0.794	0.696–0.905	0.001			
Urea	0.976	0.804–1.184	0.802			
Creatinine	1.003	0.973–1.033	0.863			
Prothrombin time	0.912	0.869–0.958	< 0.001			
INR	231.364	9.762–5483.54	0.001			
Platelets	0.989	0.980–0.999	0.023	0.983	0.969–0.998	0.023
Leukocytes	1.156	0.930–1.438	0.192			
PC/SD ratio	0.999	0.997–1.000	0.034			

OR – odds ratio; CI – confidence interval; RG – reference group; PHG – portal hypertensive gastropathy. For other abbreviations, see Table 2.

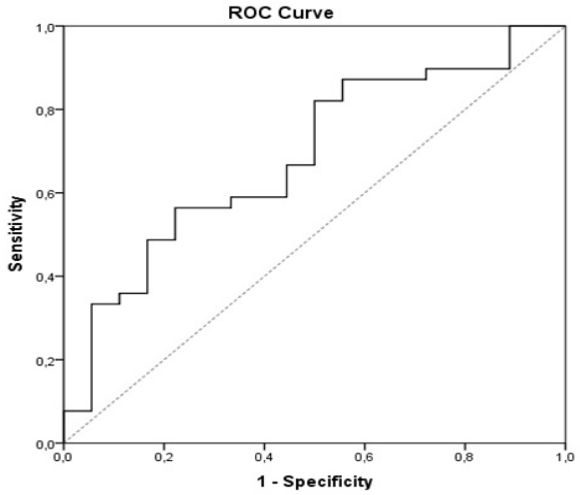

Fig. 1 – Receiver operating characteristics (ROC) curve for platelet count/spleen diameter values related to the occurrence of esophageal varices.

Results related to the size of esophageal varices

In the group of patients with EVs, 22 (56.4%) patients had small EVs, and 17 (46.3%) patients had large EVs. The univariate logistic regression analysis showed that independent risk factors for the size of EVs were: the size of the right liver lobe (OR 0.960, $p = 0.011$), leukocyte count (OR 0.689, $p = 0.009$), and PC/SD ratio (OR 0.998, $p = 0.045$) (Table 4). In the multivariate model, the size of the right liver lobe and leukocyte count, corrected for all other parameters in the model (OR 0.691, $p = 0.027$), were distinguished as statistically significant risk factors for the occurrence of large EVs.

Based on the ROC curve for PC/SD ratio in relation to the size of EVs, the obtained limit value of the test was 907 (907.11). The area under the ROC curve was 0.698 (0.524–0.872, $p = 0.036$). Sensitivity of 80.0%, specificity of 68.4%, positive predictive value of 72.7%, negative predictive value of 76.5%, and diagnostic test efficiency of 74.4% were obtained for the calculated parameters (Figure 2).

Table 4

Risk factors for the presence of large esophageal varices – logistic regression analysis

Parameter	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*	OR	95%CI	*p*
Gender	0.688	0.175–2.699	0.591			
Age	1.029	0.954–1.111	0.453			
Child-Pugh class						
A		RG				
B	0.568	0.105–3.070	0.511			
C	1.667	0.308–9.014	0.553			
PHG	4.286	0.773–23.746	0.096	4.908	0.535–44.995	0.159
Encephalopathy	3.022	0.761–11.999	0.116			
Spider angioma	2.639	0.531–13.116	0.236			
Ascites	0.956	0.213–4.284	0.953			
Right liver lobe	0.960	0.931–0.991	0.011	0.959	0.924–0.996	0.029
Spleen	1.002	0.971–1.034	0.892			
AST	0.999	0.987–1.010	0.814			
ALT	1.000	0.965–1.034	0.982			
ALP	0.995	0.983–1.007	0.409			
GGT	0.994	0.987–1.001	0.070			
Bilirubin	0.986	0.964–1.008	0.211			
Albumin	0.972	0.845–1.118	0.690			
Urea	1.082	0.868–1.350	0.482			
Creatinine	1.030	0.992–1.069	0.122			
Prothrombin time	0.952	0.897–1.011	0.109			
INR	5.874	0.337–102.406	0.225			
Platelets	0.988	0.975–1.000	0.051	1.011	0.961–1.063	0.668
Leukocytes	0.689	0.520–0.912	0.009	0.691	0.498–0.959	0.027
PC/SD ratio	0.998	0.997–1.000	0.045	0.998	0.992–1.005	0.589

OR – odds ratio; CI – confidence interval; RG – reference group; PHG – portal hypertensive gastropathy. For other abbreviations, see Table 2.

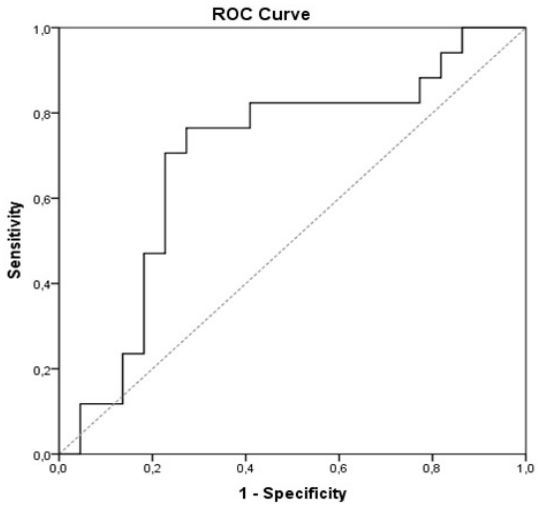

Fig. 2 – Receiver operating characteristics (ROC) curve for platelet count/spleen diameter values related to the size of the esophageal varices.

Discussion

Bleeding from EVs is one of the most urgent conditions in medicine, followed by high morbidity and mortality rates, which is 20% in the first six weeks after bleeding. The risk of VB in PH depends on the degree of PH, liver failure, size of EVs, and endoscopic appearance of EVs. Based on clinical and endoscopic characteristics, The North Italian Endoscopic Club described a formula for predicting the risk of the first episode of VB based on CP class (CP B/C), the size of EVs, and the presence of red spots on the surface of EVs [15, 23].

Given that VB can be prevented with the use of nonselective beta-blockers or band ligature, early diagnosis of EVs is essential when evaluating patients with LC.

Proximal endoscopy is the gold standard in diagnostics, grading, and assessment of surface EVs. All patients diagnosed with LC should undergo proximal endoscopy at the

time of diagnosis. Screening endoscopies are recommended at the time interval of one to three years, depending on the degree of hepatic insufficiency, presence and size of EVs, persistence of the etiological factor of the disease, and comorbidity [24].

Most patients who have undergone a screening endoscopy either have no EVs or have EVs that do not require prophylactic therapy [11]. The disadvantages of endoscopy include the risk of sedation, higher costs, bleeding, and the risk of aspiration.

Today, clinicians have an interest in identifying the "ideal" noninvasive markers that would be inexpensive, easy to perform, and easily reproducible but with high specificity and sensitivity, which would reduce the number of screening and therapeutic endoscopies in patients with EVs and cirrhosis of the liver. Such noninvasive parameters are particularly needed in developing countries with limited resources and a lack of a sufficient number of endoscopy rooms [25].

In 2003, Giannini et al. [19] recommended the use of the PC/SD ratio as a single noninvasive test that is easily calculated on the basis of parameter values that are part of a routine diagnostic assessment of patients with LC. This test with the cutoff value of 909 was found to have 100% sensitivity, 100% negative predictive value, and a specificity of 93% for EVs, which would meet the criteria of an ideal noninvasive test. Many other noninvasive markers and PC/SD ratios were calculated and correlated with esophagogastroduodenoscopy findings in many other studies with different cutoffs and predictive values for EVs [25–27]. In patients with PH, the risk of the first-time VB or rebleeding was significantly associated with the PC/SD ratio [10]. The meta-analyses of the studies whose subject matter was the PC/SD relationship did not confirm the previous allegations [28, 29].

Today, liver stiffness measurement (LSM) by transient elastography (TE) is among the best-validated noninvasive markers of liver fibrosis. Results of LSM showed a close correlation with HVPG and good accuracy (AUC = 0.93) in diagnosing PH. LSM value < 13.6 kPa assessed by TE resulted valuable to rule-out CSPH with high sensitivity (> 90–95%). More than 90% of patients with an LSM > 20–25 kPa will have clinically significant PH (specificity > 90–95%). One of the most important applications of elastometry is the identification of patients with GEVs. LSM is considered to have high sensitivity but medium or low specificity in predicting EVs in several studies [30].

A combination of measurement of liver stiffness and platelet count increases the predictive value of the method and is incorporated in the Baveno VI guidelines. In patients with chronic advanced liver disease, the Baveno VI consensus conference recommended that patients with normal platelet count (>150,000 /μL) and liver stiffness less than 20 kPa measured by TE should not undergo screening endoscopy. This strategy is safe and allows the saving of 15–25% of unnecessary endoscopies. The strategy only applies to well-compensated patients (compensated advanced chronic liver disease – cACLD), while patients with decompensated LC should undergo endoscopy regardless of the platelet count. That is a great improvement as it reduces costs and provides monitoring of varices less stressful for patients. Measuring platelet count is part of the routine laboratory processing of patients with LC, but the patient's constitution, lack of equipment, and trained personnel limit the use of TE [15, 25, 31].

The newer expanded Baveno VI criteria proposed new cutoff values for platelet count > 110×10^9 cells/L and LSM < 25 kPa to spare even more endoscopies with minimal risk of missing high-risk EVs in patients with cACLD [32, 33].

Splenomegaly is a common finding in patients with LC. Colecchia et al. [34] first demonstrated a clear and strong correlation between spleen stiffness measurement (SSM) by TE and the presence and degree of PH assessed by HVPG. With a cutoff value of < 40 kPa, the presence of CSPH and EVs can be ruled out with a sensitivity of 98.5 %. A recent meta-analysis confirmed that SSM has a strong correlation with the whole range of HVPG values and was quite useful for ruling out the presence of high-risk EVs [35, 36].

A combination of Baveno VI criteria and SSM (cut-off ≤ 46 kPa, assessed by TE) is another new diagnostic model which proved efficient in increasing the number of spared endoscopies without raising the rate of missed high-risk EVs [37].

TE is safe, reliable, and easy to use, but it is still not universally available to patients, and its application has some limitations. Therefore, there is still a need for other simple and reliable noninvasive tests.

In our study, a univariate logistic regression analysis singled out the parameters related to PH (spleen size, ascites, platelets) and parameters related to liver dysfunction or advanced disease (CP class B and C, serum bilirubin, albumins, prothrombin time), and PC/SD ratio as significant parameters for the occurrence of EVs. Our results are in agreement with the results of other authors [19, 28]. Cherian et al. [38] determined in a univariate analysis that the PC/SD ratio ≤ 666 is a significant predictor of the presence of EVs in predominantly alcoholic LC. This relationship had no statistical significance in the multivariate model. In the study by de Mattos et al. [39], thrombocytopenia, splenomegaly, PC/SD ratio, CP class, Model for End-Stage Liver Disease (MELD) score, and the presence of ascites were significantly associated with the presence of EVs. The multivariate analysis determined thrombocytopenia as the only independent factor for the presence of EVs, which is consistent with our findings.

A study by Nemichandra et al. [40] showed that the factors influencing the occurrence of EVs are the following: thrombocytopenia, decreased serum albumin levels, decreased PC/SD ratio, as well as splenomegaly, higher bilirubin levels, prothrombin time, and greater diameter of the portal vein. A multivariate analysis identified the PC/SD ratio < 1,433.1 and splenomegaly as independent predictors associated with the presence of EVs.

In our study, the multivariate analysis singled out thrombocytopenia as an independent predictive factor for the occurrence of EVs, which is in line with the results of other authors [18, 38, 41, 42].

The PC/SD ratio limit value of 1,013 was obtained based on the ROC curve. The area under the ROC curve was 0.687. For the calculated parameters, a sensitivity of 84.6%, specificity of 46.7%, positive predictive value of 56.4%,

negative predictive value of 78.9%, and diagnostic efficiency of 63.8% for predicting EVs were obtained.

A similar cutoff value of the PC/SD ratio for predicting EVs was determined by Baig et al. [43]. Compared to our results, the test had a higher sensitivity of 98.1%, specificity of 88.6%, negative predictive value of 95.4%, and the area under the curve (AUC) was 0.942, which indicated excellent diagnostic accuracy.

The univariate logistic regression analysis singled out the right liver lobe, leukocyte count, and PC/SD ratio as independent risk factors for the occurrence of large EVs. The multivariate logistic regression analysis found that the right liver lobe and leukocyte count were independent predictors of large EVs. In the study by Sharma and Aggarwal [44], a univariate analysis also singled out the diameter of the right liver lobe and leukocyte count as risk factors for the occurrence of large EVs, as well as the platelet count and splenomegaly. In the multivariate model, splenomegaly and platelet count were distinguished as independent predictors of larger EVs [44].

In our research, based on the ROC curve, the PC/SD ratio limit value of 907 was obtained, with a sensitivity of 80%, specificity of 68.4%, positive predictive value of 72.7%, negative predictive value of 76.5%, and diagnostic efficiency of the test of 74.4% for the prediction of large EVs (AUC 0.698). In the study by Barrera et al. [45], the cutoff value of the PC/SD ratio for the prediction of high-risk EVs was 830.8. The sensitivity of the test was 76.9%, the specificity was 74.2%, and the negative predictive value was 77.8% (AUC 0.78), which is in line with our results.

Our study had some limitations. The main limitations are the retrospective nature of the data, the recruitment of patients from a single center, and the relatively small number of patients included in the final analysis.

Conclusion

In summary, this study showed that splenomegaly and thrombocytopenia are predictive factors for the presence of EVs. Leucopenia and the size of the right lobe of the liver are independent predictors of the presence of high-risk EVs. There was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the PC/SD ratio. Our results indicate that the PC/SD ratio < 907 in patients with LC could be used as a noninvasive predictor of the presence of moderate to large EVs in patients with LC and should be considered a useful, simple method in identifying patients with LC at high risk of VB. A combination of all these predictors can help develop more effective and useful noninvasive methods for assessing the presence of high-risk EVs, which would improve surveillance of these patients and decrease the need for endoscopy.

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