

Manifestations of severe portal hypertension: Validation of a non-invasive score in cirrhotic patients

Manifestações de hipertensão portal grave: Validação de score não invasivo

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Abstract | BACKGROUND AND AIMS: Current guidelines recommend that cirrhotic patients should undergo upper gastrointestinal endoscopy for screening of esophageal varices. Several studies evaluated the ability of non-invasive markers to predict the presence of esophageal varices. We aimed to test the validity of platelet count-to-spleen diameter ratio (PC/SD) to predict the presence of esophageal varices as well as endoscopic signs of severe portal hypertension (large varices, red signs on esophageal varices and severe portal hypertensive gastropathy) using the 909 cut-off value. PATIENTS AND METHODS: Retrospective study of 170 cirrhotic patients, who underwent screening for esophageal varices. Liver cirrhosis etiology, laboratory, ultrasonography and endoscopy data were analyzed. Stats: Mann-Whitney test, χ^2 , ROC curves. RESULTS: 170 patients (55 female) were included. One hundred and three (60,6%) had esophageal varices (34,1% large; 11,8% with red signs). Ninety-seven patients (57,1%) had portal hypertensive gastropathy (PHG): with severe PHG in 38 (22,3%). PC/SD <909 was documented in 93 patients. It was significantly associated with the presence of esophageal varices ($P < 0,001$; AUROC = 0,84) and high-risk esophageal varices (large varices or red signs - $P < 0,001$; AUROC = 0,8). The score was also significantly associated with the presence of severe portal hypertensive gastropathy ($P < 0,001$; AUROC = 0,63). CONCLUSIONS: PC/SD is significantly associated with the presence of esophageal varices and portal hypertensive gastropathy. A PC/SD ≥ 909 is a good predictor of the absence of high-risk varices or severe portal hypertensive gastropathy. *GE-J Port-Gastroenterol* 2012;19:21-25.

KEY-WORDS: Esophageal varices, portal hypertension, platelet count to spleen diameter ratio, liver cirrhosis.

RESUMO | INTRODUÇÃO E OBJECTIVOS: O rastreio de varizes esofágicas através de endoscopia digestiva alta está recomendado nos doentes com cirrose hepática. Vários estudos têm avaliado a aplicabilidade de marcadores não-invasivos na previsão de varizes do esófago. Neste trabalho, os autores pretenderam testar a validade da razão contagem de plaquetas/diâmetro bipolar do baço para prever a presença de varizes do esófago e manifestações de hipertensão portal grave (varizes esofágicas grandes ou com sinais vermelhos e gastropatia de hipertensão portal grave), utilizando o valor de *cut-off* 909. PACIENTES E MÉTODOS: Estudo retrospectivo de 170 pacientes com cirrose hepática, que realizaram endoscopia digestiva alta para rastreio de varizes do esófago. Foram registados dados clínicos, laboratoriais, imagiológicos e endoscópicos. ANÁLISE ESTATÍSTICA: teste de *Mann-Whitney*, χ^2 , curvas ROC. RESULTADOS: Foram incluídos 170 pacientes (55 mulheres). Cento e três (60,6%) apresentaram varizes de esófago (34,1% varizes esofágicas grandes, 11,8% com sinais vermelhos). Noventa e sete pacientes (57,1%) apresentavam gastropatia de hipertensão portal: grave em 38 (22,3%). A razão contagem de plaquetas/diâmetro bipolar do baço foi <909 em 93 pacientes e associou-se significativamente com a presença de varizes de esófago ($P < 0,001$; AUROC = 0,84), presença de varizes esofágicas de alto risco de rotura (varizes grandes ou com manchas vermelhas - $P < 0,001$; valor preditivo negativo = 87%), bem como com a presença de gastropatia de hipertensão portal grave ($P < 0,001$; valor preditivo negativo = 87%). Conclusões: A razão contagem de plaquetas/diâmetro bipolar do baço associou-se significativamente com a presença de varizes esofágicas e gastropatia de hipertensão portal. A razão contagem de plaquetas/diâmetro bipolar do baço ≥ 909 foi capaz de prever com boa probabilidade a ausência de varizes

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Recebido para publicação: 28/03/2011 e Aceite para publicação: 07/07/2011

esofágicas de alto risco e gastropatia de hipertensão portal grave. *GE-J Port-Gastroenterol* 2012;19:21-25.

PALAVRAS-CHAVE: Varizes esofágicas, hipertensão portal, razão plaquetas/baço, cirrose hepática.

INTRODUCTION

Portal hypertension is associated with the development of gastroesophageal varices. Variceal bleeding is associated with a 6-week mortality of 10 to 20%. Since 1986 several consensus meetings have been held on this subject¹⁻³.

The American Association for the Study of Liver Disease (AASLD) practice guidelines on prevention and management of gastroesophageal varices recommend screening upper gastrointestinal endoscopy for the diagnosis of esophageal and gastric varices when the diagnosis of cirrhosis is made (recommendation grade C)³. Recently, the Baveno V Consensus on portal hypertension recommended that all cirrhotic patients should be screened for varices at diagnosis (level of evidence 5; recommendation grade D)².

Since only 15 to 25% of cirrhotic patients undergoing screening upper endoscopy have medium/large varices, there is currently much interest in developing non-invasive methods of predicting the presence of high-risk varices^{2,3}.

Several studies have demonstrated that platelet count, splenomegaly, PC/SD may be useful non-invasive predictors of the presence of esophageal varices in patients with cirrhosis⁴⁻¹⁷. A cut-off of 909 for platelet count to spleen diameter was proposed by *Giannini et al.* on the basis of a 100% negative predictive value for the presence of esophageal varices⁴. Validation studies have shown varying accuracy^{5-7,12}. Alternative cut-off values for PC/SD ranging from 830.8 to 1014 were proposed for predicting the presence of esophageal varices^{11,13}.

As it is important to identify patients at higher risk of bleeding (presence of large varices and red signs) some studies aimed to identify accurate non-invasive markers. *Barrera et al.* proposed a PC/SD cut-off value under 830.8 for prediction of the presence of high risk varices¹¹.

Increased portal pressure appears to be the most important factor in the development of portal hypertensive gastropathy^{17,18}. Bleeding from severe portal hypertensive gastropathy led to overt hemorrhage in 60% of patients¹⁹, with a cumulative risk of 75% over a 5 year follow-up period²⁰. *Ehab et al.* did not find significant association between platelet count to spleen diameter ratio and the presence of portal hypertensive gastropathy¹⁷.

The authors aimed to study the validity of PC/SD to predict the presence of esophageal varices and portal hypertensive gastropathy; to define a cut-off for prediction of the presence of endoscopic signs of severe portal hypertension (presence of large varices, red signs or severe portal hypertensive gastropathy).

PATIENTS AND METHODS

The authors retrospectively evaluated 170 cirrhotic patients referred to endoscopy for screening of esophageal varices, between January 2007 and December 2009. Clinical files from all patients were reviewed. Patients on beta-blockers

or nitrates, previous episodes of variceal bleeding, previous sclerosis or band ligation, transjugular intrahepatic portosystemic shunt or surgery for portal hypertension were excluded. The diagnosis of cirrhosis was confirmed by reviewing clinical, laboratory, radiological or liver histology data. Clinical data included age, gender, etiology of cirrhosis and medication use (beta-blocker or nitrates), presence of ascites, hepatic encephalopathy at the time of endoscopy. The authors collected laboratory data (within 3 months of upper endoscopy): bilirubin, albumin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), prothrombin time (%) and platelet count. All individuals were classified according to Child-Pugh score²⁰. Radiological data included abdominal ultrasonography with measurement of the maximum bipolar diameter in mm, performed in the previous 3 months. Endoscopic finding were classified according to the same criteria:

- Esophageal varices: Absence of varices (F0); small straight varices (F1), enlarged tortuous varices occupying less than one third of the oesophageal lumen (F2), and largest sized coil-shaped varices, occupying more than one third of the oesophageal lumen (F3)²¹.

- Red colour signs: cherry red spot, red weal marking and haematocystic spot²¹.

- Gastroesophageal varices: GOV type 1 - Esophageal varices extending along the lesser curvature of the stomach and GOV type 2 - varices extending from the esophagus toward the gastric fundus²².

- Isolated gastric varices: IGV type 1 - localized in the gastric fundus and IGV type 2 - occurring elsewhere in the stomach²².

- Portal hypertensive gastropathy: mild (Grade 1) - Mosaic like pattern and severe (Grade 2) - mosaic like pattern with superimposed red signs²⁰.

Statistical analysis

Mann-Whitney test was used for comparison of quantitative variables. Qualitative variables were compared using the χ^2 test. Receiver operating characteristic curves (ROC curves) were applied. P value <0.05 was considered statistically significant. Data were analyzed using the SPSS package for Windows (SPSS Inc., Chicago, Illinois, USA).

RESULTS

One hundred and seventy patients were studied. The median age was 58 years, ranging from 22 to 90 years. Gender distribution was: 115 male (67,6%) and 55 female (32,4%) - table 1.

Ninety-seven patients (57%) were Child-Pugh class A, 56 (33%) were class B and 17 (10%) were class C - table 1. The etiology of liver cirrhosis was alcohol in 102 patients (60%), chronic hepatitis C virus infection in 35 patients (20.5%), chronic hepatitis B infection in 10 patients (5.9%) and co-infection with hepatitis C and B virus in 2 individuals. Other etiologies were less prevalent: primary biliary cirrhosis (n=8; 4.7%), non-alcoholic steatohepatitis (n=6; 3.5%), autoimmune hepatitis (n=4; 2.4%) and cardiac cirrhosis in 1 patient. Combined etiology (alcohol and chronic hepatitis C virus) was seen in 2 patients.

Table 1 Clinical, laboratory and ultrasonographic characteristics of the studied population.

	N [%]
Gender (male)	115 (67%)
Age (years)	58
Child-Pugh score	A - 97 (57%) B - 56 (33%) C - 17 (10%)
Etiology	Alcohol - 102 (60%) HCV - 35 (20.5%) HBV - 10 (6%) Other - 23 (13.5%)
Esophageal varices - High-risk (large, red signs)	103 (60.6%) 58 (34%)
PHG - severe PHG	97 (57.1%) 38 (22.4%)
Bilirubin (mg/dL)	1.0
Prothrombin ratio (%)	71.7
Albumin (g/dL)	3.8
Platelet count (X10 ⁶ /mm ³)	117
Spleen diameter (mm)	136
Platelet count/spleen diameter	902

One hundred and three patients (60.6%) had esophageal varices. The classification of varices was F1 in 45 (26.5%), F2 in 44 (25.9%) and F3 in 14 (8.2%). Esophagogastric varices were observed in 11 patients: GOV 1 (n=3; 1.8%) and GOV 2 (n=4; 2.4%). Isolated gastric varices were seen in 4 patients, 2 classified as IGV 1 and 2 as IGV 2. Red signs on esophageal varices were reported in 20 patients (11.8%).

Portal hypertensive gastropathy was apparent in 97 patients (57.1%) and severe PHG in 38 (22.4%).

Association between esophageal varices and clinical, laboratory and ultrasonographic data

There was no significant difference in gender and age distribution between patients with and without esophageal varices. Child-Pugh score, total bilirubin and spleen diameter were significantly higher in individuals with esophageal varices. Prothrombin time, albumin and platelet count were significantly lower in patients with EV (table 2).

PC/SD was <909 in 93 patients and was significantly associated with the presence of esophageal varices (P<0.001). As shown in figure 1-A, the area under ROC curve was 0.84 with a 95% confidence interval (CI) of 0.78-0.89.

The authors used the PC/SD ratio 909 cut-off point to calculate sensitivity and specificity of 75% and 77%, respectively. The positive and negative predictive value were 83% and 66%.

PC/SD was found to be significantly associated with the presence of high-risk esophageal varices [presence of varices

Table 2 Comparison of clinical, laboratory and ultrasonographic data according to the presence or absence of esophageal varices (EV).

	EV present (median)	EV absent (median)	P
Gender (male %)	69.9%	64.2%	0.12
Age (years)	55	60	0.1
Child-Pugh score	7	5	0.00
Bilirubin (mg/dL)	1.3	0.7	0.00
Prothrombin time (%)	64	83.5	0.00
Albumin (g/dL)	3.6	4.3	0.00
Platelet count (X10 ⁶ /mm ³)	97	150	0.00
Spleen diameter (mm)	150	115	0.00
Platelet count/spleen diameter	633.8	1315.2	0.00

grades F2-F3 or red signs) (P<0.001). As can be seen in figure 1B, the area under ROC was 0.80 (95% confidence interval 0.72-0.87)

The authors tested the PC/SD 909 cut-off point to calculate sensitivity and specificity of 83% and 60%, respectively. The positive and negative predictive value were 52% and 87%.

Association between portal hypertensive gastropathy and clinical, laboratory and ultrasonographic data

There was no significant gender or age difference between individuals with and without portal hypertensive gastropathy. Child-Pugh score, total bilirubin and spleen diameter were significantly higher in individuals with esophageal varices. Prothrombin ratio, albumin and platelet count significantly lower in patients with portal hypertensive gastropathy (table 4). Platelets to spleen diameter ratio was found to be significantly associated with the presence of portal hypertensive gastropathy (P<0.001). Area under ROC was 0.7 (95% confidence interval: 0.62-0.78 (figure 1C).

The authors tested the PC/SD 909 cut-off point to calculate sensitivity and specificity of 65% and 60%, respectively. The positive and negative predictive value were 68% and 57%. The group of patients with severe portal hypertensive gastropathy had a significant association with platelet count to spleen diameter ratio >909 (P<0.001). Area under ROC was 0.63 (95% CI: 0.53-0.73). The authors tested the PC/SD 909 cut-off point to calculate sensitivity and specificity of 73% and 50%, respectively. The positive and negative predictive value were 30% and 87%.

DISCUSSION

There is a wide consensus that at diagnosis, all cirrhotic patients should be screened for varices^{2,3}. Presently, upper gastrointestinal endoscopy is the most accurate screening method for esophageal varices.

Table 3 Comparison of clinical, laboratory and ultrasonographic data according to the presence or absence of portal hypertensive gastropathy (PHG).

	PHG present (median)	EV absent (median)	P
Gender (male %)	71%	63%	0.12
Age (years)	57	59	0.2
Child-Pugh score	7	5	0.02
Bilirrubin (mg/dL)	1.3	0.8	0.01
Prothrombin ratio (%)	64	82	0.01
Albumin (g/dL)	3.7	4.3	0.03
Platelet count (X10 ⁶ /mm ³)	100	136	0.00
Spleen diameter (mm)	150	120	0.01
Platelet count spleen diameter	693.3	1121.4	0.00

These recommendations carry an increasing burden for endoscopy. In this context, non-invasive methods for predicting the presence of esophageal varices have been developed and validated by several studies. It has been shown that platelet count to spleen diameter ratio may be the most useful non-invasive predictor of the presence of esophageal varices in patients with cirrhosis⁴⁻¹⁷.

Our results are concordant with published studies, which have shown a significant association between Child-Pugh score, total bilirrubin, prothrombin ratio, albumin, platelet count, spleen diameter, platelet count to spleen diameter ratio and the presence of esophageal varices.

A cut-off of 909 for platelet count to spleen diameter was proposed by *Giannini et al.* with a reported sensitivity of 100%, specificity of 93%, positive predictive value of 96% and negative predictive value of 100%⁴. A multicentric validation study by *Giannini et al.* reported 91.5% sensitivity, 67.0% specificity, 76.6% positive predictive value, 87.0% negative predictive value⁶. However, the accuracy of the platelet count

to spleen diameter ratio has varied with positive predictive values between 74 to 96.9% and negative predictive values between 73 to 100%^{5-7,12}. The prevalence of esophageal varices in these studies varied between 49.5 to 61%.

In the present study, the authors found similar results to the latter showing a good accuracy (area under ROC – 0.84). However, the negative predictive value was only 66%.

While it is important to identify, patients with liver cirrhosis, it is even more important to identify those patients at higher risk of hemorrhage – those with large varices or red signs on varices. *Barrera et al.* proposed a ratio cut-off value below 830.8 for prediction of presence of high risk varices (76.9% sensitivity, 74.2% specificity and 77.8% negative predictive value)¹¹.

The authors tested the ability of platelet count to spleen diameter ratio cut-off value of <909 to predict the presence of high risk varices. The cut-off value showed a good accuracy (area under ROC of 0.8) with sensitivity of 83% and negative predictive value of 87%.

Severe portal hypertensive gastropathy may be an important cause of bleeding^{19,20}. *Ehab et al.* did not found a significant association between platelet count to spleen diameter ratio and the presence of portal hypertensive gastropathy¹⁷. In the present study, the authors found a significant association between PC/SD and portal hypertensive gastropathy. However, the performance of the score in predicting PHG was suboptimal with the area under ROC of 0.7. Platelet count-to-spleen diameter cut off value of <909 had a negative predictive value of 87% in predicting absence of severe portal hypertensive gastropathy.

Upper gastrointestinal endoscopy is the gold-standard for detecting esophageal varices. Despite the encouraging results published *Giannini et al.*⁴, several studies have been conducted on this subject and none have reproduced the same results. In our study we found similar results to the latter studies^{5-7,12}. It is our believe that PC/SD is a good adjunct following particularly those patients refusing or poorly complying with upper endoscopy screening programs.

The study has some limitations. It was a retrospective study, the measurement of spleen diameter was performed by the different operators. Sixty percent of patients had alcohol related cirrhosis which can lead to thrombocytopenia by a mechanism independent from portal hypertension.

In conclusion, the authors found that platelet count to spleen diameter ratio may be a practical tool in clinical practice

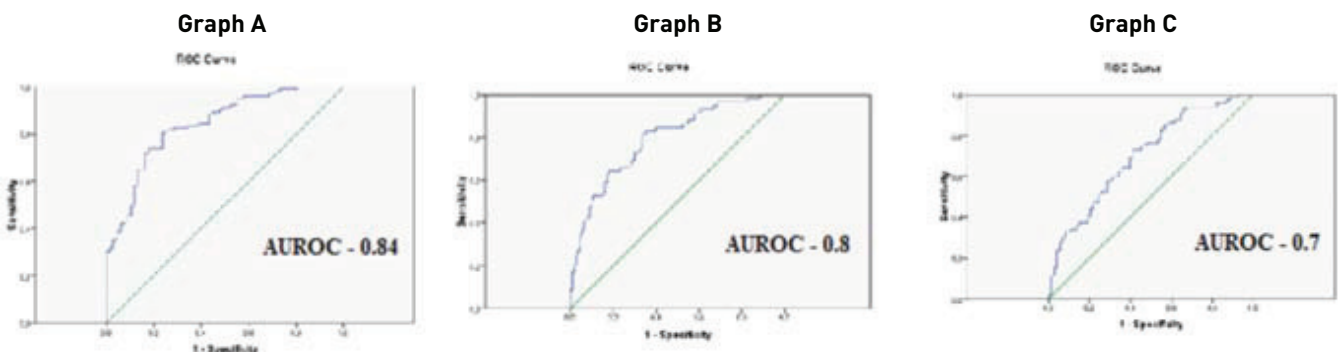


Figure 1 Accuracy of platelet count-to-spleen diameter ratio in predicting presence of high-risk esophageal varices (graph A), high-risk esophageal varices (graph B) and portal hypertensive gastropathy (graph C)

to stratify patients with low probability of having high risk varices or severe portal hypertensive gastropathy. However, the findings of the study show that the score cannot support the replacement of upper gastrointestinal endoscopy for screening of esophageal varices.

CONFLICTS OF INTEREST: The authors have not declared any conflicts of interest.

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