

Esophageal varices predictive score in liver cirrhosis

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Background

Endoscopic surveillance of esophageal varices (EV) in patients with cirrhosis is expensive and uncomfortable for many patients. Therefore, there is a particular need for noninvasive predictors for EV.

Objective The aim of the present study was to evaluate the accuracy of ultrasound and blood indices as noninvasive EV predictors among patients with cirrhosis.

Patients and methods

A total of 500 patients with cirrhosis were enrolled in this study and were divided according to their endoscopic findings into nonvariceal group (90 patients) and variceal group (410 patients). All patients underwent serum albumin, prothrombin time, aspartate aminotransferase, alanine aminotransferase, serum bilirubin, platelet count, hemoglobin level, abdominal ultrasonography (portal vein diameter and splenic size), and Child–Pugh score assessments.

Results

By evaluation of studied parameters, as predictors for EV, the splenic size was significant at cut-off greater than 13 cm. Platelet count was significant at a cut-off less than 12 3000/ml. Portal vein diameter was significant at a cut-off greater than 12 mm. Serum albumin was significant at a cut-off less than 3.2 g/dl. Prothrombin time was significant at a cut-off greater than 13.29 s. Child–Pugh score was significant with advanced scores. By multivariate regression analysis of the significant parameters, we reported that splenic size was the most significant parameter followed by platelet count followed by Child–Pugh score. EV prediction score can predict EV with sensitivity of 79.3, specificity of 83.3, and accuracy of 87.6%.

Conclusion

EV prediction score is a noninvasive parameter that can predict the presence of EV in patients with cirrhosis. Hence, its application may decrease the burden of endoscopy and provide a tool for selecting patients for whom endoscopy may be more beneficial.

Keywords:

cirrhosis, esophageal varices, predictive score

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Introduction

Bleeding from esophageal varices (EV) is the most clinically relevant complication of cirrhosis and still carries a mortality of up to 30% within 6 weeks of the bleeding episode, ranging from 0% for patients with Child–Pugh class A to ~30% for patients with Child–Pugh class C. The risk of bleeding is related to the size of varices, presence of red signs, and decompensated cirrhosis [1]. The American Association for the Study of Liver Diseases and the Baveno IV Consensus Conference on portal hypertension recommended that all patients with cirrhosis should undergo endoscopy to assess presence and size of varices at the time of liver cirrhosis diagnosis. This procedure should be repeated at 2–3 years in compensated cirrhosis and annually in decompensated cirrhosis if no varices are present at index endoscopy [2].

Portal hypertension and a large size of varices are risk factors for bleeding EVs. Red color signs are elevated red

areas which are important for predicting variceal risk, and red wale markings, dilated venules oriented longitudinally on the mucosal surface, have been considered to be the signs of highest risk. Vomiting, severe coughing, constipation, and excessive alcohol consumption may precipitate rupture of EVs [3]. However, a generalized screening program of periodical upper endoscopy in patients with cirrhosis may lead to high cost and low compliance, as the procedure is invasive and may be poorly accepted by many patients if repeatedly required [4]. Furthermore, preparation of patients with cirrhosis for upper endoscopy may be dangerous, and probable complications of diagnostic upper endoscopy may occur such as bacterial infections owing to disruption of the normal barriers [5].

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Ultrasonography is a simple, noninvasive, economical, and effective method of screening for portal hypertension. It can also show portal hemodynamics, splenic vein thrombosis, and portal vein thrombosis [6]. For these reasons, the selection of patients who may be at risk of having EV, especially those at risk for rupture, would be highly beneficial and cost effective [3]. The need for noninvasive diagnosis of EV and assessing the effect of therapy will benefit in high-risk situations [7]. Hence, the current study aimed to evaluate the accuracy of conventional sonographic indices and simple laboratory tests as noninvasive predictors of EV in Egyptian patients with cirrhosis.

Aim

This study aimed to find simple, noninvasive, and cheap methods for prediction of EV to decrease the burden of endoscopy and to provide a tool for selecting patients for whom endoscopy may be more beneficial.

Patients and methods

This study was conducted on 500 patients with cirrhosis (whatever the etiology) selected from endoscopy units of Menoufia University Hospital and National Liver Institute, Menoufia University, Egypt, in the period from January 2015 to March 2017.

Patients were classified according to their endoscopic findings into nonvariceal group I (90 patients) and variceal group II (410 patients).

Exclusion criteria

Patients with past history of variceal bleeding, patients who underwent previous endoscopic treatment for EV such as band ligation or sclerotherapy, patients who underwent surgical intervention for portal hypertension, patients with chronic liver diseases other than cirrhosis, patients on β -blockers, patients with hepatocellular carcinoma, patients with portal or splenic vein thrombosis, and patients with active infection were excluded from the study.

All patients in the study were subjected to the following: detailed history taking and full clinical examination; laboratory investigations including complete blood count, liver profile, stool analysis, hepatitis C virus antibodies, hepatitis B virus surface antigen, and antibilharzial antibodies by indirect hemagglutination test; Child–Pugh score classification; abdominal ultrasound to evaluate liver and spleen size, presence of cirrhosis, periportal fibrosis, ascites, or focal lesions focusing on splenic size and portal vein diameter (PVD); and upper endoscopy.

All patients gave their informed written consents, and the study was approved by the Ethical and Research Committee, Faculty of Medicine, Menoufia University, Egypt.

Statistical analysis

The data collected were tabulated and analyzed by SPSS statistical package version 11 on IBM compatible computer (IBM Corporation, North Castle Drive, Armonk, New York, USA). Descriptive statistics was presented mean \pm SD and number and percentage and analyzed by applying χ^2 -test. Student's *t*-test was used for comparing two groups of normally distributed variables; Mann–Whitney *U*-test, correlation coefficient test (*r*-test), and regression analysis were also performed whenever appropriate. Results were considered of significance at *P* value less than 0.05 and highly significant at *P* value less than 0.001 (Figs. 1 and 2).

Results

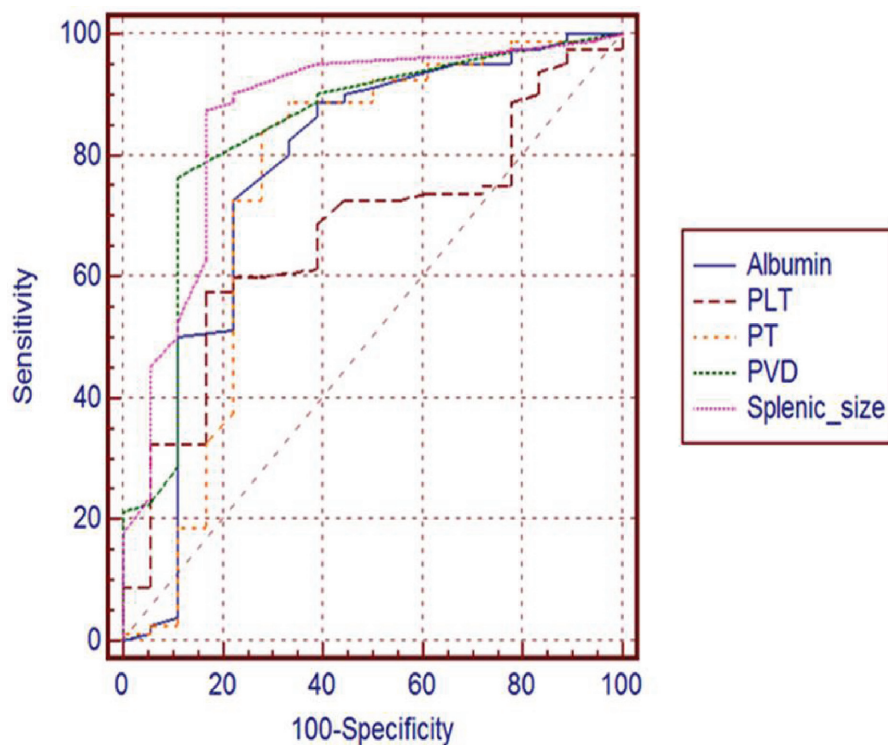
By evaluation of the studied parameters, as predictors for EV, we reported that the significant parameters were as follows (Tables 1–5):

- (1) Splenic size at cut-off greater than 13 cm was significant in prediction of EV with sensitivity of 87.7%, specificity of 83.3%, positive predictive value (PPV) of 95.9%, and negative predictive value (NPV) of 60% (Table 3).
- (2) Platelet count at a cut-off less than 12 3000/ml was significant in prediction of EV with sensitivity of 57.3% specificity of 83.3%, PPV of 94%, and NPV of 30% (Table 3).
- (3) PVD at a cut-off greater than 12 mm was significant in prediction of EV with sensitivity of 76.50%, specificity of 88.9%, PPV of 96.9%, and NPV of 45.7% (Table 3).
- (4) Serum albumin level at a cut-off less than 3.2 g/dl is significant in prediction of EV with sensitivity of 73.20%, specificity of 77.80%, PPV of 93.80% and NPV of 38.9% (Table 3).
- (5) Prothrombin time (PT) at a cut-off greater than 13.29 s was significant in prediction of EV with sensitivity of 84.1%, specificity of 72.2%, PPV of 93.2% and NPV of 50% (Table 3).
- (6) Child–Pugh score was significant in prediction of EV with advanced score (Table 3).

Then by multivariate regression analysis of the significant parameters, we reported that the following:

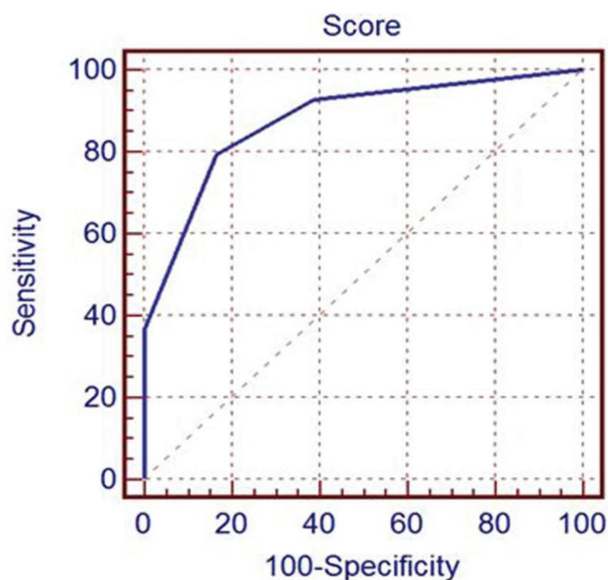
- (1) Splenic size is the most significant parameter in prediction of EV (*P*=0.022) (Table 2).

Figure 1



The receiver operating characteristic curves of serum albumin, platelet count, prothrombin time, portal vein diameter, and splenic size.

Figure 2



Receiver operating characteristic curve of esophageal varices prediction score.

Patients who had splenomegaly were at 1.56 times at higher risk for the presence of EV (Table 2).

- (2) Splenomegaly was followed secondly by thrombocytopenia in prediction of EV ($P=0.031$) (Table 2).

Patients who had thrombocytopenia were at 1.45 times at higher risk for the presence of EV (Table 2).

- (3) Child–Pugh score came third in the prediction of EV ($P=0.042$) (Table 2).

Patients with advanced Child–Pugh score were at 1.364 times at higher risk for the presence of EV (Table 2).

Discussion

In this study, we evaluated the accuracy of conventional ultrasound indices (PVD and splenic size) and simple laboratory tests (complete blood count, PT, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and serum albumin) as noninvasive predictors of EV in Egyptian patients with cirrhosis.

Results of our study showed that there was statistically significant difference between the two studied groups regarding PVD in prediction of EV at a cut-off value greater than 12 mm with sensitivity of 76.5 and specificity of 88.90. These results were in agreement with the studies by Nashaat *et al.* [8], Muhammad *et al.* [9], and Bintintan *et al.* [10] in which PVD with a cut-off of 13.5 mm, greater than 13 mm, and greater than 13 mm, respectively, could predict EV. In agreement with these results, Hong *et al.* [11] and Sarangapani *et al.* [12] reported that PVD greater than 11.75 mm and greater than 13.9 mm, respectively, could predict EV. In addition, Berzigotti *et al.* [7] stated that PVD greater than 13 mm and inversion of flow within the

Table 1 Comparison between nonvariceal and variceal groups regarding numerical parameters

	Nonvariceal group (n=90) (mean±SD)	Variceal group (n=410) (mean±SD)	P value
Red blood cells (cells/cm ³ ×10 ⁶)	3.547±0.549	3.553±0.509	0.967
AST (IU/l)	61.778±31.907	112.488±228.397	0.351
ALT (IU/l)	91.389±104.542	64.390±91.593	0.272
Total bilirubin (mg/dl)	0.758±0.441	3.352±6.386	0.089
Direct bilirubin (mg/dl)	0.326±0.380	2.048±4.719	0.126
White blood cells (cells/cm ³ ×10 ³)	7.161±2.965	9.064±5.647	0.169
Hemoglobin (g/dl)	11.928±1.972	10.529±1.554	0.235
PT	13.838±2.838	15.087±1.950	0.027*
Platelet count (cells/cm ³ ×10 ³)	162.111±54.512	96.098±43.304	0.000**
Serum albumin (g/dl)	3.589±1.063	2.697±0.784	0.000**
PVD (mm)	11.450±1.518	13.981±2.458	0.000**
Splenic size (cm)	11.850±2.512	16.362±3.038	0.000**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; PVD, portal vein diameter; *Significant parameters; **Highly significant parameters.

Table 2 Significant parameters after multivariate regression analysis of significant parameters obtained by univariate analysis of laboratory data of the patients

Regression analysis	B	SE	Wald	P value	Odd	95% CI for odd	
						Lower	Upper
Platelet count	-0.011	0.009	2.656	0.031	1.45	0.75	0.92
Splenic size (cm)	0.448	0.195	5.253	0.022	1.565	1.067	2.295
Child-Pugh score	1.009	1.193	2.540	0.042	1.364	1.035	3.775

Table 3 Comparison between cut-off levels, sensitivity, specificity, positive and negative predictive values, and area under curve of different significant parameters

	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Prothrombin time (s)	>13.29	84.10	72.20	93.20	50	0.75
Platelet count	<123	57.30	83.30	94	30	0.66
Serum albumin (g/dl)	<3.2	73.20	77.80	93.80	38.90	0.77
Portal vein diameter (mm)	>12	76.50	88.90	96.90	45.70	0.84
Splenic size (cm)	>13	87.70	83.30	95.90	60	0.87

AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value.

Table 4 Cut-off, sensitivity, specificity, and accuracy of esophageal varices prediction score in prediction of esophageal varices

ROC curve					
Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
2	79.3%	83.3%	95.6%	46.9%	87.6%

NPV, negative predictive value; PPV, Positive predictive value; ROC, receiver operating characteristic curve.

portal system are 100% specific for clinically significant portal hypertension with strong association with variceal formation and growth.

In our study, we demonstrated that there was statistical significant difference between the two studied groups regarding serum albumin in prediction of EV at a cut-off less than 3.2 g/dl with sensitivity of 73.2, specificity of 77.8, and PPV of 93.8. These results are in agreement with the study by Muhammad *et al.* [9] who demonstrated that serum albumin of 2.8 g/dl or less had very high sensitivity and specificity in predicting

Table 5 Comparison between nonvariceal and variceal groups regarding esophageal varices prediction score

EVPS	Nonvariceal group [n (%)]	Variceal group [n (%)]	Total [n (%)]
1	70 (77.8)	15 (3.6)	85 (17)
2	15 (16.7)	55 (13.4)	70 (14)
3	5 (5.5)	160 (39)	165 (33)
4	0 (0.0)	150 (36.6)	150 (30)
5	0 (0.0)	30 (7.4)	30 (6)
Total	90 (100.00)	410 (100.00)	500 (100)
χ^2	33.816		
P value	<0.001**		

EVPS, esophageal varices prediction score; **Highly significant.

EV and with the study by Galal *et al.* [13] who demonstrated that serum albumin with cut-off of 3.2 g/dl was predictive for the presence of EV.

In our study, we demonstrated that there was a statistical significant difference between the two studied groups regarding low platelet count in prediction of EV at a cut-off less than 123 000,

with sensitivity of 57.3 and specificity of 83.3. Moreover, patients with thrombocytopenia had a higher risk (1.45 times) to develop EV according to multivariate regression analysis of significant parameters. Our results were in line with what has been reported in other studies by Said *et al.* [14], Giannini *et al.* [15], and Schepis *et al.* [16] who reported that platelet count of less than 100 000 can be used as a predictor of EV and of less than 90 000 is associated with increased risk of having EV by nearly 2.5-folds. Zaman *et al.* [17] and Gana *et al.* [18] reported that the most accurate noninvasive test used for choosing children for endoscopy to identify EV is the platelet count.

In this study, there was a statistical significant difference of Child–Pugh score in prediction of EV. Moreover, patients with advanced CTP score had a higher risk (1.36 times) to develop EV according to multivariate regression analysis of significant parameters. These results came in line with the results of Said *et al.* [14] and Tafarel *et al.* [19] who reported that with increasing size of EV demonstrated by upper endoscopy, the number of patients increased with the advancement in Child score.

Moreover, a highly significant positive correlation was also found between Child score and the presence of EV ($P=0.001$), similar to Kim *et al.* [20] who found that EV was correlated significantly with Child–Pugh classifications B and C ($P=0.001$).

In our study, there was a statistical significant difference between the two groups regarding splenomegaly in prediction of EV at a cut-off greater than 13 cm, with sensitivity of 87.7, specificity of 83.3 and PPV of 95.9. Moreover, patients with splenomegaly had a higher risk (1.56 times) to develop EV. This agrees with Esmat *et al.* [21] who reported a high statistically significant correlation between the presence of EV with the splenic diameter ($P<0.001$). Amarapurkar *et al.* [22] reported that splenomegaly alone was a significant predictor for the development of large EV.

In our study, we demonstrated that there was a statistical significant difference between the two groups regarding PT in prediction of EV at a cut-off more than 13.29 s, with sensitivity of 84.1% and specificity of 72.2% ($P<0.05$). It has been reported that serum fibrosis markers can detect EV with a high accuracy. Vanbiervliet *et al.* [23] through several studies showed that PT was associated with

EV on univariate analysis. Ng *et al.* [24], Madhotra *et al.* [25], Thomopoulos *et al.* [26], Zaman *et al.* [17], and Hong *et al.* [27] found that PT could be a predictor for EV in patients with cirrhosis.

In our study, we found that with multivariate regression analysis of significant parameters that splenic size was the most significant parameter in prediction of EV followed by platelet count and then Child–Pugh score.

Patients with splenomegaly had 1.56 times higher risk to develop EV, patients with thrombocytopenia had 1.45 times higher risk to develop EV, and patients with advanced CTP score had 1.36 times higher risk to develop EV.

We calculated a net score (EV prediction score) for highly prediction of EV by introduction of the most significant parameters obtained by multivariate regression analysis into statistical equation as follows.

Splenic size less than 13 cm score 0, splenic size greater than 13 cm score 1, platelet count greater than 123 000 score 0, platelet count less than 123 000 score 1, Child–Pugh A score 1, Child–Pugh B score 2, and Child–Pugh C score 3.

The maximum score is 5. By statistical analysis, we found that EV prediction score greater than 2 is predictive of EV with sensitivity of 79.3%, specificity of 83.3%, PPV of 95.6%, and accuracy of 87.6%.

Conclusion

EV prediction score is a noninvasive parameter that can predict the presence of EV in patients with cirrhosis. Hence, we may decrease the burden of endoscopy by providing a tool for selecting patients for whom endoscopy may be more beneficial.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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