Noninvasive parameters for assessment of esophageal varices

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Objective
This study aims to assess esophageal varices (EV) by noninvasive parameters in patients with liver cirrhosis.

Background
The current guidelines recommend the screening of all cirrhotic patients by endoscopy for EV, but repeated endoscopic examinations are unpleasant for patients and have a high cost impact and burden on endoscopic units. Therefore, there is a particular need for noninvasive predictors of EV.

Patients and methods
A total of 120 cirrhotic patients were enrolled in this study and were divided into three groups: 40 cirrhotic patients with EV and a history of upper gastrointestinal bleeding, 40 cirrhotic patients with EV without a history of upper gastrointestinal bleeding, and 40 cirrhotic patients without EV. All patients in the study were subjected to an assessment of history, clinical examination, routine laboratory investigation, abdominal ultrasound, and upper gastrointestinal endoscopy.

Results
Serum albumin at cut-off less than 3.65 g/dl, platelet count at cut-off less than 99 000/mm^3, platelet count/spleen diameter ratio (PC/SD) at cut-off less than 919.6, aspartate aminotransferase-to-platelet ratio index at cut-off greater than 1.14, spleen longitudinal diameter at cut-off more than 140.5 mm, portal vein diameter at cut-off more than 15.2 mm, and prothrombin time at cut-off more than 15.1 s are significant in the prediction of EV. North Italian Endoscopy Club Index at cut-off more than 25.4, platelet count at cut-off less than 74 000/mm^3, and PC/SD at cut-off 851.6 are significant in the prediction of variceal bleeding risk.

Conclusion
Serum albumin, platelet count, PC/SD ratio, aspartate aminotransferase-to-platelet ratio index, spleen longitudinal diameter, portal vein diameter, prothrombin time, and Child score can provide information that can help in the prediction of the presence of EVs in patients with liver cirrhosis. North Italian Endoscopy Club Index, platelet count, and PC/SD ratio can provide information that can help in the prediction of variceal bleeding risk in patients with liver cirrhosis.

Keywords:
liver cirrhosis, noninvasive parameters, varices

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Introduction

Cirrhosis is the end-stage of every chronic liver disease, resulting in the formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension [1].

Portal hypertension is the underlying pathophysiological process that leads to the formation of portosystemic collaterals and the onset of a severe complication such as variceal hemorrhage [2].

The development of esophageal varices (EV) is a common clinical complication in patients with cirrhosis; severe bleeding from EVs has been estimated to occur in ~30–40% of patients with cirrhosis and carries significant morbidity and mortality [3].

Esophagogastroduodenoscopy is considered the primary modality for the detection and surveillance of EV and to determine the risk of bleeding, guidelines for adult cirrhotic patients recommend universal EV screening by esophagogastroduodenoscopy at the time of the diagnosis of cirrhosis [4].

Several studies have looked for potential noninvasive markers of EV. Although several independent

predictors have been identified, no algorithm has been developed to select patients accurately for endoscoping testing [5].

Patients and methods

This study was carried out on 120 patients with liver cirrhosis who were recruited from the Gastrointestinal Endoscopy Unit, Faculty of Medicine Menoufia University Hospital, starting from March 2015 after obtaining informed consent. Adults age older than 15 years of age of both sexes who had an established diagnosis of liver cirrhosis of any etiology attending the gastrointestinal endoscopy unit for upper gastrointestinal endoscopy were included in the study. Patients who had undergone a previous intervention for portal hypertension such as portosystemic shunts, patients with hepatocellular carcinoma, patients with portal vein thrombosis, and patients with intra-abdominal, hepatic, or extrahepatic malignancy were excluded from this study. Patients were divided into three groups:

(1) Cirrhotic patients with EVs and a history of upper gastrointestinal bleeding (40 patients).
(2) Cirrhotic patients with EVs without a history of upper gastrointestinal bleeding (40 patients).
(3) Cirrhotic patients without EVs (40 patients).

All patients in the study were subjected to the following:

(1) Assessment of history and clinical examination for the symptoms and signs of chronic liver disease such as ascites, encephalopathy, jaundice, spider naevi, and etiology of liver cirrhosis.
(2) Laboratory investigations such as complete blood count, liver function, creatinine, urea, hepatitis C antibodies (HCV Ab), and hepatitis B surface antigen (HBs Ag).
(3) Abdominal ultrasound to assess parameters such as portal vein diameter (PVD), portal vein flow velocity, spleen diameter, right lobe diameter, and the presence of collaterals.
(4) Upper gastrointestinal endoscopy: assess the presence of EVs, grading of EVs, and the presence of risky signs.
(5) Calculation of the following: Child–Pugh score [6], model for end-stage liver disease score [7], aspartate aminotransferase-to-platelet ratio index (APRI) score, North Italian Endoscopy Club Index (NIEC) [8], platelet count/spleen diameter (PC/SD) ratio, right lobe liver/albumin ratio, right lobe liver/prothrombin ratio, and fibrosis 4 score [9].

Assessment of parameters for the prediction of the presence of varices in cirrhotic patients was performed by comparing cirrhotic patients with EVs including (group A, which included cirrhotic patients with a history of variceal bleeding, and group B, which included cirrhotic patients with EV, but with no history of variceal bleeding) and cirrhotic nonvariceal patients (group C). Assessment of parameters for the prediction of variceal bleeding risk was performed by comparing cirrhotic patients with a history of variceal bleeding (group A) and cirrhotic patient with EV, but with no history of variceal bleeding (group B).

Statistical analysis

Data were analyzed using statistical package for the social sciences (SPSS) version 15 (SPSS Inc., Chicago, IL, USA). Qualitative data were presented as number and percent. Comparison between groups was performed using the χ^2-test. Quantitative data were presented as mean±SD. Student *t*-test was used to compare between two groups. *F*-test (one-way analysis of variance) was used to compare between more than two groups.

P value less than 0.05 was considered to be statistically significant.

Receiver operator characteristic curve was used to determine the cut-off value for diagnosis. Then, the sensitivity and specificity of each cut-off variable were calculated.

Results

There was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in serum albumin, prothrombin time (PT), and platelet count (Table 1).

There was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the Child score, PC/SD, PVD, and spleen diameter (Table 2).

There was no statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the etiology of cirrhosis and sex.

Serum albumin at cut-off less than 3.65 g/dl is significant in the prediction of EV with a sensitivity of 70% and a specificity of 86.2%, platelet count at cut-off less than 99 000/mm^3 is significant in the prediction of EV with a sensitivity of 87.5% and a specificity of

Table 1 Comparison between cirrhotic patients with varices group A+B and cirrhotic patients without varices group C in laboratory findings

	Variceal group A+B (*N*=80)	Nonvariceal group C (*N*=40)	*t*	*P*
Serum albumin (g/dl)	3.29±0.39	3.84±0.42	7.026	<0.001*
Alanine transaminase (IU/l)	60.01±37.05	54.23±22.10	0.909	0.365
Aspartate transaminase (IU/l)	59.20±31.19	52.28±19.04	1.288	0.200
Total bilirubin (mg/dl)	1.58±0.55	1.45±0.38	1.461	0.147
Direct bilirubin (mg/dl)	0.87±0.42	0.80±0.30	1.031	0.305
Prothrombin time (s)	15.92±2.17	13.86±1.45	6.190	<0.001*
Hemoglobin (g/dl)	11.73±1.48	11.92±1.28	0.691	0.491
Total leukocytic count (10^3/mm^3)	4378.75±1400.61	4695.00±1086.97	1.251	0.213
Serum urea (mg/dl)	26.16±6.56	26.38±5.96	0.172	0.864
Serum creatinine (mg/dl)	0.99±0.17	0.95±0.06	1.789	0.076
α-Fetoprotein (IU/ml)	19.09±13.35	15.95±6.00	1.774	0.079
Alkaline phosphatase (U/l)	116.71±29.08	107.45±27.12	1.681	0.095
Platelet count (/mm^3)	94837.50±32171.39	124100.00±21982.28	5.850	<0.001*
APRI score	1.69±1.02	1.10±0.05	4.238	<0.001*
Child score	1.57±7.00	5.48±0.99	6.500	<0.001*
MELD score	10.76±2.77	9.88±1.90	1.824	0.071

APRI, aspartate aminotransferase-to-platelet ratio index; MELD, model for end-stage liver disease. *$P<0.05$, significant.

Table 2 Comparison between cirrhotic patients with varices group A+B and cirrhotic patients without varices group C in ultrasonographic findings

	Variceal group A+B (*N*=80)	Nonvariceal group C (*N*=40)	*t*	*P*
Portal vein diameter (mm)	15.94±2.19	15.94±2.19	6.453	<0.001*
Spleen diameter (mm)	157.16±26.54	157.16±26.54	157.16±26.54	<0.001*
Right liver lobe diameter/prothrombin time	8.41±1.38	8.85±1.38	1.660	0.100
Portal vein flow velocity (cm/s)	13.90±12.08	14.78±1.46	0.454	0.650
Platelet count/spleen diameter	628.57±240.84	956.48±218.63	7.245	<0.001*
Liver right lobe diameter (mm)	131.29±10.37	134.65±10.56	1.665	0.099

*$P<0.05$, significant.

55%, PC/SD ratio at cut-off less than 919.6 is significant in the prediction of EV with a sensitivity of 57.5% and a specificity of 95%, APRI at cut-off greater than 1.14 is significant in the prediction of EV with a sensitivity of 68.8% and a specificity of 65%, spleen longitudinal diameter (SLD) at cut-off more than 140.5 mm is significant in the prediction of EV with a sensitivity of 73.8% and a specificity of 70%, PVD at cut-off more than 15.2 mm is significant in the prediction of EV with a sensitivity of 62.5% and a specificity of 90%, and PT at cut-off more than 15.1 s is significant in the prediction of EV with a sensitivity of 63.8% and a specificity of 82.5% (Fig. 1).

There was a statistically significant difference between cirrhotic patients with a history of variceal bleeding (group A) and cirrhotic patients with EV with no history of variceal bleeding (group B) in the platelet count, PC/SD, and NIEC index and (Table 1).

The following parameters showed a statistically significant difference between the cirrhotic group with EVs with a history of variceal bleeding and the cirrhotic group with EVs without a history of variceal bleeding, and can be used as predictors for the risk of variceal bleeding (Table 3).

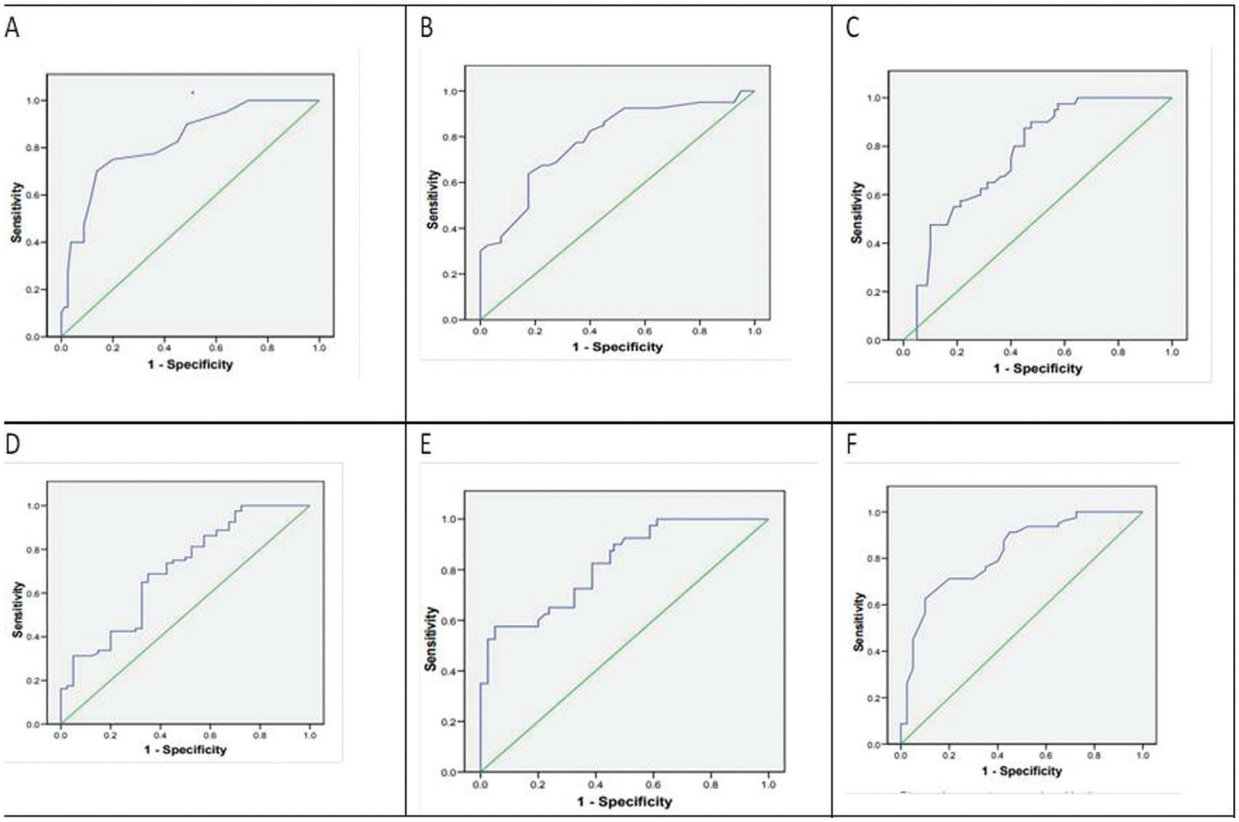
NIEC Index at cut-off more than 25.4 is significant in the prediction of variceal bleeding risk with a sensitivity of 90% and a specificity of 50%, platelet count at cut-off less than 74 000 mm^3 is significant in the prediction of variceal bleeding risk with a sensitivity of 82.5% and a specificity of 55%, and PC/SD ratio at cut-off 851.6 is significant in the prediction of variceal bleeding risk with a sensitivity of 45% and a specificity of 90% (Fig. 2).

Discussion

Liver cirrhosis follows a progressive course and eventually patients succumb to the complications of liver decompensation such as variceal bleeding from portal hypertension, ascites, hepatorenal syndrome, and hepatic encephalopathy [10].

EVs are generally the most common clinical manifestation of portal hypertension and ruptured EVs are a dreaded complication of portal hypertension [11].

Figure 1



Receiver operator characteristic curve of different significant parameters in the prediction of esophageal varices; (a) serum albumin, (b) prothrombin time, (c) platelet count. (d) Aspartate aminotransferase-to-platelet ratio index score, (e) platelet count/spleen diameter, (f) portal vein diameter.

Table 3 Comparison between cirrhotic patients with a history of variceal bleeding (group A) and cirrhotic patients with esophageal varices with no history of variceal bleeding (group B)

	Group A history of bleeding (*N*=40)	Group B no history of bleeding (*N*=40)	*t*	*P*
Platelet count (/mm^3)	84675.00±29298.10	105000.00±32036.04	2.961	0.004*
Platelet count/spleen diameter	552.58±234.18	704.56±225.42	2.957	0.004*
Northern Italian Endoscopic Club Index	36.03±8.41	28.90±8.63	3.745	<0.001*

*$P<0.05$, significant.

Because of this reason, The American Association for the Study of Liver Diseases and the Baveno IV Consensus Conference on portal hypertension recommended that all cirrhotic patients should undergo endoscopy to assess the presence, the size, and the grade of varices at the time of liver cirrhosis diagnosis. If no varices are present at index endoscopy, this procedure should be repeated at 2–3 years in compensated cirrhosis and annually in decompensated cirrhosis [12].

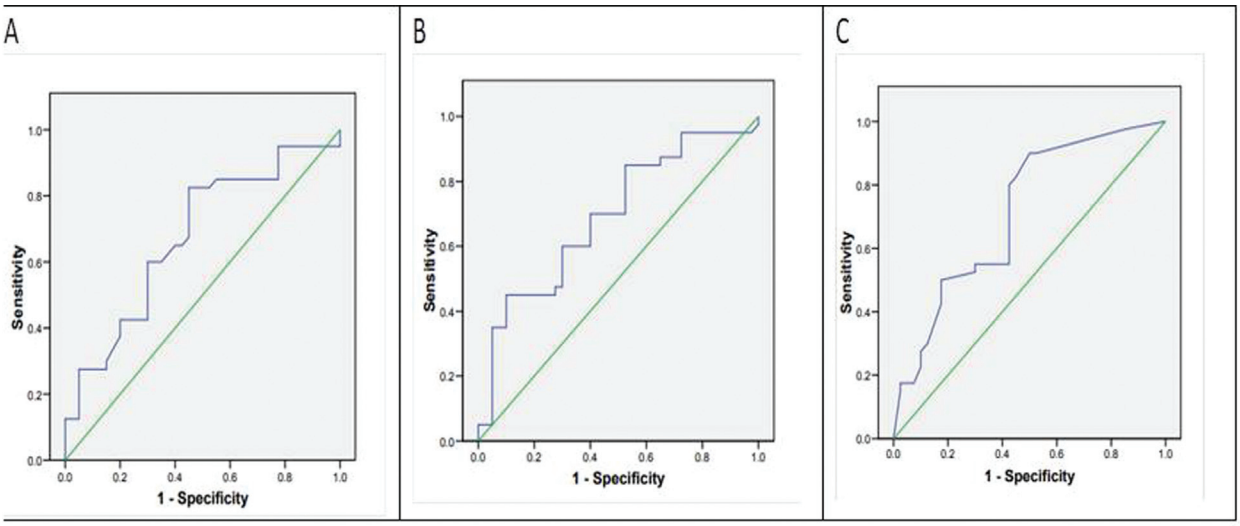
However, it was found that many patients screened either do not have varices or have nonrisky varices not requiring prophylactic therapy. Endoscopic screening in these patients is a burden to endoscopic units. In addition, patient compliance with the screening program may reduce over time [13].

Therefore, there is a need for the noninvasive diagnosis of EV and assessment of the effect of therapy. Ideally, a method for identifying patients with EV should be simple, noninvasive, inexpensive, accurate, and readily available, have high sensitivity and specificity, follow the natural history, reflect the effect of the treatment accurately, and indicate the prognosis and possibility of the success of a treatment [14].

The aim of this study was to assess EVs by noninvasive parameters in patients with liver cirrhosis using some clinical, laboratory, and ultrasonographic parameters.

The results of this study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in serum albumin in the prediction of EV at a

Figure 2



Receiver operator characteristic curve of different significant parameters in the prediction of variceal bleeding; (a) platelet count, (b) platelet count/spleen diameter, (c) North Italian Endoscopy Club Index.

cut-off less than 3.65 g/dl with a sensitivity of 70% and a specificity of 86.2%.

These results are in agreement with the study of Shehata *et al.* [15], who showed that serum albumin could predict the presence of EV at a cut-off of 3.8 or less with a sensitivity of 71% and a specificity of 57.1%, the study of Galal *et al.* [16], who reported that serum albumin could predict the presence of EV at a cut-off of 3.2 or less with a sensitivity of 70% and a specificity of 20%, and with the study by of Naggar *et al.* [17], who reported that serum albumin could predict the presence of EV at a cut-off of 3.3 or less with a sensitivity of 96.36% and a specificity of 46.67%.

This study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the platelet count; low platelet count could predict the presence of EV at a cut-off of 99 000/mm^3 or less with a sensitivity of 87.5% and a specificity of 55%.

These results are in agreement with the studies of Said *et al.* [18], who reported that platelet count could predict the presence of EV at a cut-off of 130 000 or less with a sensitivity of 80% and a specificity of 90%, Schepis *et al.* [19], who reported that platelet count of less than 100 000 could be used as a predictor of EV, and with the study of Madhotra *et al.* [20], who reported that the best cut-off value was 68 000 with a sensitivity of 71% and a specificity of 73%.

The results of this study showed that there was a statistically significant difference between the cirrhotic group with EVs with a history of variceal bleeding and the cirrhotic group with EVs without a history of variceal bleeding in platelet count; platelet count as a predictor for variceal bleeding showed a sensitivity of 82.5% and a specificity of 55% at a cut-off of 74 000/mm^3 in this study.

These results are in agreement with the studies of Umar *et al.* [21], Benedeto-Stojanov *et al.* [22], and Limquiaco *et al.* [23], who showed a statistically significant difference between the cirrhotic group with EVs with a history of variceal bleeding and the cirrhotic group with EVs without a history of variceal bleeding in the platelet count.

This study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the PC/SD.

PC/SD could be used in the prediction of EV at a cut-off less than 919.6 with a sensitivity of 57.5% and a specificity of 95%.

This study showed that there was a statistically significant difference between the cirrhotic group with EVs with a history of variceal bleeding and the cirrhotic group with EVs without a history of variceal bleeding for (PC/SD). PC/SD as a predictor for variceal bleeding showed a sensitivity of 45% and a specificity of 90% at cut-off 851.6 in this study.

These results are in agreement with the study of Agha *et al.* [24], who showed that the PC/SD ratio could

predict the presence of EV at a cut-off of 909 with a sensitivity of 100% and a specificity of 97.6%, Sheta *et al.* [25], who found a statistically significant relation to the presence and grade of EV ($P<0.001$) at a cut-off value of 570, with a sensitivity of 77.19% and a specificity of 93.02%, and the study of Giannini *et al.* [26], who used a cut-off value of PC/SD ratio of 909 to predict the presence of EVs with a sensitivity of 100% and a specificity of 93%.

El Hady *et al.* [27] reported that the cut-off value of the PC/SD ratio (750) is optimal for the accurate prediction of EV, with a sensitivity of 81% and a specificity of 81%, in agreement with this study.

This study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the APRI ratio.

This study shows that APRI a cut-off greater than 1.14 could predict the presence of EV with a sensitivity of 68.8% and a specificity of 65%.

These results are in agreement with the studies of de Mattos *et al.* [28], who reported that when APRI, at a cut-off of 1.3, was used to predict the existence of EV, it showed a sensitivity of 64.70% and a specificity of 72.70%, and Shehata *et al.* [15], who showed that APRI at a cut-off greater than 1.26 could predict the presence of EV with a sensitivity of 72.4% and a specificity of 61.9%. Galal *et al.* [16] suggested a cut-off greater than 0.16 for the detection of EV; this lower different cut-off is explained depending on that the included patients had no clinical cirrhosis which means that they were in a much earlier stage of the disease.

The present study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in SLD. SLD is significantly higher in patients with EV in comparison with patients without varices.

This study shows that SLD could be used in the prediction of EV at a cut-off 140.5 mm with a sensitivity of 73.8% and a specificity of 70%.

These findings are in agreement with the studies of Hassan *et al.* [29], who showed that SLD at least 131 mm had a sensitivity of 100% and a specificity of 65% for the prediction of the presence of EV, Thomopoulos *et al.* [30], who proved that SLD of 13.5 cm or more has a sensitivity of 95% and a specificity of 37% in the prediction of the presence of EV, and thus it can be considered a good predictor for the presence of varices, and Esmat *et al.* [31], who found a highly statistically significant correlation between the presence and grade of EVs with the splenic diameter.

El Naggar *et al.* [17] reported that spleen size is becoming increasingly important because both splenomegaly and EV may be related to high portal pressure; also, splenomegaly may increase platelet sequestration and lead to a low platelet count and thus spleen size could be used as a predictor for the presence of EV at cut-off 161 mm with a sensitivity of 69% and a specificity of 80%.

The present study showed that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in PVD in the prediction of EV at a cut-off value of 15.2 mm with a sensitivity of 62.5% and a specificity of 90%.

These results are in agreement with the studies of Nashaat *et al.* [32], who reported that the cut-off value that was used in the diagnosis of EV for PVD was 13.5 mm with a sensitivity of 80% and a specificity of 55%, Hong *et al.* [33], and Arulprakash *et al.* [34], who reported that PVD greater than 11.75 mm and greater than 13.9 mm, respectively, could predict EV.

Berzigotti *et al.* [14] reported that PVD greater than 13 mm and inversion of flow within the portal system are 100% specific for clinically significant portal hypertension with a strong association with variceal formation and growth.

In this study, there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in the Child–Pugh score in the prediction of EV. In the variceal group, 48.8% of patients had Child A score, 13.8% of patients had Child B score, and 37.5% of patients had Child C score, whereas in the nonvariceal group, 87.5% of patients had Child A score, 5% of patients had Child B score, and 7.5% of patients had Child C score.

These results are in agreement with the study of Yosry *et al.* [35], who reported that the presence of varices was significantly higher in Child B patients and Child C patients compared with Child A patients (39.8, 43.4, and 16.8%), respectively. The presence of large-sized varices, fundal varices, congestive gastropathy, and signs of impending rupture of varices were significantly higher in Child B and C patients compared with Child A patients. These results

indicated that the patients with Child B and C cirrhosis are at a higher risk of development of varices and higher risk of bleeding.Sheta *et al*. [25], Said *et al*. [18], and Tafarel *et al*. [36] showed that there was a significant correlation between EVs grade and Child classification and with advancing Child–Pugh class, the number of patients with varices increased.

This study shows that there was a statistically significant difference between the cirrhotic variceal group and the cirrhotic nonvariceal group in PT in the prediction of EV at a cut-off higher than 15.1 s with a sensitivity of 63.8% and a specificity of 82.5%.

Several studies have reported that PT is associated with EVs. Zaman *et al*. [37] and Hong *et al*. [38] found that PT could be a predictor for EVs in cirrhotic patients at a cut-off higher than 17.05 with a sensitivity of 68.8 and a specificity of 81.8%.

The results of this study show that was a statistically significant difference between the cirrhotic group with EVs with a history of variceal bleeding and the cirrhotic group with EVs without a history of variceal bleeding in the NIEC Index; the NIEC Index as a predictor for variceal bleeding showed a sensitivity of 90% and a specificity of 50% at a cut-off higher than 25.4 in this study.

These results are in agreement with the study of Merkel *et al*. [39], who reported that the NIEC Index as a predictor for variceal bleeding at a cut-off higher than 25 showed a sensitivity of 89% and a specificity of 44%.

Moodley *et al*. [40] reported that patients with NIEC Index 26 or higher have a higher rate of bleeding varices; the rate of Bleeding was 13.5% in the first year and 26.8% in the second year and the risk of bleeding increases with higher NIEC scores.

Conclusion

Serum albumin, platelet count, PC/SD ratio,APRI, SLD, PVD, PT, and Child score can provide information that can help in the prediction of the presence of EVs in patients with liver cirrhosis. The NIEC Index, platelet count, and the PC/SD ratio can provide information that can help in the prediction of the risk of variceal bleeding in patients with liver cirrhosis. The use of these noninvasive predictors may reduce the need for endoscopic screening in cirrhotic patients and do endoscopy for only those patients who have a high risk of developing varices.

Conflicts of interest

There are no conflicts of interest.

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