Non-endoscopic parameters for prediction of esophagogastric varices in chronic liver disease patients A novel prediction score for the presence of varices

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Abstract: Purpose: This study aimed at developing a predictive model for esophagogastric varices in patients with chronic liver disease using non-invasive parameters. **Methods:** This study was conducted on 120 patients with chronic liver disease admitted to Ain Shams University Hospitals or attending the outpatient clinics. They were subjected to complete clinical evaluation, laboratory investigations, abdominal ultrasonography, color doppler ultrasonographic study of portal hemodynamics and upper gastrointestinal endoscopy. **Results:** The Child staging, liver and spleen sizes (cm) were independent risk factors for the presence of varices. From this proposed model, a prediction scoring system was generated. A scoring point was given to each parameter in the model: Child A class took zero, Child B 1.5 points and Child C 2.5 points. The patient's liver and spleen sizes in cms by ultrasonography were multiplied by -0.297 and 0.607 respectively to get the scoring points for these parameters. Then the total score of the patient was the product of summation of all these points. This prediction score had a high sensitivity and specificity and a relatively high negative predictive value at cutoff points 6 and 7. Thus, above these cutoff values, the risk of the presence of varices is increased and patients should be screened by upper GIT endoscopy. **Conclusion:** From the generated predictive model using the Child staging, liver and spleen size (cm), we could predict the presence of varices in chronic liver disease patients.

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Introduction:

The prevalence of esophageal varices (EV) in patients with liver cirrhosis ranges from 35% to 70%, and the reported mortality from variceal bleeding ranges from 17% to 57% [1].

Patients with cirrhosis frequently undergo screening endoscopy for varices so that prophylactic therapy and/or follow up can be planned [2]. Routine endoscopic screening of all cirrhotic patients with or without varices has health service cost implications. Therefore, it might be cost-effective to identify those patients who would benefit most from routine screening [3].

In order to reduce the increasing burden that endoscopy units will have to bear, some studies have attempted to identify characteristics that non-invasively predict the presence of varices. These studies have shown that clinical, biochemical and Doppler ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the presence of varices [2, 4].

This study aimed at developing a predictive model for esophagogastric varices in patients with chronic liver disease using non-invasive parameters.

Materials and Methods:

- **Study Design and Sampling:** This cross-sectional study was conducted on 120 patients with chronic liver disease admitted to Ain Shams University Hospitals, Tropical Medicine and Internal Medicine Departments or attending the outpatient clinics. The sample size was calculated by Epi Info program (version 6.0) at 95% Confidence Limit, Power of the Test is 80% and Alpha Set at 0.05 (Type I error). The sample size was calculated by the following equation:

$$n = \frac{\{Z_{\alpha/2}\sqrt{2pq} + Z_{\beta}\sqrt{(p_1q_1 + p_2q_2)}\}^2}{d^2}$$

$Z_{\alpha/2}$ = Value of Z at α 0.05 (1.96)
Z_{β} = Value of Z at β (1- α) = 1.64
p = mean proportion of cases with the event in group 1 and 2.
q = 1– p

p_1 = proportion of patients with the event (esophageal varices) in unexposed group.

$q_1 = 1 - p_1$

p_2 = proportion of patients with the event (esophageal varices) in exposed group.

$q_2 = 1 - p_2$

d for the smallest difference between groups of clinical importance.

- **Inclusion Criteria:** Patients with stigmata of chronic liver disease based on clinical, laboratory and radiological data.
- **Exclusion Criteria:**

  a- Patients who refused to be enrolled in the study.

  b- Patients who had previously underwent sclerotherapy or band ligation of EV, transjugular intrahepatic portosystemic stent shunt, or surgery for portal hypertension (which alter portal haemodynamics).

  c- Patients taking drugs for primary prophylaxis of variceal bleeding.

  d- Patients with hepatocellular carcinoma.

  e- Patients with portal, splenic or hepatic vein thrombosis.

  f- Patients with severe cardiac, chest or renal disease.
- **Tools of the Study:**

  All patients were subjected to:

I- Complete Clinical Evaluation.

II- Laboratory Investigations: Complete blood picture (CBC), liver profile and hepatitis markers: hepatitis B surface antigen (HBs Ag) and hepatitis C virus antibody (HCV Ab) using third generation enzyme-linked immunosorbent assay (ELISA) test.

III- Abdominal Ultrasonography:

Using Toshiba "Just vision" real-time scanner instrument with a 3.5 MHz convex transducer (after an overnight fasting) with stress on: liver size, echogenicity, presence of periportal thickening, portal vein (PV) diameter & patency [5,6], splenic size [5,7], splenic vein (SV) diameter & patency [8], status of ascites and presence of portosystemic collaterals: e.g. left gastric vein, paraumbilical vein, porta hepatis collaterals, lienorenal collaterals or splenic hilar collaterals (which were confirmed by Doppler examination).

- ***Criteria suggestive of chronic liver disease and cirrhosis*** [7,9]***:***

Increased liver echogenicity: loss of homogenous texture to be replaced by speckled coarse texture, irregular liver margins, attenuation of intra-hepatic portal and hepatic veins and relative enlargement of caudate lobe and atrophy of right lobe (ratio of caudate /right lobe in cirrhosis > 0.65).

- ***Criteria suggestive of portal hypertension by ultrasonography:*** The presence of portal hypertension confirms the diagnosis of cirrhosis and vice versa. Findings suggestive of portal hypertension include: an increased diameter of the portal and splenic veins, the presence of portosystemic collaterals, splenomegaly and ascites [9]**.**

IV- Color Doppler Ultrasonographic Study of Portal Hemodynamics:

The examination was done in the morning after an overnight fasting using a color Doppler unit with a 3.5 MHz convex probe, with special stress on:

A) Main Portal vein:

The following parameters were assessed:

1- Confirmation of the portal vein patency.

2- Portal vein cross sectional area (PV CSA) (cm^2): It was obtained assuming the PV to be circular in cross section [10,11]**.**

3- Mean portal vein flow velocity (mean PVV) (cm/sec): Hemodynamic measurements were performed with breath-holding after shallow inspiration with an angle between the vessel and Doppler beam less than 60^o (angle of insonation or Doppler angle) [12,13,14,15,16]**.**

4- Direction of flow: If the flow was towards the transducer, it displayed red color (hepatopetal). But if the flow was away from the transducer, it displayed blue color (hepatofugal). In cases with both red and blue colors, the flow was bi-directional [7]**.**

B) Splenic vein:

The following parameters were assessed:

1- Confirmation of the splenic vein (SV) patency.

2- Splenic vein cross sectional area (SV CSA) (cm^2) and mean SV flow velocity (SVV) (cm/sec) [17]**.**

C) Hepatic artery resistance index (HARI):

It was measured in the intrahepatic main branches. The RI was calculated over one cardiac cycle from the formula: RI = (systolic velocity − end diastolic velocity)/systolic velocity [18]**.**

D) Splenic artery resistance index (SARI):

It was measured intraparenchymally, near to the hilum.

RI = (systolic velocity − end diastolic velocity)/systolic velocity [19]**.**

The reported values of the Doppler parameters were obtained by taking the average value of 3 consecutive measurements [15,20]**.**

The operator was unaware of any information about the endoscopic findings of varices [20]**.**

E) The following indices were calculated:

1- Congestion index (CI) (cm/sec^{-1}): was calculated for portal and splenic veins as: *CI = CSA/mean velocity* [10,11].
2- Modified liver vascular index (MLVI) (cm/sec): was calculated according to ***Piscaglia et al.*** [21] as: portal flow velocity/ HARI.
3- Portal hypertension index (PHI) (m/sec^{-1}): was calculated according to ***Piscaglia et al.*** [21] as: [(HARI × 0.69) × (SARI × 0.87)]/ portal vein mean velocity.

F) Portosystemic collaterals: Left gastric vein (LGV), splenic collaterals, paraumbilical vein and collaterals at the porta hepatis.

VI- Platelet Count/Spleen Diameter Ratio:

It was calculated for all patients as: platelet count/ maximum spleen bipolar diameter by ultrasound in mm [3].

VII- Upper Gastrointestinal Endoscopy:

To evaluate the presence and degree of varices in addition to any relevant upper GIT lesions. Pentax EG-3440 videoscope system was used. The endoscopic study was performed by the same examiner in all patients to avoid interobserver variability [13].

**** Esophageal varices (EV) were classified according to Westaby et al.*** [22] ***into:***

Grade I: Varix is in flush with the wall of the esophagus.

Grade II: Protrusion of the varix but not more than half way to the center of the lumen.

Grade III: Protrusion of the varix more than half way to the center of the lumen.

Grade IV: The varices are so large that they meet at the midline.

**** Gastric varices (GV) were classified into two types:***

Gastroesophageal varices (when GV are associated with EV) and isolated gastric varices (when GV occur in absence of EV) [23].

**** Red color signs:*** red wale markings, cherry red spots or hematocystic spots [24].

**** Portal hypertensive gastropathy (PHG):***

It was classified according to ***(Baveno III consensus classification)*** into mild and severe PHG [25].

Patients were classified according to modified Child's score system into: Child score A, B or C [26].

- **Data Management and Statistical Analysis:**

Data management was conducted using Statistical Package for Social Sciences (SPSS) software computer program version (11.0). Continuous variables were expressed in term of mean and standard deviation and ordinal and nominal categorical data were described as number and percentages (frequency). Chi-square test with Yates correction and Fisher-Exact were used to test association between two categorical variables. Student-t-test and one way ANOVA were used to test means' differences between two and more than two groups respectively. Variables found to be significant at $p < 0.05$ in the univariate analysis were included in a multivariate analysis by stepwise forward regression analysis.

In the logistic regression model, the predicted probability of the presence of varices was related to the covariates via the following formula [4]:

Predictivity equation:

$$\log it\ P(X_{kn}) = \log \frac{P(X_{kn})}{1 - P(X_{kn})} = \alpha + \sum_{k-1}^{k} B_k X_{kn}$$

Where:

$P(X_{kn})$ = the likelihood of event (in this case, the presence of esophageal varices) in the examined series of n patients characterized by the set of variables X_k; n = 1, 2, ……..

α = log-odds of event likelihood for a patient with a standard set of variable ($X_{kn} = 0$).

X_{kn} = vector of variables $X0n$, $X1n$, …… X_{kn} for the n-th patients. k = 0, 1, 2.

B_k = vector of parameters 0, 1, ……k that weights the contribution of each variable to the likelihood of event.

$\sum_{k-1}^{k} B_k X_{kn}$ = sum of the products of parameter k by the variables X_{kn} of the n-th patient.

The regression coefficients of the predictive variables were rounded to the nearest number ending in .5 or .0, resulting in a weighted score and subsequently the values of the predictive variables were summed. The calculated prediction scores were compared to the observed percentage of patients who had varices. The sensitivity, specificity, positive and negative predictive values were determined for several cutoff values of the prediction scores. To evaluate the diagnostic performance of the model, a receiver operating characteristic (ROC) curve was constructed. The area under the curve (AUC) values provided a measure of the overall discriminative ability of the model [27].

Results:

1- Descriptive Data:

This study was conducted on 120 patients with chronic liver disease. They were 66 males (55%) and 54 females (45%) with a mean age of 53.6 ± 1.2 years (range 44 – 63 years). According to Child Classification, 60 patients (50%) were Child A, 24 (20%) were Child B and 36 (30%) were Child C.

Positive HCV Ab was detected in 115 cases (95.8%) and positive HBs Ag was detected in only 4 cases (3.3%). Only one case (0.8%) had mixed B and C viruses.

Upper GIT endoscopy revealed varices in 67 patients (55.8%); of these patients; 51 (42.5%) had isolated EV and 16 (13.3%) had EV with gastric extension (gastroesophageal varices). None of our enrolled patients had isolated gastric varices.

Fifty three patients (44.2%) had no varices by upper GIT endoscopy

Grading of EV among studied patients showed that ten cases (14.9%) had grade I, 18 (26.9%) had grade I-II, 8 (11.9%) had grade II, 16 (23.9%) had grade II-III, 11 (16.4%) had grade III, 4 (6%) had grade III-IV EV. None of enrolled patients had grade IV EV.

Among those with varices, 9 patients (13.4%) showed evidence of risky signs. Of those, 6 patients (8.9%) had cherry red spots, two (3%) had both cherry red spots and hematocystic spots and one (1.5%) had red wale markings

Regarding the presence of portal hypertensive gastropathy (PHG), 90 patients (75%) had mild PHG, 6 (5%) had severe PHG and 24 (20%) showed no evidence of PHG

2- Statistical Analysis:

According to the results of upper GIT endoscopy, patients were classified into two groups:

- **Group I:** 67 patients (55.8%) with EV.
- **Group II:** 53 patients (44.2%) with no EV.

Comparison between patients with EV (Group I: n=67) and those without varices (Group II: n=53). (To determine independent risk factors for the presence of varices):

(A) Univariate Analysis:

Regarding clinical examination; jaundice, palmar erythema, spider naevi, lower limb edema, palpable spleen and ascites were more evident in patients with varices with a highly significant statistical difference between the two groups. However, palpable liver was more significantly detected in patients with no varices.

Patients with varices had lower serum albumin, more prolonged prothrombin time and more elevated serum bilirubin than those without varices with a highly significant difference. There was a highly significant decrease in platelet count in patients with varices in comparison to those without.

The frequency of varices in our studied patients increased with increase of their Child score. The frequency of varices was 26.7% among patients in Child class A, 75% in Child class B and 91.7% in Child class C patients with a highly significant statistical difference **(Table 1).**

Abdominal ultrasonographic findings of the studied groups are shown in **Table (2).** Liver size was highly significantly decreased, splenic size was highly significantly increased, portal and splenic vein diameters (mm) were highly significantly increased and coarse liver was significantly detected in patients with varices in comparison to those without.

Moderate to severe ascites was more significantly detected in patients with varices than in those without.

Results of Doppler examination of the studied groups are shown in **Table (3).**

The portal vein cross sectional area (CSA) and congestion index (CI) were more elevated while the mean portal vein flow velocity (PVV) was lower in patients with varices than in those without. There was a highly significant difference between the two groups. The direction of flow in the portal vein was hepatopetal in 65.7% of patients with varices and 100% in those without varices. It was hepatofugal in 34.3% of patients with varices. None of the patients with no varices had hepatofugal blood flow with a highly significant difference between patients with varices and those without.

The splenic vein cross sectional area (CSA) and congestion index (CI) were more elevated while the mean splenic vein flow velocity was lower in patients with varices than in those without. There was a highly significant difference between the two groups.

The hepatic artery resistance index (HARI) and the splenic artery resistance index (SARI) were highly significantly elevated in patients with varices in comparison to those without.

The modified liver vascular index (MLVI) was lower while the portal hypertension index (PHI) was higher in patients with varices than in those without with a highly significant difference.

There was a highly significant statistical difference between the two groups regarding the presence of portosystemic collaterals by Doppler.

The mean ± SD platelet count/ spleen diameter (mm) ratio was lower in patients with varices (730.7 ± 235.3) than in those without (1742.4 ± 481.3), with a highly significant statistical difference between the two groups ($p < 0.001$).

(B) Multivariate Analysis:

Significant variables in univariate analysis were included into a logistic regression analysis stepwise method. The best results were judged by their likelihood ratio, the significance of the introduced predictors, their odds ratio and confidence interval together with fitness and predictivity of the model. The presented model gave the highest likelihood ratio, the relatively high predictivity meanwhile showed a good fitting.

The Child staging of the patient, liver size (cm) and spleen size (cm) were found to be independent risk factors for the presence of varices in this study with a

likelihood ratio of 94.4 and a predictivity of 85.8%. Thus, the risk of the presence of varices increases with advanced Child stage, reduced liver size and enlarged spleen **(Table 4).**

The performance of this prediction model is displayed by the Receiver Operating Characteristic (ROC) curve. The Area under the Curve (AUC) was 0.89 (0.83 – 0.96). This denotes that this model gives a good discrimination between patients with varices and those without **(Figure 1).**

From this proposed model, a prediction scoring system was generated. A scoring point is given to each parameter in the model: Child A class takes zero, Child B class takes 1.5 points and Child C class takes 2.5 points. The patient's liver and spleen sizes in cms by ultrasonography are multiplied by - 0.297 and 0.607 respectively to get the scoring points for these parameters. Then the total score of the patient is the product of summation of all these points **(Table 5 and Figure 2).**

Figure (3) shows a high performance of both the prediction score and the regression model probability which is displayed by the Receiver Operating Characteristic (ROC) curve. The Area under the curve (AUC) for prediction score = 0.885 (0.820 – 0.950) and for regression model probability = 0.895 (0.833 – 0.956).

Figure (4) shows the distribution of the prediction score according to the presence of varices by endoscopy. The majority of patients with no varices by endoscopy are distributed in the lower 1/3 of the curve (i.e. they have low score values), while most patients with varices by endoscopy have high score values and are mostly distributed in the upper 1/2 of the curve.

Table (6) shows the different cutoff values for prediction scores and risk of presence of varices in our study. The higher the cutoff value, the higher the number of patients who had varices.

Table (7) shows the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the prediction score at different cutoffs from "4" to "9". A cutoff of "4" yielded a high sensitivity and a high negative predictive value (meaning a low false negative rate); however the specificity of the prediction score at this cutoff is relatively low meaning that a high percentage of false positive cases will be included. A cutoff value of "9" yielded a relatively high specificity i.e. at this point, the scoring model can exclude patients with varices (Good negative test), however, its sensitivity is relatively low. A cutoff point of "6" or "7" can be considered as the most practical one as it demonstrated a relatively high sensitivity and specificity and a relatively high NPV.

Discussion:

Although endoscopy is the gold standard procedure for diagnosing esophageal varices (EV) [28], it is not cost-effective to screen all cirrhotic patients by endoscopy [29].

Also, many cirrhotic patients are non-compliant and refuse repeated screening endoscopy. Consequently, the development of a reliable non-invasive method of identifying patients who are more likely to have varices and are candidates for endoscopic screening would greatly help relieving medical, social and economic burden [30].

The present study was designed to develop a predictive model for esophagogastric varices in patients with chronic liver disease using non-invasive parameters.

Platelet count can be considered an indirect marker of portal hypertension as it decreases in relation to the hypersplenism [2]. In our study, there was a highly significant decrease in platelet count in patients with varices in comparison to those without. This is consistent with what was found by ***Schepis et al.*** [4].

In patients with chronic liver disease, the presence of thrombocytopenia may depend on several factors such as hypersplenism, decreased thrombopoietin production from the liver, shortened platelet mean life-time, or myelotoxic effects of alcohol or hepatitis viruses [31,32,33].

In this study, we investigated the platelet count/spleen diameter ratio as a parameter linking thrombocytopenia to spleen size. We found that this ratio was highly significantly lower in patients with varices than in those without. This is consistent with the univariate analysis of ***Giannini et al.*** [3].

The presence of varices is likely proportional to the severity of the liver disease. We found that the frequency of varices in our patients increases with increase of their Child score. The frequency of EV was 26.7% among patients in Child class A, 75% in Child class B and 91.7% in Child class C patients with a highly significant statistical difference. This is in accordance to ***Madhotra et al.*** [2].

Regarding abdominal ultrasonographic findings, we found that liver size was highly significantly more decreased and coarse liver was significantly more detected in patients with varices than in those without.

In the present study, the portal vein diameter (mm) was highly significantly increased in patients with varices in comparison to those without. This is in agreement with what was reported by ***Schepis et al.*** [4]. On the other hand, ***Sabbá et al.*** [34] concluded that the normal caliber of PV can not exclude portal hypertension because the PV diameter may be affected by the development of portosystemic collaterals. ***Sabbá et al.*** [35] noted that PV dilatation may occur in the absence of portal hypertension e.g. in response to huge splenomegaly or acute PV thrombosis.

In this study, the size of the spleen and splenic vein (SV) diameter were highly significantly increased in patients with varices in comparison to those without. This is consistent with ***Madhotra et al.*** [2] ***and Schepis et al.*** [4].

As regards the results of Doppler examination of our studied groups, the PV cross sectional area (CSA) and congestion index (CI) were more increased and the mean portal vein flow velocity (PVV) was lower in patients with varices than in those without. There was a highly significant statistical difference between the two groups. These findings are due to passive congestion of blood in the portal venous system, which could be explained by the formation of regenerative nodules and fibrotic septa in liver cirrhosis, resulting in increased intrahepatic resistance to portal blood flow [13, 20].

Flow reversal in the portal or splenic veins is a variable finding in portal hypertension, because flow direction in these vessels is influenced by the development of collateral circulation [9]**.** In liver cirrhosis, the sinusoids are damaged, destroyed or replaced. As the volume of normally functioning liver parenchyma decreases, the resistance to portal venous flow increases, the portal vein dilates, and portal flow decreases and eventually reverses [11]**.** In our study, the direction of flow in the portal vein was hepatopetal in 65.7% of patients with varices and 100% in those without varices. It was hepatofugal in 34.3% of patients with varices. None of the patients with no varices had hepatofugal blood flow with a highly significant statistical difference between patients with varices and those without.

However, in the study of ***Kayacetin et al.*** [13], it was found that all patients with varices demonstrated normal (hepatopetal) flow in the PV.

In the present study, the hepatic artery resistance index (HARI) and the splenic artery resistance index (SARI) were highly significantly increased in patients with varices in comparison to those without. This is matching with previous reports [15, 21]. The pathological mechanisms resulting in portal hypertension, i.e. distortion of hepatic architecture, narrowing of the vascular bed by fibrous tissue, compression by regenerative nodules, and increased contractility in response to vasoconstrictors are responsible for the increase in the hepatic arterial resistance [15,36].

The splenic parenchyma is surrounded by an inextensible capsule. Consequently, with portal hypertension and increased splenic pulp pressure, the distensibility of the splenic terminal arterioles may be limited. The lack of wall compliance is responsible for reduction in diastolic flow, which ultimately leads to an increase in splenic artery resistance indices [37].

The modified liver vascular index (MLVI) is the ratio between PVV and HARI. ***Piscaglia et al.*** [21] reported that the MLVI was an important haemodynamic parameter which showed a specificity of 100% in the diagnosis of portal hypertension. This is in accordance to our results where the MLVI was highly significantly lower in patients with varices than in those without.

Another index, termed the portal hypertension index (PHI), was proved by ***Piscaglia et al.*** [21] to be the most accurate Doppler parameter in diagnosis of portal hypertension with gastroesophageal varices. It is calculated by the following formula:
Portal hypertension index (m/sec^{-1}) = [(hepatic artery RI × 0.69) × (splenic artery RI × 0.87)] / portal vein mean velocity. The best cutoff value for PHI was 1.4 cm/sec^{-1} (0.014 m/sec^{-1}) and above this cutoff value, patients were more likely to have gastroesophageal varices. They reported that this index may possibly limit the need for upper gastrointestinal endoscopy in chronic liver disease patients [21]. This is in agreement with the current study as the PHI was highly significantly higher in patients with varices than in those without.

In this study, there was a highly significant statistical difference between patients with varices and those without regarding the presence of portosystemic collaterals by Doppler. Previous studies reported that the extent of these portosystemic shunts varies among individuals according to the degree of portal hypertension [38]**.**

In the current study, we used the significant variables in univariate analysis and included them into multivariate analysis by the logistic regression stepwise method.

From this multivariate analysis, we found that the Child staging of the patient, liver size (cm) and spleen size (cm) were independent risk factors for the presence of varices with a likelihood ratio of 94.4 and a predictivity of 85.8%. Thus, the risk of the presence of varices increased with advanced Child stage, reduced liver size and enlarged spleen.

Other variables in our study which were significant by univariate analysis failed to reach statistical significance when they were submitted to the multivariate analysis.

The performance of our prediction model was displayed by the Receiver Operating Characteristic (ROC) curve. The Area under the Curve (AUC) was 0.89 (0.83 – 0.96). This denotes that this model gives a good discrimination between patients with varices and those without.

From this proposed model, a prediction scoring system was generated. A scoring point was given to each parameter in the model: Child A class took zero, Child B class took 1.5 points and Child C class took 2.5 points. The patient's liver and spleen sizes in cms by ultrasonography are multiplied by -

0.297 and 0.607 respectively to get the scoring points for these parameters. Then the total score of the patient was the product of summation of all these points.

We found a high performance of both the prediction score and the regression model probability by the Receiver Operating Characteristic (ROC) curve. The Area under the curve (AUC) for prediction score = 0.885 (0.820 – 0.950) and for regression model probability = 0.895 (0.833 – 0.956).

Our prediction score had a high sensitivity and specificity and a relatively high negative predictive value (NPV) at cutoff points 6 and 7. So, these cutoff points were considered the most practical ones. At cutoff 6, sensitivity was 82.1%, specificity was 83%, positive predictive value was 85.9% and negative predictive value was 78.6%. At cutoff 7, sensitivity was 78.1%, specificity was 90.6%, positive predictive value was 90.9% and negative predictive value was 77.4%.

Thus, above these cutoff values, the risk of the presence of varices is increased and cirrhotic patients should be screened by upper GIT endoscopy.

According to our knowledge, none of the previous investigators has proposed a prediction scoring system for the risk of the presence of varices among patients with chronic liver disease. However, many investigators tried to find independent risk factors for the presence of varices in their studied patients.

Zaman et al. [39] found that among the different variables in their studied 300 cirrhotic patients, the Child-Pugh class was independently associated with the presence of varices by multivariate analysis. However, they identified also low platelet count (< 90 × 10^3/μL) as independent marker for the presence of varices which is not detected by multivariate analysis in our study. This may be explained by the high percentage of alcoholic cirrhosis in their study (44%), and it has been reported that alcohol has a myelotoxic effect on bone marrow leading to more significant reduction of platelet count [33]**.** Another explanation is that they included less number of Child class A patients in their study than in ours (22% *versus* 50% respectively), thus, they included more decompensated cases with more advanced liver disease and more significant thrombocytopenia.

We are also in agreement with ***Madhotra et al.*** [2] in that splenomegaly is one of the independent predictors for the presence of varices. However, they identified two other independent variables that were different from ours; they were low platelet count and clinically detected ascites.

Our results in this aspect differ from those of ***Schepis et al.*** [4]**.** In their study, by using stepwise logistic regression multivariate analysis, they found that the presence of EV was independently predicted by prothrombin activity less than 70%, ultrasonographic PV diameter greater than 13 mm and platelet count less than 100 × 10^3/μL. The discriminating ability of their prediction rule was relevant (area under the curve: 0.80) and did not change by replacing ultrasonographic PV diameter with congestion index of PV.

This difference between our results and those of ***Schepis et al.*** [4] may be attributed to the difference in the characteristics of the enrolled patients in their study where they excluded all patients of Child class C.

On the other hand, we are in agreement with ***Schepis et al.*** [4] in that the Doppler parameters cannot be considered as independent risk factors for the presence of varices.

This may be attributed to that the Doppler haemodynamic parameters are affected by other factors such as the development of portosystemic collateral circulation [11]**.**

In conclusion, the Child staging of the patient, liver size (cm) and spleen size (cm) by ultrasonography were the most relevant significant predictors of the presence of varices. A scoring system was generated using these parameters which showed a high performance in discrimination between patients with varices and those without. Thus, we can identify patients with a high probability of having varices that are candidates for endoscopy.

Table (1): Clinical examination, Laboratory data and Child classification of studied groups:

Parameter	Group I (n=67)		Group II (n=53)		*P-value*
	N.	%	N.	%	
General examination					
Pallor	10	14.9	7	13.2	NS
Jaundice	27	40.3	5	9.4	<0.001* HS
Palmar erythema	46	68.7	10	18.9	<0.001* HS
Spider naevi	23	34.3	1	1.9	<0.001* HS
Lower limb edema	50	74.6	9	17.0	<0.001* HS
Abdominal examination					
Palpable liver	22	32.8	29	54.7	<0.05* S
Palpable spleen	48	71.6	15	28.3	<0.001* HS
Ascites:					
• None	21	31.3	50	94.3	<0.001* HS

• Moderate	39	58.2	2	3.8	
• Tense	7	10.4	1	1.9	
Laboratory data ***(Mean ± SD)***					
ALT (7-40 IU/L)	46.5 ± 19.6		50.7 ± 22.7		NS
AST (7-37 IU/L)	51.9 ± 20.4		53.1 ± 23.3		NS
S. albumin (3.5-5.3 g/dL)	2.8 ± 0.6		3.6 ± 0.5		<0.001* HS
S. total protein (6-8.3 g/dL)	7.2 ± 0.6		7.5 ± 0.5		<0.01* S
Prothrombin time (control=11.5 sec)	15.5 ± 2.3		13.6 ± 1.7		<0.001* HS
Total bilirubin (0.2-1.2 mg/dL)	2.1 ± 1.4		1.2 ± 0.9		<0.001* HS
Direct bilirubin (0-0.3 mg/dL)	0.93 ± 0.7		0.49 ± 0.5		<0.001* HS
Haemoglobin (g/dL)	11.9 ± 1.6		12.4 ± 1.5		=0.05* S
RBCs count × 10^6 /µL	3.5 ± 0.7		3.8 ± 0.7		<0.05* S
WBCs count × 10^3 /µL	5.5 ± 2.2		6.3 ± 2.5		0.06 NS
Platelets × 10^3 /µL	111.0 ± 29.4		234.6 ± 54.7		<0.001* HS
Child classification (Percentages are from rows)	**N.**	**%**	**N.**	**%**	
Child class A **(n=60)**	16	26.7	44	73.3	<0.001* HS
Child class B **(n=24)**	18	75.0	6	25.0	
Child class C **(n=36)**	33	91.7	3	8.3	

NS= Non significant S= Significant HS= Highly significant

Table (2): Abdominal ultrasonographic findings:

Parameter		**Group I (n=67)**		**Group II (n=53)**		***P-value***
		N.	**%**	**N.**	**%**	
Liver size (cm) *Mean ± SD*		13.6 ± 2.1		15.8 ± 2.3		<0.001* HS
Liver Echogenicity	Bright	0	0.0	7	13.2	<0.01* S
	Bright coarse	4	6.0	9	17.0	
	Coarse	63	94.0	37	69.8	
Periportal thickening		53	79.1	38	71.7	NS
Portal vein diameter (mm) *Mean ± SD*		14.8 ± 1.1		12.0 ± 0.8		<0.001* HS
Spleen size (cm) *Mean ± SD*		15.5 ± 1.7		13.7 ± 1.2		<0.001* HS
Splenic vein diameter (mm) *Mean ± SD*		9.6 ± 1.3		6.6 ± 1.1		<0.001* HS
Ascites	No ascites	19	28.4	47	88.7	<0.001* HS
	Minimal	2	3.0	3	5.7	
	Moderate to severe	46	68.7	3	5.7	

Table (3): Doppler findings of studied groups:

Parameter		**Group I (n=67)**	**Group II (n=53)**	***P- value***
PV CSA		1.8 ± 0.4	1.2 ± 0.3	<0.001* HS
PVV		12.3 ± 1.2	19.7 ± 2.4	<0.001* HS
PV CI		0.15 ± 0.04	0.06 ± 0.01	<0.001* HS
PV Direction of flow *N.(%)*	Hepatopetal	44 (65.7%)	53 (100.0%)	<0.001* HS
	Hepatofugal	23 (34.3%)	0 (0.0%)	
SV CSA		0.85 ± 0.3	0.55 ± 0.1	<0.001* HS
SVV		11.6 ± 1.3	13.3 ± 0.8	<0.001* HS
SV CI		0.07 ± 0.03	0.04 ± 0.01	<0.001* HS
HARI		0.78 ± 0.03	0.68 ± 0.04	<0.001* HS
SARI		0.70 ± 0.05	0.61 ± 0.03	<0.001* HS
MLVI (cm/sec)		15.8 ± 2.0	29.2 ± 4.3	<0.001* HS
PHI (m/sec^{-1})		0.03 ± 0.005	0.01 ± 0.004	<0.001* HS
Portosystemic collaterals	Left Gastric	15 (22.4%)	0 (0.0%)	<0.001* HS

N. (%)	Paraumbilical	22 (32.8%)	0 (0.0%)	<0.001* HS
	Lienorenal	11 (16.4%)	0 (0.0%)	<0.01* S
	Splenic hilar	20 (29.9%)	0 (0.0%)	<0.001* HS
	Portahepatis	5 (7.5%)	0 (0.0%)	<0.001* HS

PV: portal vein, SV: splenic vein, CSA: cross sectional area, PVV: mean PV flow velocity, CI: congestion index, SVV: mean SV flow velocity, HARI: hepatic artery resistance index, SARI: splenic artery resistance index, MLVI: Modified liver vascular index, PHI: portal hypertension index.

Table (4): Proposed model for prediction of varices in chronic liver disease patients (independent risk factors for the presence of varices):

	B (SE)	Wald	P value	OR (95% CI)
Child Staging:				
Child A	0	12.0	0.002	1.0
Child B	1.52 (0.64)	5.6	0.018	4.6 (1.3 – 15.9)
Child C	2.28 (0.74)	9.5	0.002	9.8 (2.3 – 41.5)
Liver Size in cms	-0.297 (0.13)	5.2	0.022	0.74 (0.58 – 0.96)
Spleen Size in cms	0.607 (0.18)	10.8	0.001	1.8 (1.3 – 2.6)
Constant	-5.089			
Likelihood Ratio	94.4			
Predictivity	85.8			

B (SE) = regression coefficient (standard errors of B),
OR=Odds Ratio, CI=Confidence Interval.

Table (5): Prediction scoring system invented according to the prediction model:

Parameters of the model	B (SE)	Scoring points
Child staging:		
Child A	0	0
Child B	1.52 (0.64)	1.5
Child C	2.28 (0.74)	2.5
Liver size in cms	- 0.297 (0.13)	× - 0.297*
Spleen size in cms	0.607 (0.18)	× 0.607**

*** Liver size in cms multiplied by - 0.297**
**** Spleen size in cms multiplied by 0.607**

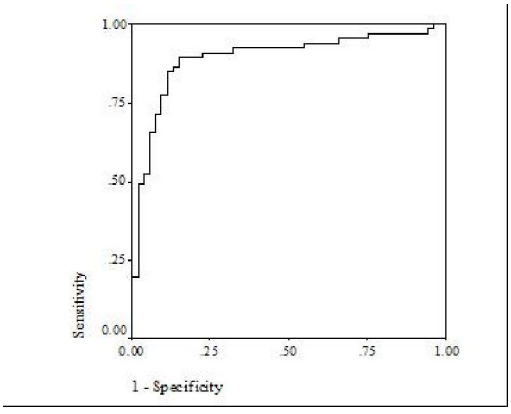
Table (6): Cutoff values for prediction scores and risk of presence of varices:

Cutoff values	Number of Patients with No Varices	Number of Patients with Varices
≤5	44 (78.6%)	12 (21.4%)
6-8	6 (26.1%)	17 (73.9%)
≥9	3 (7.3%)	38 (92.7%)

Table (7): Sensitivity, Specificity, PPV and NPV of the prediction score at different cutoffs from "4" to "9":

	Cutoff "4"	Cutoff "5"	Cutoff "6"	Cutoff "7"	Cutoff "8"	Cutoff "9"
Sensitivity	92.5%	86.4%	**82.1%**	**78.1%**	70.1%	56.7%
Specificity	63.5%	79.2%	**83.0%**	**90.6%**	92.5%	94.3%
PPV	76.5%	83.8%	**85.9%**	**90.9%**	92.2%	92.7%
NPV	86.8%	82.3%	**78.6%**	**77.4%**	71.0%	63.3%

PPV: Positive predictive value, **NPV:** Negative predictive value.



1- What is the Child Stage of the Patient?

Child A 0 points --------

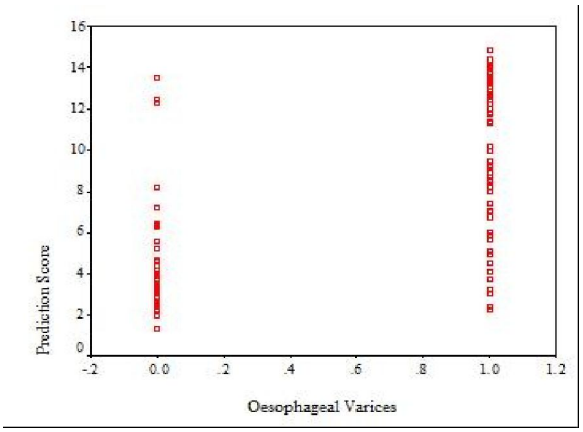
Child B 1.5 points --------

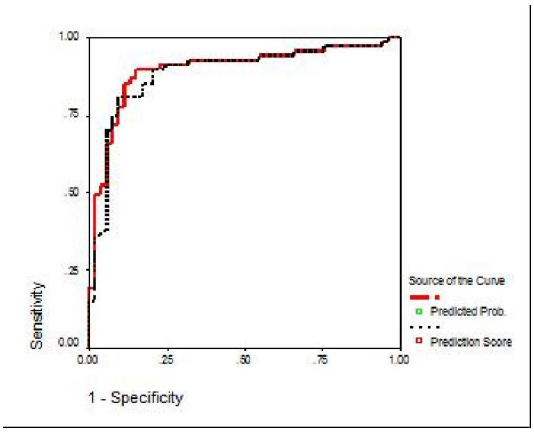
Child C 2.5 points --------

2- What is the liver size in cms (multiply by -0.297) --------

3- What is the spleen size in cms (multiply by 0.607) --------

Total Score ----------





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Abbreviations: EV: esophageal varices, PV: portal vein, SV: splenic vein, CSA: cross sectional area, PVV: mean PV flow velocity, CI: congestion index, SVV: mean SV flow velocity, HARI: hepatic artery resistance index, SARI: splenic artery resistance index, MLVI: Modified liver vascular index, PHI: portal hypertension index.

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