Study of Noninvasive Predictors of Portal Hypertension in Liver Cirrhotic Egyptian Patients

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Abstract: Back ground and aim: Hepatitis C Virus (HCV) is considered the most common aetiology of chronic liver disease in Egypt.Portal hypertension is a major complication of liver cirrhosis, and leads to the development of portosystmic shunts. Oesophageal varices are the most important among these shunts. Bleeding from oesophageal varices is the most serious complication of cirrhosis, with a high risk of death. Prevention of variceal bleeding is very important, non-selective beta blockers and prophylactic band ligation decrease the risk of bleeding by 50%. It is recommended to screen all cirrhotic patients by endoscopy, to diagnose who is at risk of bleeding so preventive treatment can be started to them. Repeated endoscopic examinations may lack compliance by many patients, and carries high cost impact and more burden on endoscopic units. For these reasons many non-invasive predictors for the presence and size of varices have been studied. The aim of this study is to evaluate the Child class, spleen size and platelet count as noninvasive predictors of oesophageal varices in Egyptian Cirrhotic patients. Patients and methods: This prospective study included one hundred patients with post hepatitis C virus liver Cirrhosis. All studied patients were subjected to detailed clinical examination and a biochemical workup, including total bilirubin, aspartate aminotransferase, alanine aminotransferase, serum albumin, prothrombin activity, complete blood count and viral markers for hepatitis C and hepatitis B viruses. Child-Pugh score was calculated for all patients using the 5 parameters (ascites, albumin, bilirubin, prothrombin activity and encephalopathy). An upper gastrointestinal endoscopy and abdominal ultrasound were performed for all patients. The maximum spleen bipolar diameter was measured and the values were recorded. Results: All predictors showed statistically significant correlation with the presence and the grade of oesophageal varices (P values <0.001). The spleen size gave the highest accuracy (89%) at a cut-off value of 131.5 (sensitivity 90.24% and specificity 83.33%) followed by the Child class B (accuracy 88%, sensitivity 91.46% and specificity 72.22%) then the platelet count at a cut-of value of 131000/mm^3(accuracy 84% , sensitivity 84.15% and specificity 83.33%) then lastly came Child class C (accuracy 65% , sensitivity 58.54% and specificity 94.44%). Conclusion: non-invasive parameters based on ultrasonographic measurement and laboratory testing may help the to restrict endoscopy on those who are highly suspected to have oesophageal varices varices in patients with liver cirrhosis.

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Key words: liver cirrhosis, noninvasive prediction of oesophageal varices, portal Hypertension, the platelet count, Oesophageal varices, post hepatitis liver cirrhosis.

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1. Introduction:

Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide and a high morbidity and mortality from chronic liver disease [(1)]. HCV is considered the most common aetiology of chronic liver disease in Egypt [(2)].

Bleeding oesophageal varices is the gravest complication of liver cirrhosis, with a high mortality [(3)]. Each variceal bleeding attack carries a mortality rate of 17%-57% [(4 - 10)].

Prevention of variceal bleeding vital, while non-selective beta blockers and prophylactic band ligation decrease the risk of bleeding by 50% [(11, 12)]. The current guidelines recommend endoscopic screening to all cirrhotic patients. Those with decompensated cirrhosis should annually repeat endoscopy even if they have no varices, while those with compensated cirrhosis and don't have varices should repeat endoscopy every 2-3 years, and every 1-2 years for those with small varices [(13, 14)]. But repeated endoscopies are unpleasant for patients, and carries high cost impact and more burden on endoscopic units which may have long daily list, while only 50% of cirrhotic patients have esophageal varices, and up to 30% have large varices. Noninvasive diagnosis of esophageal varices (EVs) in cirrhotic patients is beneficial because it help us to select the patients likely to have oesophageal varices to do endoscopy for them; at the same time, it

minimizes the cost and the potential complications related to the procedure.

In this study we try to evaluate prospectively the Child class, spleen size and the platelet count as noninvasive predictors of oesophageal varices in liver cirrhotic Egyptian patients.

2. Materials and methods:

One hundred patients with post hepatitis C virus liver Cirrhosis were prospectively studied between January 2009 and March 2010.

The included patients were either under investigations and treatment at the Gastroenterology & Hepatology outpatient clinics or those who were admitted to the Internal Medicine departments of the Cairo university hospitals.

We excluded patients with previous or active gastrointestinal bleeding, those who previously underwent injection sclerotherapy, band ligation and those who were receiving beta blockers. Patients with liver cirrhosis due to causes other than HCV were excluded. The diagnosis of cirrhosis was based on physical findings, laboratory investigations and imaging findings.

Detailed history taking and clinical examination were done to all patients who were subjected to serum sample collection for biochemical workup, including complete blood count, total bilirubin, aspartate aminotransferase, alanine aminotransferase, serum albumin, prothrombin activity, and viral markers for hepatitis C and hepatitis B viruses. Child-Pugh score was calculated for all patients using the 5 parameters (ascites, albumin, bilirubin, prothrombin activity and encephalopathy) [(15)]. An abdominal ultrasound was performed to all patients. The maximum spleen bipolar diameter was measured and the values were recorded.

Upper gastrointestinal endoscopy was done to all patients. All endoscopies were performed in a single endoscopy unit by an experienced endoscopist and a grading classification I – IV was used [(16)]. Grade I was used for varices in the level of mucosa, grade II for varices smaller than 5 mm filling less than 1/3 of the oesophageal lumen, grade III for varices larger than 5 mm filling more than 1/3 of the oesophageal lumen and grade IV for varices occupied more than 2/3 of esophageal lumen. Informed consent was obtained from all patents in the study. All the data were recorded, analyzed and correlated.

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney *U* test for independent samples when comparing 2 groups and Kruskal Wallis analysis of variance (ANOVA) test with Mann Whitney *U* test for independent samples as posthoc multiple 2-group comparisons when comparing more than 2 groups. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, -ve predictive value, overall accuracy, the likelihood ratio of a positive test and the likelihood ratio of a negative test. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results:

The main clinical characteristics of all patients are shown in table 1.

We correlated the mean values of PLT count and Spleen diameter to the presence and grade of varices and both of them showed significant correlation to the presence and grade of varices as shown in table 2 and table 3.

The Child class showed a significant correlation with the presence and the grade of varices (table 4).

We applied the ROC curve to find the best cut off values for sensitivity and specificity of PLT count and spleen diameter, in prediction of oesophageal varices (table 5, Fig 1 and Fig 2).

The sensitivity and specificity of both Child class B and C in prediction of oesophageal varices was measured, also the accuracy of PLT count, spleen diameter, Child class B and Child class C and all of them were compared together (table 5 and Fig 3). The spleen size gave the highest accuracy (89%) among the studied parameters at a cut-off value of 131.5 for the spleen diameter (sensitivity 90.24% and specificity 83.33%) followed by the Child class B (accuracy 88%, sensitivity 91.46% and specificity 72.22%) then the platelet count at a cut-of value of 131000/mm^3(accuracy 84% , sensitivity 84.15% and specificity 83.33%) then lastly came Child class C (accuracy 65% , sensitivity 58.54% and specificity 94.44%).

Table 1: showing the patients clinical characteristics

Main clinical characteristics of all patients	
Total	100
Gender (M/F)	48/52
Age (range)	20 - 70
Child class.(A/B/C)	20/31/49
Varices present (yes/no)	82/18
Varices grade (I, II, III, IV)	7/15/35/25
PLT count,mm^3 (mean ±SD)	117070 ± 66145.883
Spleen diameter, mm (mean ±SD)	150.92 ± 23.371
HB concentration, gm./dl(mean ±SD)	10.012 ± 0.88
Prothrombin conc. % (mean ±SD)	57.89 ± 0.19 %
Albumin concentration , gm./dl (mean ±SD)	2.543 ± 0.5699
Bilirubin level, mg/dl (mean ±SD)	2.1± 3.19

Table 2: Correlation of PLT count and Spleen diameter in patients with and without varices

Varices presence		PLT count	Spleen diameter
No	Mean	215,055.56	121.22
	SD	69,772.295	13.584
Yes	Mean	95,560.98	157.44
	SD	41,519.919	19.745
P		<0.001	<0.001

Table 3: Correlation between PLT count and Spleen diameter and grades of varices

Grade of varices		PLT count	Spleen diameter
I	Mean	167,428.57	136.29
	SD	59,969.040	15.966
II	Mean	99,466.67	149.87
	SD	37,015.183	16.296
III	Mean	96,000.00	160.60
	SD	31,167.479	14.136
IV	Mean	72,480.00	163.48
	SD	25,932.798	24.395
P		<0.001	0.007

Table 4: Correlation between child class and grade of oesophageal varices

Child Class % within grade of varices		Grade of varices				P Value
		I	II	III	IV	
	Child A	71.4%	13.3%	0.0%	0.0%	<0.001
	Child B	28.6%	66.7%	31.4%	16.0%	<0.001
	Child C	0.0%	20.0%	68.6%	84.0%	<0.001

Table 5: Comparison of accuracy of the 4 parameters in predicting the presence of oesophageal varices

Predictor	AUROC	Cut off point	Sensitivity (%)	Specificity (%)	(+)ve PV(%)	(-)ve PV(%)	Accuracy (%)	LR+	LR-
Spleen size	0.934	131.5	90.24	83.33	96.10	65.22	89.00	5.41	0.12
Child Class B			91.46	72.22	93.75	65.00	88.00	3.29	0.12
PLT count	0.912	131000	84.15	83.33	95.83	53.57	84.00	5.05	0.19
Child Class C			58.54	94.44	97.96	33.33	65.00	10.54	0.44

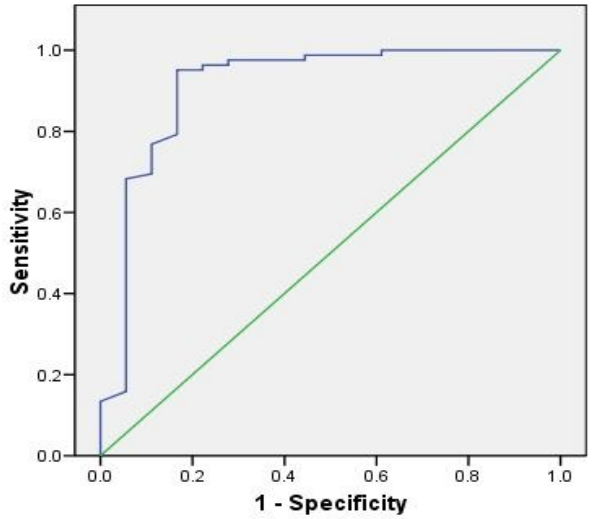

Figure 1: ROC curve for sensitivity and specificity of platelet count for the prediction of varices

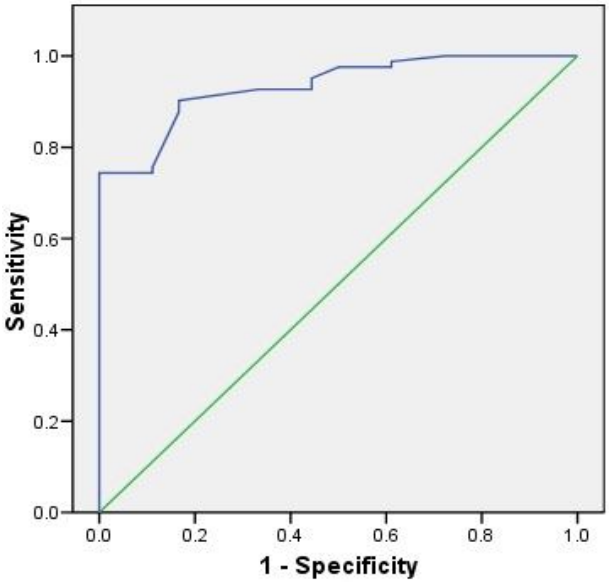

Figure 2: ROC curve for sensitivity and specificity of spleen size for the prediction of varices.

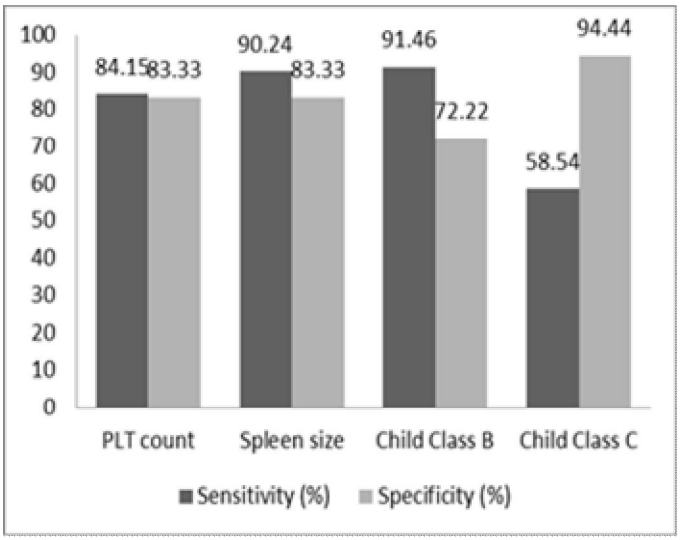

Figure 3: Comparison between sensitivity & specificity of the 4 parameters in predicting the presence of oesophageal varices

4. Discussion:

Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide and a high morbidity and mortality from chronic liver disease [(1)]. HCV is considered the most common aetiology of chronic liver disease in Egypt [(2)].

Noninvasive predictors of oesophageal varices represent a special importance in developing countries like Egypt where it is not easy to perform screening endoscopies to the huge number of cirrhotic patients.

The subject of noninvasive prediction of oesophageal varices attracted the investigators interest in the last decade; many studies have been done in order to find noninvasive method that can predict the presence of oesophageal varices to reduce the cost and burden on endoscopy units [(17-21)].

As mentioned in the introduction bleeding oesophageal varices is the gravest complication of liver cirrhosis, with a high mortality and Each variceal bleeding attack carries a mortality rate of 17%-57% , these data reflects the importance to find a reliable noninvasive method for detection of

oesophageal varices specially when the number of patient requiring endoscopic screening is in millions, which is the situation in Egypt.

The prevalence of oesophageal varices cirrhotic patients may reach up to 80% in some studies, [22, 23]. Prevention of variceal bleeding is of great importance, the first step in prevention of variceal bleeding is to diagnose those at risk of bleeding so we can select for whom we should start preventive measures as nonselective beta blockers or endoscopic variceal band ligation. The main importance of predicting oesophageal varices by a noninvasive method r is to save endoscopy those who have high probability of having varices as bleeding oesophageal varices is still the leading cause of death in patients with cirrhosis.

In a study by Giannini et al [21] he mentioned the use of the platelet count/spleen diameter ratio as a predictor of oesophageal varices. The idea of this ratio is to combine thrombocytopenia to splenomegaly to conclude a variable that takes into consideration that thrombocytopenia is mainly due to hyperslenism secondary to portal hypertension. At a cut-off value of 909 the sensitivity was 100% and specificity was 93%. In another study by Giannini et al [24] he mentioned the results of a multicenter study to use of platelet count/spleen diameter ratio in the prediction of oesophageal varices, however in his second study the cut-off value of 909 showed sensitivity 92% and specificity 67%. Different studies [16, 24- 27] have been made using different best cut-off values to detect this parameter as a predictor for the presence of oesophageal varices.

The results of the present study showed that both platelet count and spleen diameter have a significant relation with the presence of oesophageal varices which was the same finding of many other studies [28-34]. The presence of splenomegaly in cirrhotic patients is mainly related to portal hypertension, while thrombocytopenia is caused by more than one factor in addition to portal hypertension including diminished thrombopoietin production, toxic effects of hepatitis C virus on the bone marrow and decreased mean platelet lifetime [35].

In the present study the cut-off value of 131.5 for the spleen diameter was used to give the highest accuracy (89%) (sensitivity 90.24% and specificity 83.33%) followed by the Child class B (accuracy 88%, sensitivity 91.46% and specificity 72.22%) then the platelet count at a cut-of value of 131000/mm^3(accuracy 84% , sensitivity 84.15% and specificity 83.33%) then lastly came Child class C (accuracy 65% , sensitivity 58.54% and specificity 94.44%) as shown in table 5 and figure 3.

The accuracy, sensitivity and specificity of Child class A was not measured in this study as the total number of patients with Child class A was 22 which was not enough number statistically to estimate the accuracy of Child class A as a noninvasive parameter for the detection of the presence of oesophageal varices. Ultrasound elastography (Fibroscan) is a new technique that measure the degree of liver stiffness. Liver stiffness can be measured in kiloPascals (kPa). Ultrasound elastography is now getting a big attention as it is non-invasive.

Liver fibrosis is a main cause of portal hypertension and measuring the relation between stiffness and portal pressure may be a valuable theory.

Ultrasound elastography proved to correlate strongly with portal pressure.

The role of elastography as a noninvasive predictor of oesophageal varices is the concern of more than one study.

The assumed cutoff value for liver stiffness is 13.9 kPa to provide 95% sensitivity and 43% specificity[8].

5. Conclusion:

Among the noninvasive parameters studied in this study, the spleen diameter had the highest accuracy for noninvasive diagnosis of oesophageal varices (89%) at a cut-off value of 131.5 (sensitivity 90.24% and specificity 83.33%).

The use of the 4 studied predictors in this study can help the physicians to restrict endoscopy on those who are highly suspected to have oesophageal varices to start the prophylactic therapy and not to use the endoscopy for all the patients.

Endoscopy is still the gold standard for the diagnosis of oesophageal varices, but the use of the noninvasive predictors especially spleen diameter may be beneficial of to reduce the number of endoscopies in patients with post hepatitis C virus liver cirrhosis in Egypt. Each effort in studying noninvasive prediction of oesophageal varices will be of a special importance in Egypt where it is not easy to screen the very large number of patients with liver Cirrhosis by endoscopy.

More studies are required in a larger sample of post hepatitis C cirrhosis patients for validation of platelet count/spleen diameter ratio and to determine a cut-off value that can be safely recommended for the noninvasive diagnosis oesophageal varices.

The limitations of the present study includes: relatively small number of patients especially those with Child class A, liver biopsy was not done and the diagnosis of cirrhosis was based on clinical and laboratory results.

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