Platelet Count/Spleen Diameter Ratio, as a Non-Invasive Diagnosis of Esophageal Varices in Egyptian Patients with Liver Cirrhosis

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Abstract:Background: Upper gastrointestinal bleeding associated to esophageal varices is the most dramatic complication of cirrhosis. It is recommended screening every cirrhotic for esophageal varices with endoscopy.**Aim of the work:-**The objective of this study was to investigate the PC/SD ratio as a predictor of the presence and absence of esophageal varices in Egyptian patients with liver cirrhosis.**Patients and methods:-**One hundred and twenty five cirrhotic patients were included from the Hepatology department; Al-Azhar Faculty of Medicine and Ahmed Maher Hospital during the period from June 2011 till Feb. 2012. The diagnosis of hepatic cirrhosis by physical, biochemical, and imaging examinations, and confirmed by histological examination of Tru-cut needle-isolated liver biopsy. Once the patients were included in the study, a complete medical history was taken, medical examination was performed and biochemical parameters were measured.**Results: -** Comparison between cases with EV and those without EV was presented in table 2; and results showed that, age was significantly increased in cases with EV [50.32±5.26 vs. 44.51±4.38]. In addition, hepatic encephalopathy and ascites were significantly increased in cases with EV [25.6%, 47.7% vs. 7.7%, 28.2% respectively]. Cases with EV had higher grades of child Pugh scoring, low platelet count [117711.50±16529.65 vs. 205905.89±27809.35], high Pugh score [9.29±2.78 vs. 6.53±1.87], high spleen diameter [158.09±11.20 vs. 145.79±7.82], and low PC/SD ratio [751.71±138.30 vs. 1421.21±239.27]. Running ROC curve, it was found that, the test had a good diagnostic accuracy [AUC= 0.99]; the best cutoff value was 976.0 with sensitivity of 99.3% and specificity of 97.4%.**Conclusion:-**The PC/SD ratio is an accurate method for prediction of EV in cirrhotic patients and it can substitute it or at least can be used as a useful noninvasive method for identifying patients with esophageal varices and thereby may help reduce the number of unnecessary endoscopies

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1.Introduction

Portal hypertension is the most common and main complication of hepatic cirrhosis[1], and it had been reported that about 80% of cirrhotic patients will develop esophageal varices at some point, and at least one bleeding episode occurs due to rupture of varix in about 30.0% of those patients [2]. The majority of first bleeding episodes happen during the first year after the diagnosis of varices, with a 5%-10% mortality attributed to the first episode hemorrhage[3]. So, identification of esophageal varices is a complementary part of the diagnostic work-up in patients with cirrhosis, and it is also a prognostic marker of the illness. The first crucial preventive step is the identification of those patients with bleeding risk and selection for prophylactic treatment.

Endoscopy is still the gold standard in diagnosis and assessment of varices[4], But it carries some limitations of being invasive, not available in all medical centers, and some patients will not have varices [varices diagnosed in 24-80%], making it a cost ineffective method. Thus, the presence of a noninvasive method to predict the presence of esophageal varices would help restrict endoscopic studies

Different studieshave attempted to identify variables that can predict the presence of esophageal varices noninvasively, using different biochemical, clinical, and ultrasono-graphic parameters alone or in combination, with promising results. This can lead to avoid endoscopy in low-risk cases[5,6,7].

However, such studies have many limitations that makes it difficult to develop a widely applicable predictive model. Early studies were retrospective and were done in a specific subgroup of patients. Thus, the study groups lacked homogeneity and the widerepresentation of the cirrhotic population that is seen inclinical practice. Further, in patients with chronic liverdisease, the presence of thrombocytopenia isdue primarily to portal hypertension[8], but, it can depend on other factors, such as shortenedmean platelet lifetime or decreased thrombopoietin production[9].

Giannini*et al.* [8]proposed the use of the platelet count [PC]/spleen diameter [SD] ratio as a noninvasive tool for predicting the presence of varices. The use of the PC/SD ratio for the noninvasive assessment of varices is based on pathophysiological criteria with strict methodological criteria. The diagnostic precision ofthis parameter was validated using endoscopic diagnosisin a follow-up of patients free of esophageal varices[10].

The earlier results obtained by other authors have demonstrated that the diagnostic accuracy of the PC/SD ratio is maintained in patient subgroups with different hepatic disease etiologies and when applying different methodologies[11], suggesting that, this method can be a universal diagnostic method. However, studies confirming such situation in Egyptian patients are scare. The researcher can only identify one study dealing with Expatiation patients.

Aim of the work

The objective of this study was to investigate the PC/SD ratio as a predictor of the presence and absence of esophageal varices in Egyptian patients with liver cirrhosis.

2. Patients and methods

The present study was cross-sectional study of a diagnostic test. One hundred and twenty five cirrhotic patients were included from the Hepatology[Tropical Medicine] department; Al-Azhar Faculty of Medicine and Ahmed Maher Hospitalduring the period from June 2011 till Feb. 2012The diagnosis of hepatic cirrhosis by physical, biochemical, and imaging examinations, and confirmed by histological examination of True-cut needle-isolated liver biopsy for patients with Child-Pugh class A

The inclusion criteria were a diagnosis of hepatic cirrhosis by histology or physical, biochemical, and imaging examinations; both men and women with a diagnosis of hepatic cirrhosis.

The exclusion criteria included hepatocellular carcinoma, active variceal bleeding at admission, a history of endoscopic varicealsclerotherapy or band ligation, transjugular intra-hepatic portosystemic stent shunt placement, a history of surgery for portal hypertension, medication use for primary prophylaxis of variceal bleeding, alcohol abuse, and immune-mediated thrombocytopenia.

Once the patients were included in the study, a complete medical history was taken, medical examination was performed and biochemical parameters were measured.

After obtaining informed consent to participate in the study, all patients under-went upper GIT endoscopy and according to presence of absence of varices, they were divided into two groups; the first included patients with esophageal varices [86 cases;

68.8%] and the second without [39 cases; 31.2%]. All endoscopies were performed by a single endoscopist who was blinded to the patient's data.

Venous blood was drawn to determine the complete blood count, prothrombin time and concentration, liver function, and renal function.

On ultrasound, the diagnosis of cirrhosis was diagnosed according to criteria of Tchelepi*et al.* [12]. Maximum bipolar spleen diameter was measured and expressed in millimeters as described by Lamb *et al.*[13].

The platelet count/spleen diameter [PC/SD] ratio was calculated by dividing the number of platelets/SD by the maximum bipolar diameter of the spleen in millimeters.

Statistical analysis: the collected data were organized, tabulated and statistically analysis using statistical package for social science [SPSS] for windows, version 16 [SPSS Inc, USA].Numerical data were expressed as mean±SD, and categorical data were expressed as relative frequency and percentage. T-test was used to compare 2 independent groups of numerical data. Chi-square test was used to compare categorical groups of data. Receiver operating characteristic [ROC] curves were generated to determine the cutoff values for the best sensitivity and specificity of the variables with regard to the presence of EVs. A *P*-value was considered to be non-significant if > 0.05 and significant if ≤ 0.05.

3. Results

The descriptive data of studied cases were depicted in table [1]; males represented 64.8% of patients; age ranged from 37 to 60 years with a mean of 48.51±5.65; hepatic encephalopathy reported in 20%, while ascites was reported in 41.6%; Child's A, B and C was represented in 31.2%, 39.2% and 29.6% respectively; esophageal varices was reported in 68.8% and it was of grades I, II and III in 23.3%, 46.5% and 30.2% respectively; platelet count was reported from 101250 to 245300 with a mean of 14228.15±456906.48; spleen diameter ranged from 136 to 176 mm with a mean of 154.25±11.72 and finally PC/SD ratio ranged from 584.97 to 1777.54 with a mean of 960.59±357.28.

Comparison between cases with EV and those without EV was presented in table 2; and results showed that, age was significantly increased in cases with EV [50.32±5.26 vs. 44.51±4.38]. In addition, hepatic encephalopathy and ascites were significantly increased in cases with EV [25.6%, 47.7% vs. 7.7%, 28.2%] respectively. Cases with EV had higher grades of child Pugh scoring, low platelet count [117711.50±16529.65]vs.[205905.89±27809.35], high Pugh score [9.29±2.78]VS.[6.53±1.87], high spleen

diameter [158.09±11.20] VS.[145.79±7.82], and low PC/SD ratio [751.71±138.30] VS.[1421.21±239.27].

Running ROC curve, it was found that, the test had a good diagnostic accuracy [AUC= 0.99]; the best cutoff value was 97.6 with sensitivity of 99.3% and specificity of 97.4% [table 3 and figure 1]. Thus, value equal to this value or less than it are a good predictor of esophageal varices presence in cirrhotic patients.

Table [1]: Descriptive data of studied cases

Variable	Statistics
Sex [male/female] n, %	81/44[64.8%/35.2%]
Age[years][mean±SD; range]	48.51±5.67; 37-60
Hepatic encephalopathy	25[20.0%]
Ascites	52[41.6%]
Child Pugh[A/B/C] n,%	39/49/37[31.2%/39.2%/29.6%]
Presence of varices [Yes/no], n,%	86/39[68.8%/31.2%]
Variceal grading [I/II/III], n,%	20/40/26[23.3%/46.5%/30.2%]
Platelet count [n/CC][mean±SD; range]	145228.15±45906.48; 101250.0-245300.0
Child Pugh score[mean±SD; range]	8.43±2.83; 5.0-14.0
Spleen diameter [ml][mean±SD; range]	154.25±11.72; 136.0-176.0
PC/SD ratio	960.59±357.28; 584.97- 1777.54

Table [2]: Comparison between cases with EV and those without as regard studied parameters

Variable	With EV	Without EV	Test	P value
Sex [male/female] n, %	57/29[66.3%/33.7%]	24/15[61.5%/38.5%]	0.26	0.60
Age[years][mean±SD]	50.32±5.26	44.51±4.38	6.01	<0.001*
Hepatic encephalopathy	22[25.6%]	3[7.7%]	5.36	0.021*
Ascites	41[47.7%]	11[28.2%]	4.18	0.041*
Child Pugh[A/B/C] n,%	16/35/35[18.6%, 40.7%, 40.7%]	23/14/2[59.0%, 35.9%, 5.1%]	25.64	<0.001*
Platelet count [mean±SD]	117711.50±16529.65	205905.89±27809.35	22.08	<0.001*
Child Pugh score[mean±SD]	9.29±2.78	6.53±1.87	5.62	<0.001*
Spleen diameter[mean±SD]	158.09±11.20	145.79±7.82	6.19	<0.001*
PC/SD ratio	751.71±138.30	1421.21±239.27	19.72	<0.001*

Table [3]: Sensitivity, specificity and best cut off value of PC/SD ratio in diagnosis of EV

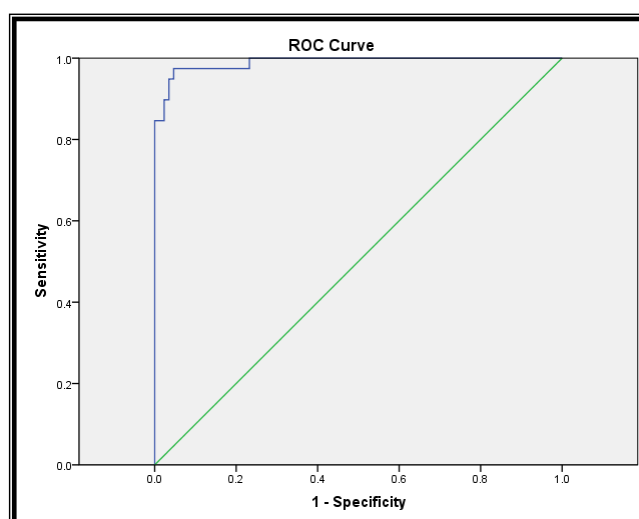| Area under the curve	Std. Error	Best Cut offvalue	Sensitivity	Specificity
0.99	0.007	976.0	99.0%	97.4%

Figure [1]: Receiver operative curve for PC/SD in diagnosis of esophageal varices

4. Discussion

As endoscopic studies are not available in all centers, and as it is difficult to provideendoscopy for the detection of esophageal varices everyyear or two in high-risk patients. Thus, there is a need for noninvasive parameters or tests associated with high-risk esophageal varices mayhelp reduce the need for endoscopy, and, above all, lowerthe cost. These parameters could be used to distinguishbetween high- and low-risk patients; the high-risk patientscould then be followed up with endoscopic examinations.

Reviewing literature, there was a principal noninvasive predictor of esophagealvarices. It may be the PC/SD ratio because it has highsensitivity and specificity in patients with hepatic cirrhosis.This ratio could represent an acceptable parameterof clinical relevance in patients with portal hypertension[10,14].

The best cut off value and its sensitivity and specificity still needed to be determined and validated. Thus, the present study was designed to investigate the PC/SD ratio as a predictor of the presence and absence of esophageal varices in Egyptian patients with liver cirrhosis.

In the present work, EV.was reported in 86 cases [68.8%]; Age was significantly increased in cases with EV.[50.32±5.26]VS.[44.51±4.38]. In addition, hepatic encephalopathy and ascites were significantly increased in cases with EV.[25.6%, 47.7%]VS.[7.7%, 28.2% respectively]. Cases with EV had higher grades of child Pugh scoring, low platelet count [117711.50±16529.65] VS.[205905.89±27809.35], high Pugh score [9.29±2.78]VS.[6.53±1.87], high spleen diameter [158.09±11.20]VS.[145.79±7.82], and low PC/SD ratio [751.71±138.30]VS.[1421.21±239.27]. These results are comparable to those reported by Abu El Makaremet al. [15] who reported that, one hundred fifteen men and 60 women were included in the study. The mean age was 48 years [range 36–60 years]. Forty-six patients were Child-Pugh class A [26.3%], 59 were class B [33.7%], and 70 were class C [40%]. EVs were detected in 131 patients [74.9%]. Further, EVs were observed in 14 [30.4%] in the 46 patients with compensated cirrhosis. The presence of EVs correlated significantly with the severity of liver cirrhosis [*p* = 0.001], as measured by Child-Pugh score. In addition, the prevalence of EV.in the present study is comparable to the range of 24% to 80% showed in literature and reminds us that a significant part of cirrhotic patients are unnecessarily submitted to this procedure.

Up to date, the available data do not support the substitution of any method for upper gastrointestinal endoscopy when identifying esophageal varices, but the PC/SD ratio may be helpful for stratifying patients with cirrhosis into different risk categories. This may be especially relevant to those whose general health conditions do not permit the use of an invasive study, but whose history suggests the possibility of esophageal varices, thus reducing the number of endoscopies. A large number of patients undergo an endoscopic study to diagnose chronic hepatic illness, and there is a particular interest in finding noninvasive predictors of esophageal varices that could replace the need for scrutinizing endoscopies and thus lower the economic, medical, and social costs[8, 11, 16].

In the literature, a low PC and splenomegaly are the most studied noninvasive predictors of esophageal varices, and these parameters produce better results than do parameters such as serum bilirubin and albumin levels, Child-Pugh functional classification, and portal vein diameter[6, 17, 18].

In the present study, the analysis of the noninvasive predictors was based on the maximum diameter of the spleen, measured in millimeters using abdominal ultrasound, and the platelet count [PC]. These two parameters were used to calculate the PC/SD ratio. A cutoff point of ≤ 976.0 produced sensitivity of 99.3% and specificity of 97.4%. These results are slightly higher than that reported by Abu El Makaremet al. [15] who reported that, the cutoff of the platelet count:spleen diameter ratio [939.7] was the optimal value for accurate prediction of EVs with an AUC of 0.95. In addition, these results of the present study are better than those of a recent meta-analysis[19], that included 1275 patients and reported a sensitivity of 89% [95%CI: 87-92] and specificity of 74% [95% CI: 70-78]. These parameters are easy to obtain, reproducible, and above all, noninvasive. Another advantage is that no additional expense is involved because these studies are performed routinely in patients with hepatic cirrhosis. The possible explanation for better sensitivity and specificity in the present study may be explained by the fact that, we choose a higher value as a best cut off when compared to studies included in this meta-analysis. The cutoff point for the PC/SD ratio in our study was higher than that reported by Gianniniet al. [14][<909]. This difference is probably influenced by racial characteristics.

The difference in PC/SD ratio between our study and previous studies indicate that it is important to determine a cutoff point for the PC/SD ratio in any specific population.

To explain the lower PC/SD ratio in those patients, it was reported that, thrombocytopenia can be caused by splenic sequestration or by a decrease in hepatic production of thrombopoietin caused by a failing liver and antibody platelet destruction[3, 5, 16].

In addition, in some studies where non-invasive parameters in the diagnosis of esophageal varices was evaluated, have found that splenomegaly can have a

high sensitivity but a low specificity, whereas thrombocytopenia shows the opposite, that is, a low sensitivity and intermediate specificity. For example, in the study by Chalasani*et al.* [20], the PC and splenomegaly independently predicted the presence of esophageal varices. In the study by Madhotra*et al.* [21], 32% of the patients had a PC < 68000/μL without splenomegaly. These differences may reflect differences in the etiology of cirrhosis, action of immunological mediators, or reduction in thrombopoietin and not just splenic sequestration[4].

On the other hand, results of the present study are in contradiction to those reported by Mattos*et al.*[22] who reported that, platelet count/spleen diameter ratio did not show the same negative or positive predictive values, nor the sensitivity, specificity or accuracy published before. Their results do not support the use of this test, once the risk of missing people with EV would be great, and its consequences could be very deleterious. The explanation for this contradiction may be attributed to different inclusion criteria and sample size or racial differences.

In short, it can be said that, the PC/SD ratio is an accurate method for prediction of EV in cirrhotic patients and it can substitute it or at least can be used as a useful noninvasive method for identifying patients with esophageal varices and thereby may help reduce the number of unnecessary endoscopies. It is easy to calculate and can reduce the financial and sanitary burdens of endoscopy units, particularly in developing countries. Additional large multicenter studies on this ratio should be performed.

Conflicts of interest
There are no conflicts of interest

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