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Prediction of Large Esophageal Varices by Ultrasound Doppler and Serum Markers in Portal Hypertensive Cirrhotic Patients in Sharkia

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ABSTRACT

Background: Liver cirrhosis is the most common cause of portal hypertension (PH). Esophageal varices (OV) are the most critical portosystemic shunts that develop secondary to portal hypertension, which is considered a main complication of liver cirrhosis.

Objective: The purpose of this study was to compare the performance of serum marker – based indices and portal vein diameter assessed by ultrasound in patients of portal hypertension due to liver cirrhosis in prediction of large esophageal varices, graded on endoscopy.

Patients and Methods: This cross-sectional study included sixty-six patients with liver cirrhosis who were admitted to Internal Medicine Department, Zagazig University Hospitals for screening the presence of esophageal varices and investigating and/or treating of the patients. The study was performed at a period from September 2019 to February 2020 Diagnosis of liver cirrhosis depended on typical clinical, laboratory, and ultrasound features.

Results: There were statistically significant differences between large and small esophageal varices regarding AST, ALT, INR (higher in patients with large OV), platelet count (higher in patients with small OV).

Conclusions: It could be concluded that Doppler ultrasonography is a non-invasive quantitative technique for the assessment of hemodynamic changes in patients with portal hypertension and appears to be useful in the identification of patients with liver cirrhosis at risk of upper gastrointestinal bleeding.

Keywords: Oesophageal varices, Portal vein diameter, Serum markers, Ultrasound doppler, Portal Hypertensive

INTRODUCTION

Portal hypertension is a syndrome characterized by an increased portal pressure gradient. Cirrhosis is the most common cause of portal hypertension. Cirrhosis is defined as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over weeks to years [(1)].

Gastroesophageal varices are a direct consequence of portal hypertension that, in cirrhosis, results from both increased resistance to portal flow and increased portal venous blood inflow. Increased resistance is both structural (distortion of liver vascular architecture by fibrosis and regenerative nodules) and dynamic (increased hepatic vascular tone due to endothelial dysfunction and decreased nitric oxide bioavailability) [(2)].

A number of non-invasive tests of fibrosis have been studied in identifying patients with portal hypertension and large varices. On the other hand, the performance of non-invasive tests in assessing the response to nonselective beta-blockers is suboptimal and often unclear [(3)].

Elastography is a promising imaging technique because the elastic modulus of tissues measured by this technique provides the most broad-banded properties compared with other quantitative values measured by computed tomography (attenuation value), magnetic resonance (MR) imaging (T1 relaxation time), and conventional ultrasonography (bulk modulus) [(4)].

The gold standard for assessment of risk of variceal bleeding is esophagogastroduodenoscopy, possibly with endoscopic color Doppler ultrasonography. However, despite its advantages, esophagogastroduodenoscopy is an unpleasant and expensive test for regular follow-ups and also carries the risk of bleeding due to manipulation, especially in patients with large varices. Moreover, there is evidence for the use of ultrasonography instead of endoscopy in determining the presence of varices [(5)].

In spite of moderate to high diagnostic accuracy, noninvasive methods for the prediction of varices need high skills in elastography and ultrasound techniques. By comparison, aspartate aminotransferase-to-platelet ratio (APRI), aspartate aminotransferase-to-alanine aminotransferase ratio (AAR), FIB-4, FI, King, Lok, Forns, and FibroIndex scores, which are primarily composed of regular laboratory tests and readily available demographic data, do not need any special experiences in imaging techniques. They are more convenient and cheap in clinical practices [(6)].

So we designed this study to compare the performance of serum marker – based indices and portal vein diameter assessed by ultrasound in patients of portal hypertension due to liver cirrhosis in prediction of large esophageal varices, graded on endoscopy.

PATIENTS AND METHODS

This cross-sectional study included a total of 66 patients with liver cirrhosis, attending at Department

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of Internal Medicine, Zagazig University Hospitals. Patients were screened for the presence of esophageal varices, investigated and/or treated. This study was conducted between from September 2019 to February 2020.

Ethical Consideration:

This study was ethically approved by the Medical Ethical Committee, Zagazig Faculty of Medicine. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria:

Patients having signs of portal hypertension with liver cirrhosis, as diagnosis was based on physical findings, laboratory investigations, ultrasonographic findings or histopathological findings whenever available.

Exclusion criteria:

Patients presenting with variceal bleeding or history of endoscopic therapy (sclerotherapy or band ligation). Patients presenting with portal vein thrombosis. Patients presenting with gastro-esophageal varices. Patients on current or past treatment with beta-adrenergic receptor blockers. Patients with hepatocellular carcinoma. Pregnant and lactating women. Patient refusal.

All the participants were subjected to full history taking, clinical examination including body built, stigmata of chronic liver disease (such as spider nevi, palmar erythema, jaundice, symptoms of bleeding tendency or lower limb edema) and abdominal examination for the liver, spleen and presence of ascites or abdominal masses. Evaluation of the severity of liver disease was done using the Child's score. This score system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin and prothrombin time.

Laboratory investigations:

Included complete blood count (CBC), liver function tests (alanine transaminase, ALT, aspartate transaminase, AST, serum albumin, serum total and direct bilirubin and prothrombin time). Viral markers (Anti-HCV Ab and HBsAg). Serum creatinine.

All patients underwent an upper gastrointestinal endoscopy(UGIE) using a videoscope. All endoscopies were performed by experienced endoscopists, and a grading classification of I–IV was used**,** according to AASLD practice guidelines criteria (no varices, small varices and large varices)**.**

Video gastroscope was used for endoscopy after taking informed written consent from each patient for the procedure under topical anaesthesia of oropharynx.

Aspartate aminotrasferase to Platelet Ratio Index (APRI), Fibrosis 4 score (FiB4), Forn'x index and Lok score were calculated for all patients.

APRI = [(AST/ULN) * 100] / platelet count 10^9/L] (ULN= upper limit of normal)

FiB4= [age (years)*AST (IU/L)] / platelet count (10^9/L) * ALT (IU/L)1/2]

Forn's Index = 7.811-3.131*In [platelet count (109/L)] + 0.781*

In [GGT(IU/l)] +3.467* In[age(years))]-0.014[cholesterol (mg/dl)]

Lok Score = log odds = -5.556 -0.0089* platelet count (10^3/mm^3) + 1.26* (AST/ALT) +5.27* INR

Lok= [exp (log odds)]/ [1+exp (log odds)]

Statistical Analysis

Data analysis was done by using Epi-Info version 6 and SPP for Windows version 8. Paired t test was used for comparison of paired observation. The results was considered: Significant when the probability of error is less than 5% ($p < 0.05$). Non-significant when the probability of error is more than 5% ($p > 0.05$). Highly significant when the probability of error is less than 0.1% ($p < 0.001$). The smaller the p-value obtained, the more significant are the results.

RESULTS

Table (1): Distribution of the studied patients according to demographic characteristics

Demographic characteristics	Total	
	N=66	%
Gender:		
Male	43	65.2
Female	23	34.8
Age: (years)		
Mean ± SD	51.73 ± 8.82	
Range	33 - 68	

About 35% of the studied patients were females with age ranged from 33 to 68 years and mean age was 51.73 years table 1.

Table (2): Distribution of the studied patients according to laboratory data**,** Doppler findings**,** OV grading by endoscopy

	Mean ± SD
Laboratory data	
Platelet count (x10^9 /L)	93.56 ± 5.5
Hemoglobin (g /dl)	11.06 ± 0.93
TLC (x10^9 /L)	3.94 ± 0.71
AST (U/L)	56.83 ± 5.73
ALT (U/L)	52.09 ± 5.16
Serum albumin (g/dl)	3.42 ± 0.57
Total bilirubin (mg/dl)	1.15 ± 0.33
Prothrombin time (seconds)	82.55 ± 7.29
INR	1.21 ± 0.13
Doppler findings	
Splenic index	110.12 ± 6.76
Splenoportal index	8.5 ± 0.92
Portal vein velocity	12.75 ± 1.05
Hepatic artery resistive index	0.72 ± 0.16
Hepatic artery pulsatility index	1.49 ± 0.16
Splenic artery resistive index	0.68 ± 0.12
Splenic artery pulsatility index	1.4 ± 0.17
OV grading by endoscopy	
I, II	26
III, IV	40

Platelet count in the studied patients ranged from 50 to 160 (x10^9 /L) with mean 93.56(10^6/mm^3). Total leucocytic count in the studied patients ranged from 2.9 to 5.5 (10^3/mm^3) with mean 3.94 (x10^9 /L). Hemoglobin level in the studied patients ranged from 9.5 to 12.9 (g/dL) with mean 11.06 (g/dL). AST in the studied patients ranged from 35 to 93 (U/L) with mean 56.83 (U/L). ALT in the studied patients ranged from 30 to 58 (U/L) with mean 52.09 (U/L). Serum albumin in the studied patients ranged from 2.5 to 5 (g/dL) with mean 3.42 (g/dL). Total bilirubin in the studied patients ranged from 0.5 to 2.5 (mg/dL) with mean 1.15 (mg/dL). Prothrombin time ranged from 60 to 95 second with mean 82.55 second. INR ranged from 1.01 to 1.5 with mean 1.21 (table 2).

Splenic index ranged from 99 to 136 with mean 110.12 while splenoportal index ranged from 6.45 to 10.9 with mean 8.5. Portal vein velocity ranged from 10.2 to 15 mm/second. Hepatic artery resistive index ranged from 0.43 to 0.99 with mean 0.72 while splenic artery resistive index ranged from 0.49 to 0.98. Hepatic artery pulsatility index ranged from 1.19 to 1.82 with mean 1.49 while splenic artery pulsatility index ranged from 1.12 to 1.76 with mean 1.4. (table 2) showed that larger percentage of the studied patients had grade III and IV OV (large OV).

Table (3): Comparison between the studied patients regarding liver function test and bleeding profile, serum markers**,** Doppler ultrasonographic findings

LFT	**OV**		**Test**	
	Large (n=40)	**Small (n=26)**	**t**	**p**
	Mean ± SD	**Mean ± SD**		
AST (U/L)	62.98 ± 15.74	47.38±10.19	4.885	<0.001**
ALT (U/L)	58.05±5.04	42.92±10.03	4.902	<0.001**
Serum albumin (g/dl)	3.43 ± 0.61	3.41 ± 0.5	0.112	0.911
Total bilirubin (mg/dl)	1.19 ± 0.4	1.09 ± 0.18	1.376	0.174
Prothrombin time (seconds)	82.1 ± 7.38	83.23 ± 7.25	-0.612	0.542
INR	1.25 ± 0.13	1.15 ± 0.11	3.197	0.002*
Serum markers				
APRI	2.01 ± 0.62	1.1 ± 0.25	8.283	<0.001**
FIB 4	1.44 ± 0.49	1.08 ± 0.32	3.375	0.001**
Lok score	0.82 ± 0.09	0.7 ± 0.1	4.983	<0.001**
Doppler parameters				
Splenoportal index	8.701 ± 0.962	8.199 ± 0.771	2.232	0.029*
Splenic index	111.925±7.244	107.346±4.858	2.832	0.006*
Portal vein velocity	12.47 ± 1.069	13.187± 0.862	-2.864	0.006*
Hepatic artery resistive index	0.751 ± 0.155	0.67 ± 0.156	2.074	0.042*
Hepatic artery pulsatility index	1.521±0.159	1.431±0.143	2.346	0.022*
Splenic artery resistive index	0.642 ± 0.085	0.747 ± 0.149	-3.658	0.002*
Splenic artery pulsatility index	1.353 ± 0.169	1.461 ± 0.145	-2.682	0.009*

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant t: Independent sample t test

Table 3; there was statistically significant difference between the studied patients regarding AST, ALT, and INR (higher in patient with large OV). There is non-significant difference between them regarding total bilirubin, prothrombin time or serum albumin. Table 3; there was statistically significant difference between the studied patients regarding APRI, FIB-4 and Lok score (all were higher in patients with large OV). Table 3; there was statistically significant difference between the studied patients regarding splenoportal index, splenic index, hepatic artery pulsatility index, hepatic artery resistive index (all were higher in patients with large OV). There is also significant difference between them regarding Portal vein velocity, splenic artery resistive index and splenic artery pulsatility index (higher in patients with small OV).

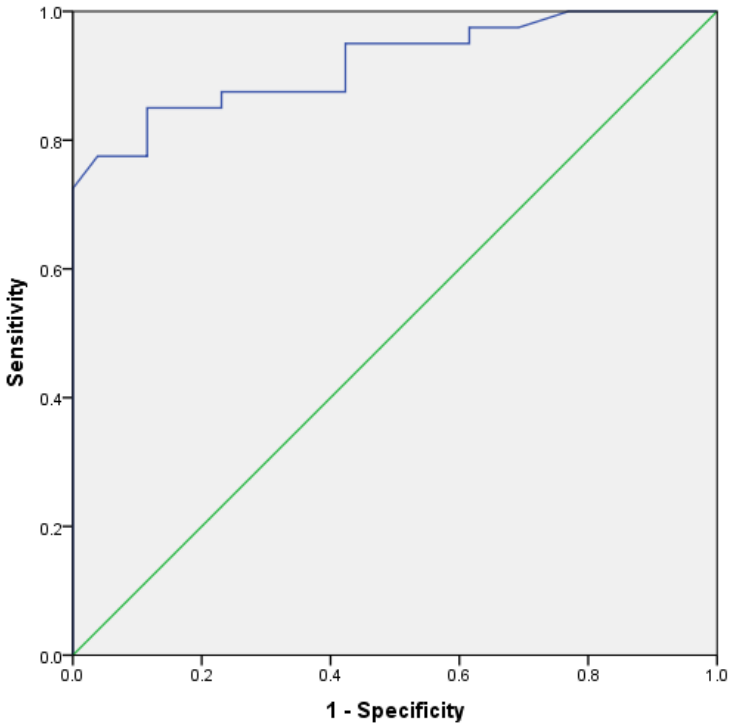

Figure (1): ROC curve showing performance of APRI in diagnosis of large OV among the studied patients.

The best cutoff of APRI in diagnosis of large OV is ≥1.3017 with area under curve 0.919, sensitivity 87.5%, specificity 76.9%, positive predictive value85.4%, negative predictive value 80% and accuracy 83.3% (p<0.05). Figure 1

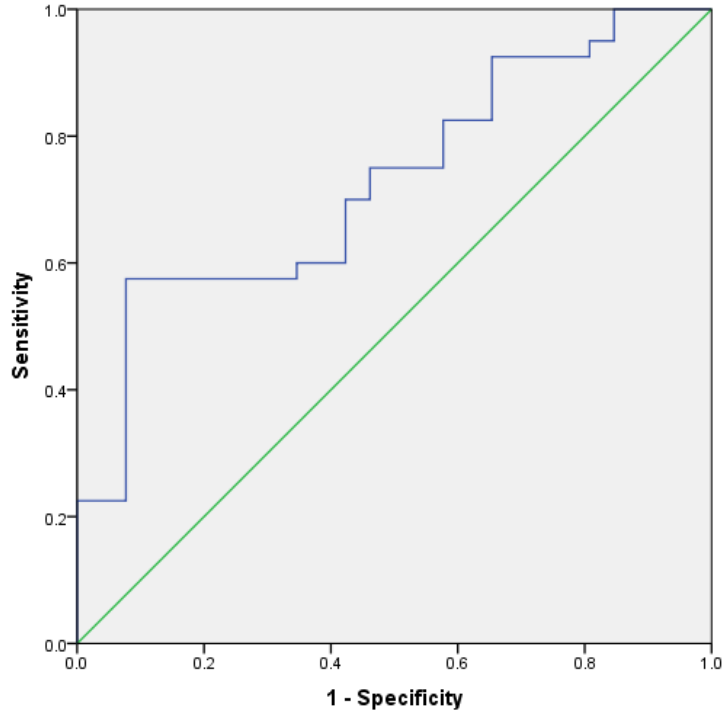

Figure (2): ROC curve showing performance of FIB-4 in diagnosis of large OV among the studied patients.

The best cutoff of FIB-4 in diagnosis of large OV is ≥1.2251 with area under curve 0.728, sensitivity 60%, specificity 61.5%, positive predictive value 70.6%, negative predictive value 60% and accuracy 60.6% (p<0.05). Figure 2

DISCUSSION

In the current study, male patients (65%) were more than female ones (35%). This observation goes in agreement with **Cherian *et al.*** [7] who stated that males were 61.5% of cases. **Siregar *et al.*** [8] found that most patients were male (34 persons or 66.7%). **Wang *et al.*** [9] evaluated the diagnostic efficacy of noninvasive liver fibrosis indexes in the diagnosis of PH in 238 cirrhotic patients (161 males and 77 females).

This observeration does not go in agreement with **Barrera *et al.*** [1] who observed gender distribution was male 29 (43.3%) and female 38 (56.7%). HREV patients showed a higher proportion of females [25/34 (73.5%)] compared with no HREV patietns [13/33 (29.4%)].

The current study showed that platelet count in the studied patients ranged from 50 to 160 ($x10^9$ /L) with mean of 93.56 ($x10^9$ /L). Total leucocytic count in the studied patients ranged from 2.9 to 5.5 ($x10^9$ /L) with mean of 3.94 ($x10^9$ /L). Hemoglobin level in the studied patients ranged from 9.5 to 12.9 g/dL with mean of 11.06 g/dL. **Siregar *et al.*** [8] found that the medians of platelet count and gamma GT of the patients in their study were respectively 104 (31- 144) ($x10^9$ /L) and 66 (6-530) U/L, while mean total cholesterol was 149.12 ± 67.55 mg/dL.

In our study, AST ranged from 35 to 93 U/L with mean of 56.83 U/L. ALT ranged from 30 to 58 U/L with mean of 52.09 U/L. Serum albumin ranged from 2.5 to 5 g/dL with mean of 3.42 g/dL. Total bilirubin ranged from 0.5 to 2.5 mg/dL with mean of 1.15 mg/dL. Prothrombin time ranged from 60 to 95 seconds with mean 82.55 seconds. INR ranged from 1.01 to 1.5 with mean 1.21.

Sharma *et al.* [10] found that platelet count and splenomegaly were independent predictors for presence of large oesophageal varices. **Barrera *et al.*** [1] observed higher total bilirubin (2.34 ± 2.3 versus 2.09 ± 2.37).

Serag *et al.* [11] found that mean of albumin was 2.5 g/dl, mean of total bilirubin was 2.9 mg/dl and mean of prothrombin concentration was 58%. **Cherian *et al.*** [7] concluded that the presence and higher grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and spleen diameter.

The current study stated that splenic index ranged from 99 to 136 with mean of 110.12, while splenoportal index ranged from 6.45 to 10.9 with mean of 8.5. Portal vein velocity ranged from 10.2 to 15 mm/second. Hepatic artery resistive index ranged from 0.43 to 0.99 with mean of 0.72, while splenic artery resistive index ranged from 0.49 to 0.98. Hepatic artery pulsatility index ranged from 1.19 to 1.82 with mean of 1.49, while splenic artery pulsatility index ranged from 1.12 to 1.76 with mean of 1.4.

Other authors have also evaluated the use of ultrasound in predicting variceal bleeding. **Schmassman *et al.*** [12] argued that ultrasonography is a good way to predict recurrent variceal bleeding. **Pilette *et al.*** [13] have proposed non-invasive screening of patients for primary prevention of gastrointestinal bleeding, based on clinical, laboratory and ultrasound findings.

In this studied patients, larger percentage had grade III and IV OV (large OV). **Plestina *et al.*** [14] examined the role of Doppler ultrasonography of the portal vein in predicting esophageal variceal bleeding in 99 patients with liver cirrhosis and portal hypertension by comparing the ultrasound data to the endoscopic findings. There were 48 patients (48.5%) with grade I and grade II varices, 41 patients (41.4%) with grade III varices and 10 patients (10.1%) with grade IV varices. **Siregar *et al.*** [8] found that there were esophageal varices of F1 size in 15 people (29.4%), F2 size in 19 people (37.3%), and F3 size in 17 people (33.3%).

In this study, there are statistically significant differences between large and small oesophageal varices regaring AST, ALT, INR (higher in patients with large OV), platelet count (higher in patients with small OV). This is in line with **Suk** [15] who reported that low platelet count was an independent risk factor or predictor for the presence of esophageal varices and their size.

This study documented that there is statistically significant difference between the studied patients regarding APRI, FIB-4 and Lok score (all were higher in patients with large OV). **Vaishnav *et al.*** [16] compared the serum markers-based indices between large oesophageal varices and control group. There was no statistically significant difference.

The current study found that there are statistically significant differences between the studied patients regarding splenoportal index, splenic index, hepatic artery pulsatility index, hepatic artery resistive index (all were higher in patients with large OV). There is also significant difference between them regarding portal vein velocity, splenic artery resistive index and splenic artery pulsatility index (higher in patients with small OV).

Vaishnav *et al.* [16] showed that portal vein size was significantly different. The mean portal vein diameter in control group was significantly lower than varices group in comparison with large varices having mean variceal size larger.

In this study, liver biopsy and elastography were not taken as variables, but ultrasound Doppler and serum-based indices were compared as an indirect evidence of portal hypertension due to liver fibrosis based on ultrasonographic evaluation.

This study illustrated that area under ROC curve was excellent with the best cutoff point for APRI to diagnose large OV among the studied patients. The best cutoff of APRI is ≥1.3017 with area under curve of 0.919, sensitivity of 87.5%, specificity of 76.9%, positive predictive value of 85.4%, negative predictive value of 80% and accuracy of 83.3% ($p<0.05$).

Forestier *et al.* [17] have shown the APRI correlates with HVPG, and an APRI of ≥1.09 had a sensitivity 66%, specificity 73%, positive predictive value 85%, negative predictive value 47%, and diagnostic accuracy 68% for predicting HVPG>12 mmHg. **Wang *et al.*** [18] reported that lower APRI cut off

(0.77) predicted the esophageal varices with a sensitivity of 71%.

Raza *et al.*[19] determined the diagnostic accuracy of Aspartate Aminotransferase Platelet Ratio Index (APRI) as a predictor for esophageal varices. Area under the receiver operating characteristic (ROC) curve was 0.559 [95% CI (0.471 to 0.644)] with 100% sensitivity and 100% specificity. They signified that APRI is an unsuitable replacement for endoscopy and cannot help in the screening of esophageal varices among cirrhotics because of low specificity and negative predictive value.

In this study, the best cutoff of FIB-4 in diagnosis of large OV is ≥1.2251 with area under curve of 0.728, sensitivity of 60%, specificity of 61.5%, positive predictive value of 70.6%, negative predictive value 60% and accuracy of 60.6% ($p<0.05$).

Xiao *et al.*[20] suggested that FIB-4 should have moderate sensitivity and specificity of detecting the presence of liver fibrosis. The mean AUC of FIB-4 for the prediction of significant fibrosis was 0.76, respectively. **Kraja *et al.* [21]** suggested that the FIB-4 is the most reliable predictor of esophageal varices in liver cirrhosis patients. Despite the low diagnostic accuracy, FIB-4 is the most efficient non-invasive liver fibrosis marker which can be used as an initial screening tool for cirrhotic patients in the areas with lack of endoscopy facilities.

CONCLUSIONS

It could be concluded that Doppler ultrasonography is a non-invasive quantitative technique for the assessment of hemodynamic changes in patients with portal hypertension and appears to be useful in the identification of patients with liver cirrhosis at risk of upper gastrointestinal bleeding.

We recommend follow up of cirrhotic patients of high risk to have esophageal varices by upper endoscopy, variceal band ligation and selective beta blockers. Future studies as elastography and CT should be performed in combination with ultrasound Doppler and serum markers as predictors for esophageal varices in larger samples.

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