COMPARATIVE STUDY FOR THE PREDICTION OF LARGE OESOPHAGEAL VARICES BY ULTRASOUND DOPPLER AND SERUM MARKERS IN PORTAL HYPERTENSIVE CIRRHOTIC PATIENTS IN SHARKIA

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ABSTRACT

Background: Portal hypertension is the most frequently complication of hepatic cirrhosis, and subsequently leads to development of esophagogastric varices. The prevalence of esophageal varices among these patients may range from 60 to 80%. The purpose of this study was to compare the validity of serum marker – based indices and portal vein diameter assessed by ultrasound in patients of portal hypertension due to chronic liver cirrhosis in prediction of large oesophageal varices, graded on endoscopy.

Methods: This cross-sectional study was conducted on sixty six patients with liver cirrhosis to predict and manage oesophageal varices in patients with portal hypertension due to liver cirrhosis. Diagnosis of liver cirrhosis depended on typical clinical, laboratory, and ultrasound features. The study was carried on for at least six months.

Results: There is statistically significant difference between the studied patients regarding APRI, FIB-4 and Lok score (all were higher in patients with large OV). Also, 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).

Conclusions: The Forns index, APRI, FIB-4 and LOK were non-invasive markers, with modest diagnostic accuracy in the detection of PH in patients with cirrhosis in our patients.

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

I. INTRODUCTION

Liver cirrhosis is the most common cause of portal hypertension (PH)(¹). Esophageal varices are the most critical portosystemic shunts that develop secondary to portal hypertension, which is considered a main complication of liver cirrhosis(²).

Variceal bleeding occurs in 20–40% of cirrhotic patients with esophageal varices and is associated with a high morbidity and mortality. The mortality associated with each episode of variceal bleeding ranges from 17% to 57%(³).

In recent years, a number of non-invasive tests of fibrosis have been studied in identifying patients with portal hypertension and large varices. Leung et al. (⁴) supported the use of such tests as initial evaluation to select patients for varices screening. On the other hand, the performance of non-invasive tests in assessing the response to nonselective beta-blockers is suboptimal and often unclear.
Due to the less accuracy of individual markers, scores or indices combining array of markers are being used due to “sufficient” diagnostic accuracy. APRI score is based on AST and platelet count. FIB4 score combines the platelet count, ALT, AST and age. Lok index is an extrapolation of the APRI combining platelet count, INR and AST/ALT ratio. So we designed this study to compare the validity of serum marker – based indices and portal vein diameter assessed by ultrasound in patients of portal hypertension due to chronic liver cirrhosis in prediction of large oesophageal varices, graded on endoscopy.

II. PATIENTS AND METHODS:

This cross-sectional study was conducted on sixty six patients with liver cirrhosis to predict and manage oesophageal varices in patients with portal hypertension due to liver cirrhosis, who were admitted to Internal Medicine Department, Zagazig University Hospitals during period from September 2019 to February 2020. Age ranged from 33 to 68 years and mean age was 51.73 years. Males were more than females, about 35% of the studied patients were females.

Inclusion Criteria were 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 were patients presenting with variceal bleed or history of endoscopic therapy (sclerotherapy or band ligation). Patients presenting with portal vein thrombosis. Patients presenting with gastrointestinal 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 was taken from all patients, Clinical examination including body built, stigmata of chronic liver disease 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.

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 aminotransferase to Platelet Ratio Index (APRI), Fibrosis 4 score (FIB4), Forn'x index and Lok score were calculated for all patients.

\[
\text{APRI} = \frac{[(\text{AST/ULN}) \times 100]}{\text{platelet count (10^9/L)}}, \quad \text{ULN}= \text{upper limit of normal}
\]

\[
\text{FIB4} = \frac{\text{age (years)} \times \text{AST (IU/L)}}{\text{platelet count (10^9/L)} \times \text{ALT (IU/L)}^{1/2}}
\]

\[
\text{Forn's Index} = 7.811-3.131*\ln \text{[platelet count (10^9/L)]} + 0.781^* \ln \text{[GGT (IU/I)]} + 3.467^* \ln \text{[age(years)]} - 0.014 \times \text{cholesterol (mg/dl)}
\]

\[
\text{Lok Score} = \log \text{odds} = -5.556 - 0.0089 \times \text{platelet count (10^3/mm^3)} + 1.26^* \times \text{AST/ALT} + 5.27^* \times \text{INR}
\]

\[
\text{Lok} = \exp \text{(log odds)} / [1 + \exp \text{(log odds)}]
\]

Statistical Analysis:

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8 (Dean, 2006). Paired t test was used for comparison of paired observation. Highly significant when the probability of error is less than 0.1% (p < 0.001).
RESULTS:

Table (1): Distribution of the studied patients according to laboratory data, Doppler findings, OV grading by endoscopy

<table>
<thead>
<tr>
<th>laboratory data</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>93.56 ± 25.5</td>
<td>50 - 160</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.06 ± 0.93</td>
<td>9.5 – 12.9</td>
</tr>
<tr>
<td>TLC</td>
<td>3.94 ± 0.71</td>
<td>2.9 – 5.5</td>
</tr>
<tr>
<td>AST</td>
<td>56.83 ± 15.73</td>
<td>35 - 93</td>
</tr>
<tr>
<td>ALT</td>
<td>52.09 ± 15.16</td>
<td>30 - 58</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.42 ± 0.57</td>
<td>2.5 – 5</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.15 ± 0.33</td>
<td>0.5 – 2.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>82.55 ± 7.29</td>
<td>60 – 95</td>
</tr>
<tr>
<td>INR</td>
<td>1.21 ± 0.13</td>
<td>1.01 – 1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Doppler findings</th>
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</thead>
<tbody>
<tr>
<td>Splenic index</td>
<td>110.12 ± 6.76</td>
<td>99 - 136</td>
</tr>
<tr>
<td>Splenoportal index</td>
<td>8.5 ± 0.92</td>
<td>6.45 – 10.9</td>
</tr>
<tr>
<td>Portal vein velocity</td>
<td>12.75 ± 1.05</td>
<td>10.2 – 15</td>
</tr>
<tr>
<td>Hepatic artery resistive index</td>
<td>0.72 ± 0.16</td>
<td>0.43–0.99</td>
</tr>
<tr>
<td>Hepatic artery pulsatility index</td>
<td>1.49 ± 0.16</td>
<td>1.19–1.82</td>
</tr>
<tr>
<td>Splenic artery resistive index</td>
<td>0.68 ± 0.12</td>
<td>0.49–0.98</td>
</tr>
<tr>
<td>Splenic artery pulsatility index</td>
<td>1.4 ± 0.17</td>
<td>1.12 – 1.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OV grading by endoscopy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I, II</td>
<td>26</td>
<td>39.4</td>
</tr>
<tr>
<td>III, IV</td>
<td>40</td>
<td>60.6</td>
</tr>
</tbody>
</table>

Platelet count in the studied patients ranged from 50 to 160 (10⁶/mm³) with mean 93.56(10⁶/mm³). Total leucocytic count in the studied patients ranged from 2.9 to 5.5 (10³/mm³) with mean 3.94 (10³/mm³). 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 1).

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. (table1) that larger percentage of the studied patients had grade III and IV OV (large OV).

Figure (1): 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.

Figure (1): Combined bar chart showing comparison between the studied groups regarding AST and ALT
Table (2): Comparison between the studied patients regarding serum markers

<table>
<thead>
<tr>
<th>OV</th>
<th>Large (n=40)</th>
<th>Small (n=26)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APRI</td>
<td>2.01 ± 0.62</td>
<td>1.1 ± 0.25</td>
<td>8.283</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>FIB 4</td>
<td>1.44 ± 0.49</td>
<td>1.08 ± 0.32</td>
<td>3.375</td>
<td>0.001**</td>
</tr>
<tr>
<td>Lok score</td>
<td>0.82 ± 0.09</td>
<td>0.7 ± 0.1</td>
<td>4.983</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

*p<0.05 is statistically significant  **p≤0.001 is statistically highly significant

Independent sample t test

Table 2: There was statistically significant difference between the studied patients regarding APRI, FIB-4 and Lok score (all were higher in patients with large OV).

**Figure 2:** 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 (2):** Doppler ultrasonographic
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 value 85.4%, negative predictive value 80% and accuracy 83.3% (p<0.05). Figure 3

Figure (3): ROC curve showing performance of APRI in diagnosis of large OV among the studied patients

Figure (4): 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 4

The best cutoff of Lok score in diagnosis of large OV is ≥0.755 with area under curve 0.815, sensitivity 82.5%, specificity 80.8%, positive predictive value 86.8%, negative predictive value 75% and accuracy 81.8% (p<0.05). Figure 5

**III. DISCUSSION:**

The current study showed that platelet count in the studied patients ranged from 50 to 160 x 10^6/mm^3 with mean of 93.56 x 10^6/mm^3. Total leucocytic count in the studied patients ranged from 2.9 to 5.5 x 10^3/mm^3 with mean of 3.94 x 10^3/mm^3. 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. (6) found that the medians of platelet count and gamma GT of the patients in this 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 this study, AST in the studied patients ranged from 35 to 93 U/L with mean of 56.83 U/L. ALT in the studied patients ranged from 30 to 58 U/L with mean of 52.09 U/L. Serum albumin in the studied patients ranged from 2.5 to 5 g/dL with mean of 3.42 g/dL. Total bilirubin in the studied patients 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.

Serag et al. (7) found that mean of albumin was 2.5 gm/dl, mean of total bilirubin was 2.9 mg/dl and mean of prothrombin concentration was 58%. Cherian et al. (8) 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.
This 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.

According to Yin et al.\(^9\), the ratio of the splenic/portal vein flow volume and the spatial distribution of flow velocity in a cross-section of these vessels (color Doppler velocity profile) are valuable parameters for assessing the risk.

Giannini et al.\(^{10}\) shows that the mean of spleen diameter in patients with varices is 159.7±29.9. Barrera et al.\(^{11}\) observed that larger spleen diameter was observed in HREV patients compared with no HREV patients (136.4 ± 23.9 versus 113.5 ± 20).

In a study reported by Sudha Rani et al.\(^{12}\), measurement of PVD (> 13 mm) and ultrasound findings were independent non-invasive predictors for presence of oesophageal varices in patients with chronic liver disease with portal hypertension.

In this study, larger percentage had grade III and IV OV (large OV). Plestina et al.\(^{13}\) 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.\(^{6}\) 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 regarding AST, ALT, INR (higher in patients with large OV), platelet count (higher in patients with small OV). This is in line with Suk\(^{14}\) reporting that low platelet count was an independent risk factor or predictor for the presence of oesophageal 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.\(^{15}\) 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.\(^{15}\) 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).

In a study conducted by Civan et al.\(^{16}\), an APRI score of 0.4 was used to guide early management of acute upper gastrointestinal bleed. Similarly, another study with a value of ≥1.0 showed a sensitivity, specificity, positive predictive value and negative predictive value 68%, 89%, 77%, and 83% respectively for envisaging EV. Globally, the AST/ALT ratio detected EV in 81% patients. The AST/ALT ratio cutoffs were different for different pathological basis; however, they cannot foretell EV accurately\(^{17}\). Xiao et al.\(^{18}\) suggested that APRI should have moderate
sensitivity and specificity of detecting the presence of liver fibrosis. The mean AUC of APRI for the prediction of significant fibrosis was 0.72.

Wang et al.\(^{19}\) found that APRI exhibited the best performance, as indicated by AUC of 0.742 to detect Clinically Significant PH (CSPH). APRI also exhibited the highest accuracy (76.89%) and the lowest -LR (0.31). To detect Severe PH (SPH), APRI showed good performance, as indicated by AUC of 0.722.

Sarkar et al.\(^{20}\) assessed the value of APRI for predicting esophageal varices in cirrhotic patients. They concluded that APRI had a wide range of cut of points that proves there is no satisfactory cutoff value for APRI to be used as a predictor of EVs. Variceal bleeding is a serious complication of cirrhosis; APRI must have an excellent negative predictive value to exclude EVs.

Raza et al.\(^{21}\) 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.\(^{18}\) 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.\(^{22}\) suggested that the 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.

The current study found that the best cutoff of Lok score in diagnosis of large OV is ≥0.755 with area under curve of 0.815, sensitivity of 82.5%, specificity of 80.8%, positive predictive value of 86.8%, negative predictive value of 75% and accuracy of 81.8% (p<0.05).

Sungkar et al.\(^{23}\) evaluated association of esophageal varices and Lok Score as non-invasive parameter in liver cirrhosis patients. They concluded that Lok score was significantly associated with esophageal varices. Lok score is a good noninvasive predictor of large esophageal varices in cirrhotic patients.

Wang et al.\(^{19}\) found that the Lok index exhibited good performance to detect CSPH, as indicated by AUC of 0.740. To detect SPH, Lok index showed the best performance, as indicated by AUC of 0.717. The Lok index exhibited the highest accuracy (68.91%) with the lowest -LR (0.45).

IV. CONCLUSIONS

The Forns index, APRI, FIB-4 and LOK were non-invasive markers, with modest diagnostic accuracy in the detection of PH in patients with cirrhosis in our patients.

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