Measurement of Liver and Spleen Stiffness by Fibroscan in Comparison to other Validated Indices for Non-Invasive Assessment of Esophageal Varices in Egyptian Patients with HCV-Related Cirrhosis

Mohsen M Maher¹, Tarek Youssef¹, Wesam A Ibrahim¹*, Sara M Abdelhakam², Ghada Abdelrahman¹, Ahmed Hussein³

¹Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
²Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
³Department of Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

*Correspondence to: Wesam A Ibrahim, MD, Assistant Professor of Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Abbassia, Cairo 11341, Egypt.
E-mail: wesamahmed74@yahoo.com

Abstract

Background and Aim: Several investigators have devised non-invasive predictors for presence of esophageal varices (EV) in cirrhotic patients, thus avoiding unnecessary endoscopic screening. This work aimed at evaluating the role of liver and spleen stiffness measurements by Fibroscan in comparison to other validated indices for non-invasive assessment of EV in Egyptian patients with HCV-related cirrhosis. Methods and Material: This cross-sectional study included sixty patients with HCV-related cirrhosis who underwent complete clinical evaluation, laboratory investigations, abdominal ultrasonography, liver and spleen stiffness measurements (LSM and SSM) using Fibroscan and upper gastrointestinal endoscopy. Also, non-invasive predictive scores were calculated: AST-to-ALT ratio (AAR), platelet count/spleen diameter ratio (PSR) and AST-to-platelet ratio index (APRI). The diagnostic performance of each parameter was assessed using receiver operating characteristic (ROC) curves.

Results: Patients were classified into two groups; Group 1: 33 patients (55%) with EV, and Group 2: 27 patients (45%) with no EV. There was a highly significant difference between the two groups regarding spleen diameter, PSR, APRI, LSM and SSM (P < 0.01). SSM showed a good performance as regards EV detection in comparison to LSM. At cut-off value ≥29 for SSM, sensitivity was 94.4%, specificity 86.4%, PPV 85% and NPV 95% (AUROC 0.934). Conclusion: Spleen stiffness measurement is a sensitive and reliable tool for detection of EV.

Key words: Spleen stiffness measurement, Liver stiffness measurement, Fibroscan, Esophageal varices, Non-invasive assessment, Cirrhosis, HCV.

Introduction

The development of esophageal varices (EV) is a major complication of portal hypertension which may occur in up to 90% of cirrhotic patients and variceal bleeding is life threatening. Therefore, guidelines recommend upper gastro-intestinal endoscopy for variceal detection in all cirrhotic patients, to be repeated after 1–3 years depending on clinical situation and results of the first endoscopy¹. However, a generalized
screening program of periodic upper endoscopy in cirrhotic patients may lead to low compliance since endoscopy is an unpleasant, uncomfortable, invasive and costly procedure\(^2\).

Accordingly, several investigators have devised predictors to discriminate cirrhotic patients at a high risk for presence of varices from those at a low risk, thus avoiding endoscopic screening in the latter category\(^3,4\).

Most predictors are based on combinations of platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST/ALT ratio, spleen diameter, albumin, increased portal vein diameter at ultrasonography, prothrombin time, liver stiffness, ascites, Child–Pugh class and the Fibro Test\(^5\).

This work aimed at evaluating the role of liver and spleen stiffness measurements by Fibroscan in comparison to other validated indices for non-invasive assessment of esophageal varices in Egyptian patients with HCV-related cirrhosis.

**Patients and Methods**

This cross-sectional study was conducted on sixty consecutive patients with HCV-related cirrhosis who were presented to Internal Medicine and Tropical Medicine Departments and outpatient clinics at Ain Shams University Hospital, during the period from September 2014 to December 2015.

Cirrhotic patients were diagnosed by clinical, laboratory and radiological criteria in the form of:

- Clinical stigmata suggestive of liver cirrhosis i.e. (bleeding tendency, jaundice, gynecomastia, lower limb edema, splenomegaly and ascites).
- Laboratory manifestations of liver cell failure i.e. (low serum albumin, increased serum bilirubin and INR).
- Radiological data implying hepatic affection i.e. (coarse liver, splenomegaly and ascites). This was confirmed by Fibroscan examination showing liver stiffness measurement of 14.5-75 kilopascal (Kpa)(F4)\(^6\).

Patients with co-infection with hepatitis B, other causes of liver disease, acute liver cell failure, massive ascites, variceal bleeding, hepatocellular carcinoma, portal, splenic or hepatic vein thrombosis, obesity (BMI \(>35\) kg/m\(^2\)), other co-morbid diseases, as well as those who had previously underwent sclerotherapy or band ligation of EV, treatment with B-blockers, transjugular intrahepatic portosystemic shunt or liver transplantation were excluded.

Informed written consent was obtained from each patient prior to inclusion. The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

All of the included patients underwent:

1. A complete clinical evaluation;
2. Laboratory investigations: CBC, liver and renal profile, HBs Ag, HBcAb IgM and IgG and HCV Ab using third generation ELISA;
3. Abdominal ultrasonography for evaluation of liver span and echogenicity, spleen size (length of its longest axis), portal vein diameter and presence of ascites.
4. Non-Invasive Predictive Scores:

   The following non-invasive indices were determined in all patients; according to previously published formulas:

   - AST-to-ALT ratio (AAR)\(^7\).
   - Platelet count/spleen diameter ratio (PSR): as the ratio between platelet count (N/mm\(^3\)) and bipolar diameter of the spleen in millimeters\(^8\).
   - AST-to-platelet ratio index (APRI) = \([(\text{AST}/\text{ULN}) \times 100]/\text{platelet count (10}\(^9\)/L)\) (ULN = the upper limit of normal and was set at 40 IU/L)\(^9\).

5. Liver and spleen stiffness measurements using the Fibroscan apparatus (Echosens, Paris, France). The medium probe was used for all patients and all measurements were performed by the same operator.

**Liver Stiffness Measurement (LSM):** The examination was performed after at least 6 hours of fasting. Patient was lying supine with the right arm placed behind the head to facilitate access to the right upper quadrant of the abdomen. The tip of the probe transducer was placed on the skin between the rib bones at the level of the right lobe of the liver. Results were expressed in KiloPascals (kPa) and corresponded to the median of 10 validated measurements\(^10\). The examination was considered reliable if more than \(\geq10\) valid measurements were acquired, the success rate (number of valid acquisitions divided by the number
of attempts) was over 60%, and the ratio of the interquartile range to the median of 10 measurements (IQR / M) was less than or equal 0.3\(^{(11)}\).

**Spleen Stiffness Measurement (SSM):** The patient was lying in supine position with his left arm in maximum abduction. The transducer was placed in the left intercostal spaces, usually on the posterior axillary line. The same quality thresholds as for LSM were used (IQR < 30%, success rate > 60%). We used ultrasonography to depict the spleen parenchyma and to choose the right place for SSM\(^{(12)}\).

(6) Upper gastrointestinal endoscopy: All patients underwent upper gastrointestinal endoscopy for assessment of esophageal and gastric varices. If EV were present, their size was graded using the Paquet grading system: **Grade 0:** no varices, **Grade 1:** varices disappearing with insufflation, **Grade II:** larger, clearly visible, usually straight varices, not disappearing with insufflation, **Grade III:** more prominent varices, locally coil-shaped and partly occupying the lumen, **Grade IV:** tortuous, sometimes grape-like varices occupying the esophageal lumen\(^{(13)}\). Furthermore, patients were classified into either having small EV (grade I-II) or large EV (grade III-IV).

**Statistical Analysis**

It was performed using the SPSS software version 15.0. Continuous variables were presented as median values and range (minimum and maximum values). Data were compared using the Mann–Whitney U-test and the X\(^2\) test for continuous and categorical variables, respectively. The differences between more than two independent groups were tested by the Kruskal–Wallis test. The relationships between the parameters were characterized using the Spearman correlation coefficients. The diagnostic performance of LSM and SSM was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and receiver operating characteristic (ROC) curves.

The ROC curve is a plot of sensitivity versus 1-specificity for all possible cutoff values. The most commonly used index of accuracy is the area under the ROC curve (AUROC), with values close to “1” indicating higher diagnostic accuracy. Optimal cutoffs for liver and spleen stiffness were chosen so that the sum of sensitivity and specificity would be maximal; positive and negative predictive values were computed for these values.

The \(P\)-value was considered as: \(P > 0.05\): non significant, \(P < 0.05\): significant and \(P < 0.01\): highly significant.

**Results**

This cross-sectional study included 60 consecutive Egyptian patients with HCV-related cirrhosis. Their mean age was 52 ± 8.58 years and included 39 males (65%) and 21 females (35%). According to modified Child-Pugh classification, 30 patients (50%) were Child A, 24 patients (40%) were Child B and 6 patients (10%) were Child C.

According to the presence or absence of esophageal varices (EV) by upper GIT endoscopy, our studied patients were classified into two groups: **Group 1:** Included 33 patients with EV (55%). Among them, 21/33 patients (63.6%) had small EV (grade I-II) and 12/33 patients (36.4%) had large EV (grade III-IV). 5/33 patients (15.2%) had EV with gastric extension. None of our enrolled patients had isolated gastric varices. **Group 2:** Included 27 patients with no EV (45%).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Positive EV)</th>
<th>Group 2 (Negative EV)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>PC (\times 10^3 / \text{mm}^3)</td>
<td>118.8 ± 39.4</td>
<td>187.7 ± 54.7</td>
<td>0.000*</td>
</tr>
<tr>
<td>Spleen diameter (cm)</td>
<td>15.82 ± 1.87</td>
<td>12.72 ± 2.31</td>
<td>0.000*</td>
</tr>
<tr>
<td>PSR</td>
<td>751.08 ± 623.17</td>
<td>1476.82 ± 601.17</td>
<td>0.000*</td>
</tr>
<tr>
<td>AAR</td>
<td>1.57 ± 0.61</td>
<td>1.33 ± 0.44</td>
<td>0.240</td>
</tr>
<tr>
<td>APRI</td>
<td>2.02 ± 1.55</td>
<td>0.91 ± 0.27</td>
<td>0.002*</td>
</tr>
<tr>
<td>LSM</td>
<td>34.78 ± 19.28</td>
<td>19.43 ± 4.73</td>
<td>0.000*</td>
</tr>
<tr>
<td>SSM</td>
<td>56.3 ± 26.3</td>
<td>24.6 ± 13.7</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

Table (1) shows a highly significant difference between the two studied groups regarding the platelet count (PC), spleen diameter, platelet count/spleen diameter ratio (PSR), AST-to-platelet ratio index (APRI), liver stiffness measurement (LSM) and spleen stiffness measurement (SSM). In patients with positive EV, the mean spleen diameter, APRI, LSM and SSM were higher; while the mean PC and PSR were lower than in those with negative EV (P < 0.01).

SSM showed a good performance as regards EV detection in comparison to LSM. At cut-off value ≥29 for SSM, sensitivity was 94.4%, specificity 86.4%, PPV 85%, NPV 95% and AUROC 0.934. While at cut-off value ≥16.5 for LSM, sensitivity was 94.4%, specificity 72.7%, PPV 73.9%, NPV 94.1% and AUROC 0.895 (Table 2 and Figure 1).

Table (2): The diagnostic performance of LSM versus SSM in esophageal varices detection.

<table>
<thead>
<tr>
<th></th>
<th>Cut-off</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM</td>
<td>≥16.5</td>
<td>0.895</td>
<td>94.4%</td>
<td>72.7%</td>
<td>73.9%</td>
<td>94.1%</td>
</tr>
<tr>
<td>SSM</td>
<td>≥29</td>
<td>0.934</td>
<td>94.4%</td>
<td>86.4%</td>
<td>85%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Liver stiffness measurement, SSM : spleen stiffness measurement, AUROC : area under the ROC curve, PPV: positive predictive value, NPV: negative predictive value.

Figure (1): The diagnostic performance of liver stiffness measurement (LSM) versus spleen stiffness measurement (SSM) in esophageal varices detection.

Comparison between SSM versus other parameters (AAR, APRI, PSR and PC) showed that SSM had the highest sensitivity (94.4%), specificity (86.4%), PPV (85%) and NPV (95%) for detection of EV at cut-off value ≥29 (AUROC=0.993) (Table 3 and Figure 2).
**Table (3):** The diagnostic performance of SSM versus AAR, APRI, PC and PSR in esophageal varices detection

<table>
<thead>
<tr>
<th></th>
<th>Cut-off</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSM</td>
<td>≥29</td>
<td>0.993</td>
<td>94.4%</td>
<td>86.4%</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>AAR</td>
<td>≥1.45</td>
<td>0.610</td>
<td>50%</td>
<td>54.4%</td>
<td>47.4%</td>
<td>57.1%</td>
</tr>
<tr>
<td>APRI</td>
<td>≥0.7</td>
<td>0.785</td>
<td>83.3%</td>
<td>72.7%</td>
<td>71.4%</td>
<td>84.2%</td>
</tr>
<tr>
<td>PSR</td>
<td>≤937</td>
<td>0.854</td>
<td>88.9%</td>
<td>77.3%</td>
<td>76.2%</td>
<td>89.5%</td>
</tr>
<tr>
<td>PC × 10^7 / mm³</td>
<td>≤148</td>
<td>0.812</td>
<td>83.3%</td>
<td>68.2%</td>
<td>68.2%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

SSM: spleen stiffness measurement, AAR: AST-to-ALT ratio, APRI: AST-to-platelet ratio index, PSR: platelet count/spleen diameter ratio, PC: platelet count, AUROC: area under the ROC curve, PPV: positive predictive value, NPV: negative predictive value.

**Figure (2):** The diagnostic performance of spleen stiffness measurement (SSM) versus AST-to-ALT ratio (AAR), AST-to-platelet ratio index (APRI), platelet count (PC) and platelet count/spleen diameter ratio (PSR) in esophageal varices detection.

Regarding large EV detection, all parameters showed a moderate diagnostic performance. APRI was the most sensitive parameter at cut-off value ≥ 1.38 with sensitivity 75%, specificity 50%, PPV 30%, NPV 87.5% and AUROC 0.661 (Table 4 and Figure 3).

**Table (4):** The diagnostic performance of LSM, SSM, AAR, APRI, PSR and PC in large EV detection:

<table>
<thead>
<tr>
<th></th>
<th>Cut-off</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM</td>
<td>≥47.1</td>
<td>0.643</td>
<td>25%</td>
<td>71.4%</td>
<td>20%</td>
<td>76.9%</td>
</tr>
<tr>
<td>SSM</td>
<td>≥72.1</td>
<td>0.545</td>
<td>75%</td>
<td>35.7%</td>
<td>25%</td>
<td>83.3%</td>
</tr>
<tr>
<td>AAR</td>
<td>≥1.45</td>
<td>0.527</td>
<td>50%</td>
<td>50%</td>
<td>22.2%</td>
<td>77.8%</td>
</tr>
<tr>
<td>APRI</td>
<td>≥1.38</td>
<td>0.661</td>
<td>75%</td>
<td>50%</td>
<td>30%</td>
<td>87.5%</td>
</tr>
<tr>
<td>PSR</td>
<td>≤649</td>
<td>0.536</td>
<td>75%</td>
<td>50%</td>
<td>30%</td>
<td>87.5%</td>
</tr>
<tr>
<td>PC × 10^7 / mm³</td>
<td>≤86</td>
<td>0.571</td>
<td>50%</td>
<td>57%</td>
<td>25%</td>
<td>80%</td>
</tr>
</tbody>
</table>

LSM: liver stiffness measurement, SSM: spleen stiffness measurement, AAR: AST-to-ALT ratio, APRI: AST-to-platelet ratio index, PSR: platelet count/spleen diameter ratio, PC: platelet count, AUROC: area under the ROC curve, PPV: positive predictive value, NPV: negative predictive value.
Discussion

Development of esophageal varices (EV) is the most common complication of liver cirrhosis, therefore endoscopic screening for EV at the time of diagnosis is strongly recommended by all clinical guidelines. This approach may identify those patients who can benefit from non-selective beta-blocker therapy or should start endoscopic prophylaxis. However, endoscopy is an invasive technique that is not easily accepted by patients.

This cross-sectional study aimed at evaluating the role of liver and spleen stiffness measurement by transient elastography for the non-invasive assessment of esophageal varices in comparison to other validated indices such as platelet count to spleen diameter ratio (PSR), AST/ALT ratio (AAR), AST-to-platelet ratio index (APRI) and platelet count (PC).

Our study was conducted on 60 consecutive Egyptian patients with HCV-related liver cirrhosis. According to upper GIT endoscopic findings, 55% of them had EV and 45% had no EV.

We found a highly significant difference between patients with EV and those without regarding the spleen diameter, PSR, APRI, LSM and SSM. AAR was the only parameter which didn’t show a statistical significance between the two groups. This is consistent with Saad et al. Also, SSM and LSM were evaluated by Calvaruso et al., and like our results both of them were sensitive to detect the presence of EV. We observed a highly significant difference in mean SSM values between patients with EV and those without (65.3±26.3 versus 24.6 ± 13.7 kPa respectively; P < 0.01). Also, the mean values of LSM were significantly higher in patients with EV than in those without EV (34.78± 19.28 versus 19.43± 4.73kPa respectively; P < 0.01).

We compared the performance of LSM and SSM as regards to EV detection. LSM showed better performance than SSM. A cut-off value ≥ 16.5 kPa for LSM had AUROC 0.895, sensitivity 94.4%, specificity 72.7%, PPV 73.9% and NPV 94.1%. While a cut-off value ≥ 29 kPa for SSM had AUROC 0.934, sensitivity 94.4%, specificity 86.4%, PPV 85% and NPV 95%. Also SSM was the most sensitive parameter when compared with AAR, APRI, PSR and PC as regards EV detection. SSM with cut-off value ≥ 29 had sensitivity 94.4%, specificity 86.4%, PPV 85%, NPV 95% and AUROC 0.993. PSR came in the 2nd place at a cut-off value of ≤ 937 with sensitivity 88.9%, specificity 77.3%, PPV 76.2%, NPV 89.5% and AUROC 0.854.
Similarly, Liu et al., Sharma et al. and Fraquelli et al. suggested a superiority of SSM in detection of EV in comparison to LSM. Also, Colecchia et al. concluded that SSM and LSM were more accurate than other non-invasive parameters in identifying patients with EV. In their study, LSM could predict EV with cut-off ≥ 25 with sensitivity 56% and specificity 97%, while SSM could predict EV with cut-off value ≥ 55 with sensitivity 71% and specificity 95%.

Giannini et al. proposed PSR of ≤ 909, as an accurate non-invasive marker for the presence of EV. This was further validated in a multicenter trial. Like our study, Cherian et al. and González-Ojeda et al. found that PSR was significantly lower in patients with EV than in those without.

We agreed with Mangone et al. who concluded that PSR is not a useful parameter to avoid unnecessary upper endoscopy in cirrhotic patients. Using the ROC curves, they found that PSR < 936.4 for the prediction of presence of EV showed sensitivity 64.5%, specificity 64.3%, PPV 50% and NPV 76.6% (accuracy 0.671). Chawla et al. supported these data in their meta-analysis where they concluded that PSR cut-off level of 909 may not be adequate to completely replace upper GI endoscopy as a non-invasive screening tool for EV.

On the contrary, Abu El Makarem et al. found that PSR had a better diagnostic performance than ours. In their study, PSR in patients with EV was significantly lower than in those without. In an analysis of the receiver operating characteristic curves (ROCs), an optimal cutoff value of 939.7 for this ratio, gave sensitivity 100%, specificity 86.3%, PPV 95.6%, NPV 100% and AUROC of 0.94.

Regarding APRI, our results agreed with Zambam de Mattos et al. that APRI was not a good index for the prediction of EV, because its sensitivity, specificity and predictive values were insufficient. In their cross-sectional study, APRI with a cutoff point of 1.3 demonstrated a sensitivity 64.7%, specificity 72.7%, PPV 86.5% and NPV 43.2%.

Regarding large EV detection, all parameters in the current study showed a moderate performance. The most sensitive parameter among them was APRI followed by SSM. APRI cut-off value ≥ 1.38 had sensitivity 75%, specificity 50%, PPV 30%, NPV 87.5% and AUROC 0.661. SSM cut-off value ≥ 72.1 kPa showed sensitivity 75%, specificity 35.7%, PPV 25%, NPV 83.3% and AUROC 0.545.

Similar to our results, Shi et al. in their meta-analysis; concluded that LSM showed moderate diagnostic utility for the prediction of EV or large EV. The cut-off values of liver stiffness ranged from 15.1 to 28.0 kPa for detection of EV and 17.8 to 48.0 kPa for detection of large EV. Also, Hua et al. found that LSM couldn't assess EV accurately with no significant difference in LSM value between patients with severe EV and those having no or non-severe EV (31 kPa versus 28.18 kPa).

Similarly, in the meta-analysis of Singh et al., they concluded that current techniques for measuring spleen stiffness are limited in their accuracy regarding large EV detection.

**Conclusion**

In conclusion, spleen stiffness measurement by Fibroscan is a sensitive and reliable tool for detection of esophageal varices, but it showed less diagnostic accuracy as regards variceal grading.

**References**


