Measurement of liver and spleen stiffness by acoustic radiation force impulse elastography for noninvasive detection of esophageal varices in Egyptian cirrhotic patients
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Introduction and aim
Screening for esophageal varices (EVs) is recommended in patients with cirrhosis. Recent studies have focused on noninvasive prediction of EVs. The aim of the study was to evaluate the accuracy of liver stiffness (LS) and spleen stiffness (SS) measured by acoustic radiation force impulse (ARFI) elastography for noninvasive detection of EVs in Egyptian cirrhotic patients.

Patients and methods
In this prospective study, we performed ARFI elastography to measure LS and SS on 30 patients with cirrhosis undergoing endoscopic screening for EVs and on 15 healthy volunteers (controls). The diagnostic utility of LS and SS for identifying the presence of EVs was compared.

Results
Patients with EVs showed higher LS and SS values than patients without varices. The diagnostic performance of LS for the detection of varices at a cutoff value of more than 2.47 showed a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 73.3, 66.7, 68.7, 71.4, and 71.3%, respectively. Regarding SS, at a cutoff value of more than 3.02, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 93.3, 73.3, 77.8, 91.7, and 87.6%, respectively.

Conclusion
SS measured using ARFI imaging is superior to LS with excellent diagnostic performance for predicting EVs and may be used as a noninvasive screening tool for the detection of EVs.

Keywords:
acoustic radiation force impulse elastography, esophageal varices, liver stiffness, spleen stiffness

Introduction
As variceal bleeding is a life-threatening condition, current guidelines recommend routine upper gastrointestinal endoscopy at the time of diagnosis in all cirrhotic patients for screening of esophageal varices (EVs) [1]. This invasive test is potentially associated with complications related to sedation and the procedure itself, and also increased costs of medical care [2]. Hence, there is great interest in developing noninvasive techniques to detect EVs [3].

Acoustic radiation force impulse (ARFI) imaging has recently been used to estimate liver fibrosis by measuring liver stiffness (LS) and could monitor disease progression or predict the development of complications [4].

Published studies have suggested that spleen stiffness (SS) measurement can be used to predict the presence of EVs in patients with chronic liver disease (CLD) with high diagnostic accuracy [5]. SS measured by ARFI elastography in CLD patients had a very good predictive value for the presence of cirrhosis [6].

In this study, we aimed to evaluate the accuracy of LS and SS stiffness measured by ARFI elastography for noninvasive detection of EVs in Egyptian cirrhotic patients.

Patients and methods
Study population
This prospective study was conducted between August 2015 and February 2016. Thirty patients with liver
Liver and spleen stiffness in EVs

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parameter and to find out the best cutoff value with detection of sensitivity and specificity at this cutoff value.

(5) Probability ($P$-value):

(a) $P$-value less than 0.05 was considered significant.

(b) $P$-value less than 0.001 was considered as highly significant.

(c) $P$-value more than 0.05 was considered insignificant.

Results

This study was conducted on 45 participants who were divided into two groups: group I included 30 cirrhotic patients among them 15 patients who had EVs and group II included 15 healthy persons with no history of CLD, and normal liver functions at the time of enrollment.

The demographic, laboratory, and ultrasonographic findings among patients and controls are shown in Table 1.

The mean age of patients was 50.57 years, whereas the mean age of controls was 27.6 years. Of the patients, 21 (70%) were men, and controls included 13 (86.7%) men.

The viral status of patients showed 27 cases of hepatitis C virus (HCV) and only three cases were hepatitis B virus-positive. Five cases had ascites, whereas two patients were complaining of hepatic encephalopathy. As regards Child classification of patients, 23 patients were Child A and seven cases were Child B.

Table 2 shows high statistical difference between patients and controls as regards LS (2.50±0.80 vs. 0.91±0.29, respectively, $P<0.001$). Similarly, SS was statistically higher among patients compared with controls (3.14±0.80 vs. 1.89±0.26, respectively, $P<0.001$).

Patients with EVs showed higher LS values than patients without varices and the difference was statistically significant (2.80±0.73 vs. 2.20±0.77 respectively, $P=0.037$). Similarly, the SS was higher among those with varices compared with the nonvariceal group and the difference was of high statistical significance (3.62±0.42 vs. 2.66±0.81, respectively, $P<0.001$) as shown in Table 3.

On correlating LS and SS with other parameters (Table 4), a positive correlation was found between LS and all of aspartate aminotransferase, alanine aminotransferase, creatinine, and spleen size. Also, a positive correlation was detected between SS and creatinine, international normalized ratio, serum bilirubin, liver size, and spleen size. In contrast, a negative correlation was seen between platelets count and LS and SS.

Table 1 Baseline characteristics of patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (mean±SD)</th>
<th>Control (mean±SD)</th>
<th>t-Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.57±6.45</td>
<td>27.60±3.66</td>
<td>12.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (70)</td>
<td>13 (86.7)</td>
<td>1.504</td>
<td>0.220</td>
</tr>
<tr>
<td>Female</td>
<td>9 (30)</td>
<td>2 (13.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/l)</td>
<td>39.57±22.98</td>
<td>15.00±4.42</td>
<td>4.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/l)</td>
<td>34.43±18.79</td>
<td>14.87±3.64</td>
<td>3.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets ($\times 10^9$/l)</td>
<td>206366.7±75578.5</td>
<td>326200.0±16209.3</td>
<td>-6.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.95±0.26</td>
<td>0.77±0.11</td>
<td>2.54</td>
<td>0.015</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.09±0.11</td>
<td>1.00±0.00</td>
<td>3.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.83±0.47</td>
<td>4.47±0.22</td>
<td>-5.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>1.62±0.84</td>
<td>0.69±0.14</td>
<td>4.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver size (cm)</td>
<td>11.29±1.77</td>
<td>9.43±0.47</td>
<td>4.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen size (cm)</td>
<td>14.06±3.01</td>
<td>9.02±0.56</td>
<td>6.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 Comparison patients and control groups as regards liver and spleen stiffness

<table>
<thead>
<tr>
<th>Stiffness</th>
<th>Patients (mean±SD)</th>
<th>Control (mean±SD)</th>
<th>t-Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness (m/s)</td>
<td>2.50±0.80</td>
<td>0.91±0.29</td>
<td>7.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spleen stiffness (m/s)</td>
<td>3.14±0.80</td>
<td>1.89±0.26</td>
<td>5.89</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3 Comparison between variceal and nonvariceal patients as regards liver and spleen stiffness in the patient group

<table>
<thead>
<tr>
<th>Stiffness</th>
<th>Variceal (mean±SD)</th>
<th>Nonvariceal (mean±SD)</th>
<th>t-Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness (m/s)</td>
<td>2.80±0.73</td>
<td>2.20±0.77</td>
<td>2.19</td>
<td>0.037</td>
</tr>
<tr>
<td>Spleen stiffness (m/s)</td>
<td>3.62±0.42</td>
<td>2.66±0.81</td>
<td>4.08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Studying the receiver operating characteristic curve to define the best cutoff value to discriminate patients from controls (Table 5), we found that at an LS of at least 1.4, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were 93.3, 92, 92, 88.2, and 98.2%, respectively. Also, SS at a cutoff value of at least 2.2 a sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 90, 93.3, 96.4, 82.4, and 66.7%, respectively, were achieved.

The distribution of both patients and control groups regarding LS and SS was shown by the interactive dot diagram in Figs 1 and 2, respectively.

To detect the presence of varices among patients, the diagnostic performance of LS at a cutoff value of more than 2.47 showed a sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 73.3, 66.7, 68.7, 71.4, and 71.3%, respectively. Regarding SS, at a cutoff value of more than 3.02, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 93.3, 73.3, 77.8, 91.7, and 87.6%, respectively (Table 6 and Fig. 3).

**Table 4** Correlation between liver stiffness, spleen stiffness, and other parameters using Pearson’s correlation coefficient test in the patient group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Liver stiffness</th>
<th></th>
<th>Spleen stiffness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>−0.030</td>
<td>0.876</td>
<td>−0.044</td>
<td>0.817</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/l)</td>
<td>0.664</td>
<td>&lt;0.001</td>
<td>0.292</td>
<td>0.118</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/l)</td>
<td>0.645</td>
<td>&lt;0.001</td>
<td>0.235</td>
<td>0.212</td>
</tr>
<tr>
<td>Platelets (x10⁹/l)</td>
<td>−0.442</td>
<td>0.015</td>
<td>−0.478</td>
<td>0.008</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.376</td>
<td>0.041</td>
<td>0.518</td>
<td>0.003</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>0.263</td>
<td>0.161</td>
<td>0.359</td>
<td>0.050</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>−0.109</td>
<td>0.565</td>
<td>−0.285</td>
<td>0.126</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>0.233</td>
<td>0.216</td>
<td>0.422</td>
<td>0.020</td>
</tr>
<tr>
<td>Liver size (cm)</td>
<td>0.131</td>
<td>0.489</td>
<td>0.377</td>
<td>0.040</td>
</tr>
<tr>
<td>Spleen size (cm)</td>
<td>0.384</td>
<td>0.036</td>
<td>0.534</td>
<td>0.002</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.

**Table 5** Diagnostic performance of liver and spleen stiffness in discriminating patients and control

<table>
<thead>
<tr>
<th>Items</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness (m/s)</td>
<td>≥1.4</td>
<td>93.3</td>
<td>94</td>
<td>92</td>
<td>88.2</td>
<td>98.2</td>
</tr>
<tr>
<td>Spleen stiffness (m/s)</td>
<td>≥2.2</td>
<td>90</td>
<td>93.3</td>
<td>96.4</td>
<td>82.4</td>
<td>66.7</td>
</tr>
</tbody>
</table>

This study evaluated the diagnostic role of LS and SS measured by ARFI elastography in the detection of EVs in Egyptian cirrhotic patients.

As transient elastography (TE) has some limitations in obese patients and cirrhotic patients with ascites [9], we used ARFI elastography instead of TE in this study.

The higher success rates of LS and SS measurements shown with ARFI imaging compared with TE may be caused by the difficulty in obtaining accurate values using TE, because the images obtained with TE are not seen in real time. ARFI measurement depth can be adapted according to the distance between the skin and liver capsule, allowing measurement of slim and obese patients with the same probe [10].

Takuma et al. [11] reported high diagnostic performance of SS for the presence of high-risk EVs [area under the receiver operating characteristic curve (AUROC)=0.930]. In contrast, Vermehren et al. [12] reported significantly low diagnostic accuracy of SS for predicting large EVs (AUROC=0.58), and Rifai et al. [13] also showed that SS measured by ARFI elastography was inferior to LS for detecting PH (AUROC=0.68 vs. 0.90). Thus, the diagnostic performance of SS measured using ARFI elastography for the diagnosis of PH or detection of EVs is still debatable.

Gallotti et al. [14] published the first ARFI measurements in different upper abdominal organs.
(liver, spleen, kidney, and pancreas). They found that
the spleen was the toughest abdominal organ with the
highest tissue stiffness mean value (2.44 m/s).

In this study, LS was superior to SS in discriminating
liver cirrhosis from controls with higher sensitivity,
NPV, and diagnostic accuracy (93.3, 88.2, and

Interactive dot diagram between patients and control groups as regards liver stiffness (m/s).

Interactive dot diagram between patients and control groups as regards spleen stiffness (m/s).

<table>
<thead>
<tr>
<th>Items</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness (m/s)</td>
<td>&gt;2.47</td>
<td>73.3</td>
<td>66.7</td>
<td>68.7</td>
<td>71.4</td>
<td>71.3</td>
</tr>
<tr>
<td>Spleen stiffness (m/s)</td>
<td>&gt;3.02</td>
<td>93.3</td>
<td>73.3</td>
<td>77.8</td>
<td>91.7</td>
<td>87.6</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.
98.2% vs. 90, 82.4, and 66.7%, respectively), but in contrast, SS was superior to LS in detection of the presence of EVs with higher sensitivity, NPV, and diagnostic accuracy (93.3, 91.7, and 87.6% vs. 73.3, 71.4, and 71.3%, respectively). Thus, these results suggest that EVs could be ruled out in most patients evaluated by SS, thereby avoiding screening endoscopy or prophylactic treatments.

This finding agrees with the results obtained from a meta-analysis by Ma et al. [15] which concluded that SS is significantly superior to LS for detection of varices in CLD patients and that SS measurement may help to select those patients who need endoscopic screening.

It is clear that LS only reflects the high vascular pressure within the liver, but not the portosystemic collaterals secondary to PH [16]. For this reason, SS is superior to LS in the detection of EVs as part of portosystemic collaterals caused by splanchnic hemodynamic changes [5], which is consistent with our results.

Our report is the first study using AFRI elastography conducted on Egyptian cirrhotic patients with HCV-predominant population (90%), confirming that the measurement of SS using ARFI imaging is a useful noninvasive method for the detection of EVs. Similarly, a study from Italy by Colecchia et al. [5] highlighted the diagnostic accuracy in patients with HCV-related cirrhosis, a test so far evaluated only in patients with hepatitis B virus-related cirrhosis [17].

In contrast, Mori et al. [18] concluded that SS significantly correlates with the presence of ascites but not EVs in chronic hepatitis C patients.

Analysis of this study and that of Mori et al. [18] showed that both sample size and HCV positivity were almost comparable in both studies. The difference in the results between the two studies may be attributed to: first, the heterogenous study population of Mori et al. [18] (nine cases of chronic hepatitis were included in the patient group, the two subgroups were not matched; 12 cases with varices and 21 cases with no
varices (including the nine cases of chronic hepatitis). Second, the study of Mori et al. [18] did not mention whether they excluded those patients with previous gastrointestinal bleeding or not. In contrast, this study excluded such patients. And finally, in our study, endoscopic assessment and ARFI measurement were performed by two examiners with evaluation of both intraobserver and interobserver agreement, whereas in the study of Mori et al. [18], all procedures were performed by an endoscopist and a sonographer without assessment of intraobserver agreement.

Our study has shown a positive correlation between LS and aspartate aminotransferase, alanine aminotransferase. This finding is consistent with Ye et al. [19] who found that the LS values were significantly higher in cirrhotic patients with high liver enzymes compared with those with normal liver enzymes, whereas the difference in SS between the two groups did not reach statistical significance.

This study has shown a positive correlation between LS and spleen size and also a positive correlation between SS and liver and spleen size.

In PH, splenomegaly is believed to be caused by portal congestion and tissue hyperplasia [20].

Other studies have reported that an increase in the size of the spleen in patients with CLD is almost always the expression of increased portal pressure and presence of EVs [21].

Regarding SS in this study, at a cutoff value of more than 3.02, the NPV, sensitivity, and diagnostic accuracy were 91.7, 93.3, and 87.6%, respectively. Our results are similar to that of Takuma et al. [11] who found that SS measurement using ARFI elastography in HCV-predominant patients was effective in detecting varices (optimal SS cutoff of 3.18 m/s with 98.4% NPV, 98.5% sensitivity, and 75% accuracy).

Consistent with this study, many previous studies have excluded patients with prior or ongoing variceal hemorrhage from the study populations, most likely because those studies focused on investigating whether SS measurement could reduce the need for endoscopic examination by easily detecting the EVs associated with a high risk of bleeding [5,11].

The limitations of this study include the fact that correlation between LS and SS measurements using ARFI imaging and portal venous pressure measurements with hepatic venous pressure gradient was not performed and the timing of stiffness measurements was not fixed. Other limitations of our study are the sample size of 45 participants was relatively small, unavoidable selection bias caused by the clinical diagnosis of cirrhosis without a liver biopsy in all the patients, a single-center study without external validation, and the absence of comparison with TE, and lack of inclusion of different grades of EVs. Therefore, further studies are needed to overcome these limitations.

Conclusion
SS measured using ARFI imaging is superior to LS with an excellent diagnostic performance for predicting EVs. Because of the small sample size of our study, it is difficult to reach a valid clinical message about SS; however, it is worthy to mention that SS may be a promising noninvasive screening tool of EVs. Further studies on larger number of patients are needed to clarify whether it can be a substitute to endoscopy as a screening tool of EVs when endoscopy is unavailable or contraindicated. This may lead to a reduction in the number of screening endoscopies and may also help alleviate the financial and disinfection burdens of endoscopy units as well as the medical costs associated with EVs.

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Nil.

Conflicts of interest
There are no conflicts of interest.

References


