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

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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

cirrhosis presented to the National Research Centre, Egypt, in addition to 15 healthy volunteers who serve as controls were enrolled in our study. The diagnosis of liver cirrhosis was on the basis of history, clinical examination, laboratory, and radiological findings (nodular liver surface, coarse echogenicity, large caudate lobe, wide portal vein, and presence of collaterals).

Patients were excluded from the study if they had any of the following: active gastrointestinal bleeding, alcoholism, hepatic focal lesions, portal vein thrombosis, and previous or current treatment modality for portal hypertension (PH) (β-blocker therapy, splenectomy, splenic embolization, or endoscopic therapies).

Participants of the control group were healthy volunteers without any history of liver disease. They had normal liver functions, negative virologic markers, and normal liver sonographic findings.

The enrolled patients were further subdivided according to the presence of EVs into two subgroups: variceal and nonvariceal groups. Then by using the envelope method, 15 patients were randomly selected from each group to constitute the sample size of this study.

This study was approved by the Institutional Review Board of the National Research Center. All participants signed a written informed consent before enrollment.

All patients were subjected to full history taking and thorough clinical examination as regards general and local abdominal examination for liver and splenic sizes, presence of ascites, jaundice, and encephalopathy. Laboratory tests were performed including the serum bilirubin and albumin, liver enzymes, complete blood count, and viral serum markers.

Endoscopic examination

Upper gastrointestinal endoscopy was performed in all patients to detect the presence of varices and assess their grades. Endoscopic examination was performed by two experienced endoscopists (O.A. and Y.A. with 11 and 12 years of experience, respectively), who were blinded to clinical, laboratory, and stiffness measurement data. The patients were classified according to the presence of varices into variceal and nonvariceal groups.

Liver stiffness and spleen stiffness measurement

For all patients, ultrasonographic examination was performed by two independent radiologists (with >10 years of experience as sonographers), who were blinded to the clinical data throughout the study, using a Siemens Acuson S2000 ultrasound system (Siemens Medical Solutions, Mountain View, California, USA). After overnight fasting, conventional B-mode imaging was done for ultrasonographic assessment of the liver, gallbladder, and spleen before performing elastography.

Positioning of the patient

After overnight fasting, the examined patient was placed in supine position maximally abducting his right arm to increase intercostal space (to improve the acoustic window) to measure LS. For SS, the patient was in the right lateral position with left arm maximally abducted.

To minimize rib shadowing, the probe was placed in the intercostal space with sufficient gel. The size of the region of interest was fixed at 10×5 mm avoiding any large blood vessels or abnormal lesions from the field at a depth from 3 to 5.5 cm below the liver and spleen capsule [7]. Ten measurements were taken in the right intercostal space for LS and other 10 measurements in the left intercostal space for SS while the patient was holding his/her breath. The results of measurements of shear waves are expressed in m/s.

To evaluate interobserver and intraobserver agreements on ultrasonographic examinations, ultrasonographic examinations of 30 cirrhotic patients who were not included in our study were independently performed by the two sonographers on the same day. To evaluate interobserver agreement on endoscopic examinations, the digital imaging endoscopic records of 50 cirrhotic patients other than those included in the study were independently evaluated by the two endoscopists.

Statistical methodology

Data were analyzed using the Statistical Package for the Social Sciences, version 20 (SPSS 20, IBM, Armonk, NY, United States of America). Quantitative data were expressed as the mean±SD. Qualitative data were expressed as frequency and percentage. The following tests were done:

(1) Independent-samples *t*-test of significance was used when comparing between two means.
(2) χ^2-test of significance was used to compare the proportions between two qualitative parameters.
(3) Pearson's correlation coefficient (*r*) test was used for correlating data.
(4) Receiver operating characteristic curve analysis was used to find out the overall predictivity of the

Table 1 Baseline characteristics of patients and controls

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

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

Stiffness	Patients (mean±SD)	Control (mean±SD)	*t*-Test	*P*-value
Liver stiffness (m/s)	2.50±0.80	0.91±0.29	7.44	<0.001
Spleen stiffness (m/s)	3.14±0.80	1.89±0.26	5.89	<0.001

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

Stiffness	Variceal (mean±SD)	Nonvariceal (mean±SD)	*t*-Test	*P*-value
Liver stiffness (m/s)	2.80±0.73	2.20±0.77	2.19	0.037
Spleen stiffness (m/s)	3.62±0.42	2.66±0.81	4.08	<0.001

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

Parameters	Liver stiffness		Spleen stiffness	
	R	*P*-value	*r*	*P*-value
Age (years)	–0.030	0.876	–0.044	0.817
Aspartate aminotransferase (IU/l)	0.664	<0.001	0.292	0.118
Alanine aminotransferase (IU/l)	0.645	<0.001	0.235	0.212
Platelets ($\times 10^9$/l)	–0.442	0.015	–0.478	0.008
Creatinine (mg/dl)	0.376	0.041	0.518	0.003
International normalized ratio	0.263	0.161	0.359	0.050
Serum albumin (g/dl)	–0.109	0.565	–0.285	0.126
Serum bilirubin (mg/dl)	0.233	0.216	0.422	0.020
Liver size (cm)	0.131	0.489	0.377	0.040
Spleen size (cm)	0.384	0.036	0.534	0.002

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

Items	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Liver stiffness (m/s)	≥1.4	93.3	94	92	88.2	98.2
Spleen stiffness (m/s)	≥2.2	90	93.3	96.4	82.4	66.7

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

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).

Discussion

Hepatic venous pressure gradient and upper endoscopy are considered the reference standard methods to diagnose PH and assess the grade of EVs. Because both methods are invasive, expensive, and perceived as unpleasant by patients, several noninvasive methods have been proposed recently to diagnose PH and predict the severity of EVs [8].

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

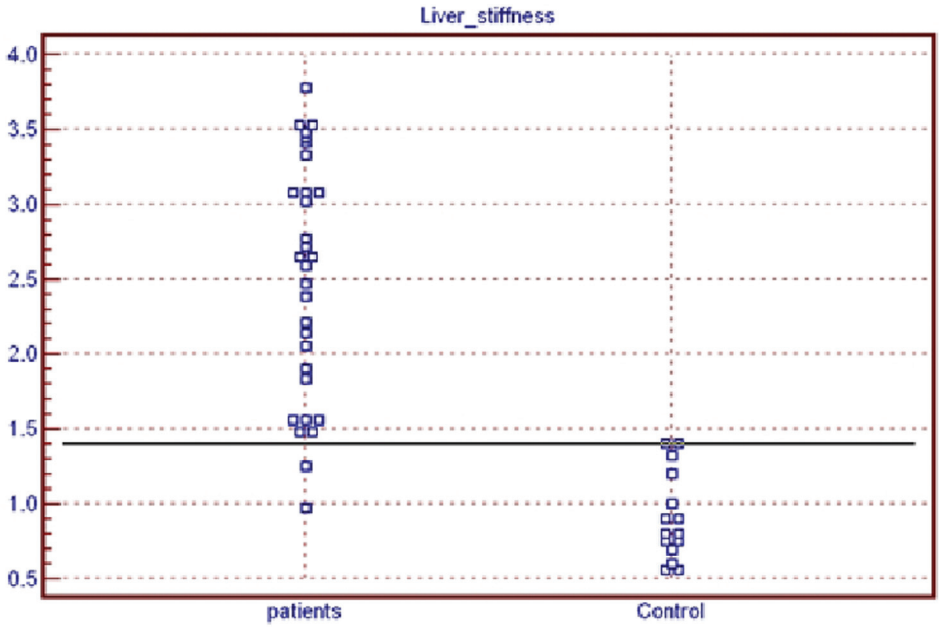
As transient elastography (TE) has some limitations in obese patients and cirrhotic patients with ascites [9], we used ARFI elastography instead of TE in this study.

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.

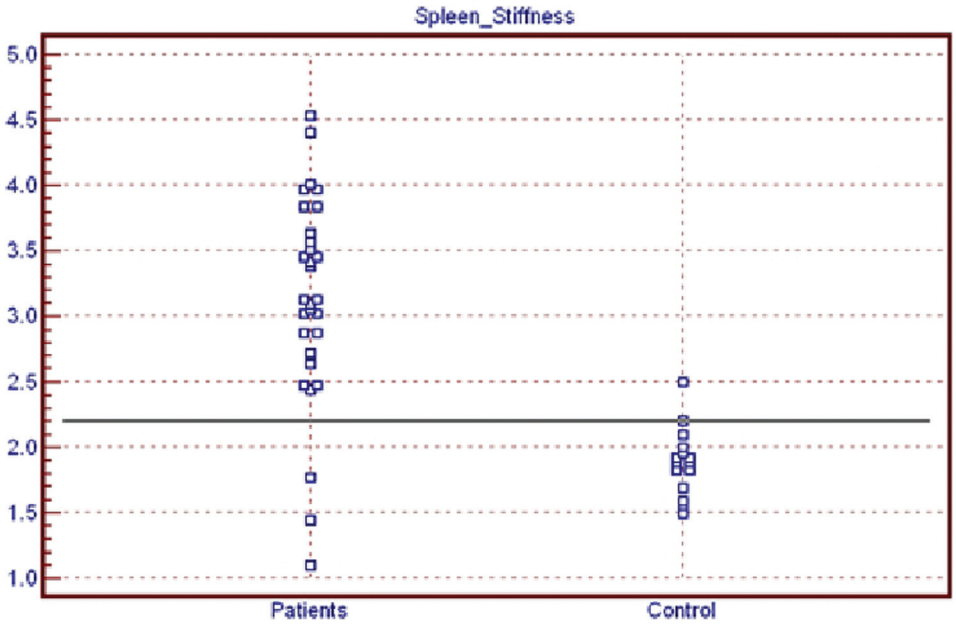
Gallotti *et al.* [14] published the first ARFI measurements in different upper abdominal organs

Figure 1



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

Figure 2



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

Table 6 Diagnostic performance of liver and spleen stiffness in discriminating endoscopic findings

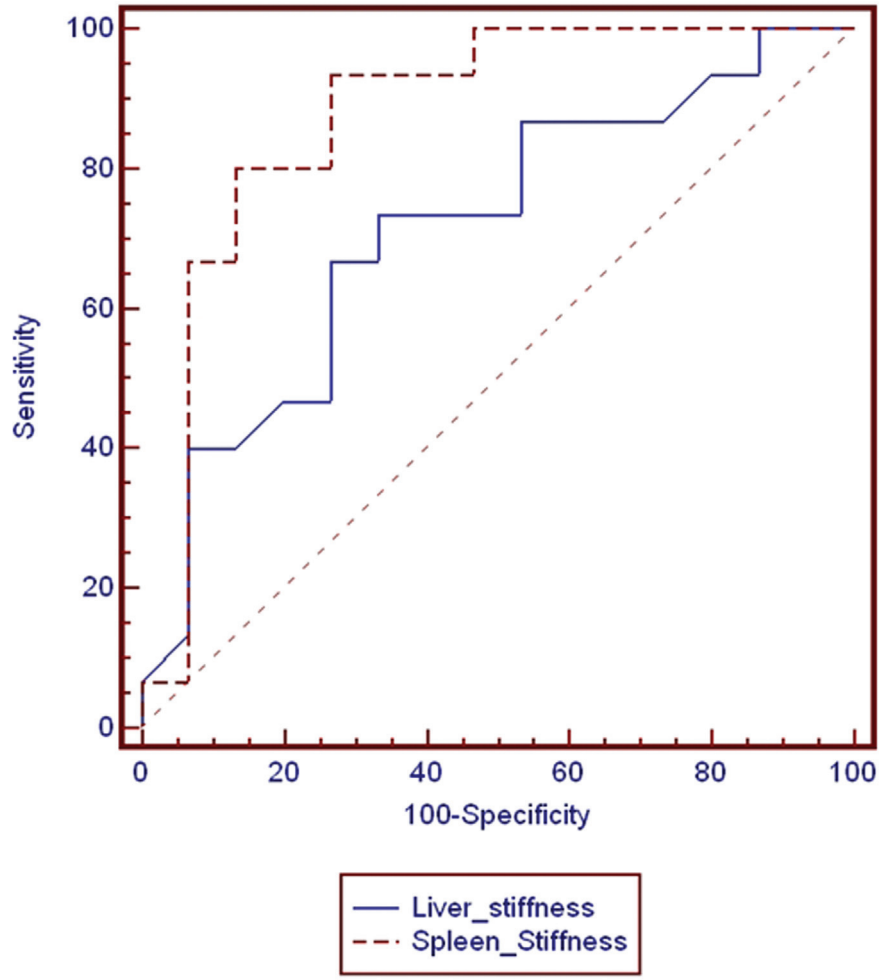
Items	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Liver stiffness (m/s)	>2.47	73.3	66.7	68.7	71.4	71.3
Spleen stiffness (m/s)	>3.02	93.3	73.3	77.8	91.7	87.6

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

(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

Figure 3



Receiver operating characteristic curve analysis of liver and spleen stiffness in the detection of esophageal varices.

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 heterogonous 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 AFRI 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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Conflicts of interest

There are no conflicts of interest.

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