*Original papers*

*Med Ultrason 2016, Vol. 18, no. 1, 11-17*
DOI: 10.11152/mu.2013.2066.181.sff

# Is the spleen stiffness value acquired, using acoustic radiation force impulse (ARFI) technology, predictive of the presence of esophageal varices in patients with cirrhosis of various etiologies?

**Jaehyung Park[1], Heejin Kwon[1], Jinhan Cho[1], Jongyoung Oh[1], Sangyun Lee[1], Sangyoung Han[2], Sung Wook Lee[2], Yanghyun Baek[2]**

[1]Department of Radiology, [2]Department of Internal Medicine, Dong-A University Hospital, Busan, South Korea

**Abstract**

**Aim:** This study's aim was to determine the accuracy of the spleen stiffness value acquired using acoustic radiation force impulse (ARFI) technology, to predict the presence of esophageal varices (EVs) in patients with liver cirrhosis of various etiologies. **Material and methods:** Of the 366 enrolled patients, 192 had hepatitis B virus, 74 had hepatitis C virus, and 100 had alcohol-related cirrhosis. All patients underwent biochemical tests, gastrointestinal endoscopy, and liver and spleen elastography by ARFI. We evaluated the correlation between the presence of EVs and factors including liver and spleen stiffness measured by ARFI, biochemical tests, and other noninvasive measurements, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count (PLT), spleen diameter (SD), PLT to SD ratio, AST to ALT ratio (AAR) score, the AST to PLT ratio index (APRI) score. **Result:** A univariate analysis revealed that the AAR score, APRI score, PLT, PLT/SD ratio, and spleen elastography variables were all independently associated with EVs ($p<0.05$). On multivariate analysis, only spleen elastography was associated with EVs ($p=0.001$). However, in cases of alcohol-induced liver cirrhosis, spleen stiffness was not reliable for the prediction of EVs. **Conclusion:** Spleen elastography measured using ARFI may serve as a non-invasive method for determining the presence of EVs. However, it is not an appropriate predictor for EVs in alcoholic cirrhosis.

**Keywords:** ARFI,esophageal varices, spleen,cirrhosis

## Introduction

In cirrhotic patients, screening for esophageal varices (EVs) using esophagogastroduodenoscopy (EGD) is highly recommended in the current guidelines, as bleeding may be a serious consequence of portal hypertension (PTH) [1]. However, the general unpleasantness and need for sedation associated with EGD are important limitations of the method [2]. For these reasons, noninvasive methods have been introduced to serve as markers for the evaluation of EVs. For example, the platelet count [3], the spleen diameter (SD) determined by ultrasound scan [4], and the platelet (PLT) count/SD ratio in particular [5,6] have all been identified as noninvasive methods to classify patients with cirrhosis and EVs. Unfortunately, these markers have not been associated with a high sensitivity or specificity. Additionally, attempts to use liver transient elastography (TE, Fibroscan) to indirectly evaluate the degree of PHT and the likelihood of EVs presence [7,8], have produced disappointing results.

Acoustic radiation force impulse (ARFI) imaging technology involves the mechanical excitation of tissue by using short duration acoustic pulses (push pulses) in a region of interest chosen by the operator. These pulses produce shear waves that spread away from the region of interest perpendicularly to the acoustic push pulse. This process results in the generation of localized waves. By detecting these waves, quantitative assessment of tissue stiffness is available through the measurement of shear wave speed [9]. The ability to measure spleen stiffness by ARFI elastography in patients with chronic liver disease has also been recently reported. However, these stud-

Received 25.10.2015 Accepted 23.12.2015
Med Ultrason
2016, Vol. 18, No 1, 11-17
Corresponding author: Heejin Kwon, MD,
Department of Radiology,
Dong-A University Hospital,
Dongdaesingdong 3 ga, Seo-gu,
Busan 602-715, South Korea
Phone: +82-51-2405367
Fax: +82-51-2534931
E-mail: risual@dau.ac.kr

ies focused primarily on the simple correlation between spleen stiffness and EVs without consideration of cirrhosis etiology [10-12].

The aim of the current study was to evaluate the reliability of ARFI elastography-measured liver and spleen stiffness in patients with liver cirrhosis, as well as to investigate whether liver and spleen stiffness values, along with several other non-invasive tests, may be suitable predictors for the presence of EVs. Additionally, the utility of cirrhosis etiology for prediction of esophageal varices by ARFI elastography-measured liver or spleen stiffness was also assessed.

## Materials and methods

This prospective, single institution study was Health Insurance Portability and Accountability Act compliant, and the study protocol was approved by the Institutional Review Board of Dong A University Hospital, Busan, Republic of Korea. Written informed consent was obtained from each patient.

***Patient Population***

From June 2014 to April 2015, 614 participants, previously diagnosed with liver cirrhosis were enrolled. To meet inclusion criteria, patients had to have hepatic cirrhosis resulting from an infection with a hepatitis virus or heavy alcohol consumption. The exclusion criteria included patients with autoimmune disease, carcinoma, ascites, portal vein thrombosis, expected survival <3 months, and refusal to participate in the study. Of the initial 614 patients, 488 met the inclusion criteria. The origins of cirrhosis among these patients were chronic hepatitis B virus (HBV)-related in 262 patients, chronic hepatitis C virus (HCV)-related in 96 patients, and alcohol-related in 130 patients.

To recruit patients, we used our patient information system to identify those scheduled for an upper endoscopy EVs assessment and serologic tests up to two weeks prior to ARFI elastography.

***Liver and spleen stiffness measurement by ARFI***

After overnight fasting, patients underwent an upper abdomen ultrasound. ARFI was performed in the left lateral decubitus position for the liver (right lobe) and the right lateral decubitus position for the spleen, with the contralateral side of the arm in maximum reduction. The scanning was done in the best visualized area between the intercostal spaces. The size of the region of interest (ROI) was fixed at 10x5 mm and positioned in the parenchyma free of vascular or biliary structure. The standard ROI measurement depth was 3 cm below the liver and spleen capsule. During the procedure, patients were asked to stop breathing for a moment in order to minimize motion. Previous reports demonstrated that >5 successful measurements should be collected for reliability [13,14]. Therefore, the mean values of 5 successful measurements were taken from the liver and from the spleen, and were expressed in kPa. A 3-5 MHz convex transducer and sonographic equipment (XMatrix iU22, iU22; Philips, Seattle, WA, USA) were used. All measurements were performed independently and blindly by a board-certified and fellowship-trained abdominal radiologist with 10 years of experience. For the best correlation between ARFI and stiffness, the interquartile range (IQR) interval had to be <30% [15].

***Upper gastrointestinal endoscopy***

All patients underwent upper endoscopy using flexible video gastroscopy (GIF-XQ-2400 endoscope, Olympus Optical CT, Ltd, Tokyo, Japan) in the maximum 14 days before ultrasonography. EVs were evaluated according to the published criteria [16].

***Spleen diameter***

Maximum spleen bipolar diameter expressed in cm [17] was estimated by means of an ultrasound scan using the same machine in the same session as the ARFI measurement. All examinations were performed by the same individual.

***Other non-invasive measurements***

Laboratory tests including serum aspartate aminotransferase (AST), alanine aminostransferase (ALT), albumin, and PLT count were performed for all patients within 2 weeks of study initiation. To evaluate the influence of other known non-invasive measurements for liver cirrhosis, the AST/ALT ratio (AAR) [18], PLT/SD [5,6], and AST to PLT ratio index (APRI) score were calculated. The APRI score was calculated as follows: APRI = (sample AST/reference AST) × 100/PLT, where reference is the upper limit of normal for AST (34 IU/L) and the PLT count is assessed as $x10^9$ cells/L [19].

***Statistical Analysis***

All statistical analyses were conducted using a computer software package (SPSS version 21.0; Inc., Chicago, IL, USA), and a medical statistician reviewed all data. These results were expressed as the mean ± standard deviation. The data were analyzed by comparing the eminence of EVs at EGD and the stiffness of the liver and spleen using ARFI. The Levene test was used to investigate the homogeneity of variance. Analysis of variance and the least significant difference t-tests were used to compare the differences in mean liver and spleen stiffness values in the cirrhosis patients according to the presence of varices in endoscopy. The independent t-test was used to compare the other non-invasive measurements between cirrhotic patients with and without varices. In each test, $p<0.05$ was considered statistically significant.

Table I. Analysis of non-invasive measurements for predicting EVs

| **All etiologies** (n=366) | **Varices (-)** (n=172) | **Varices (+)** (n=194) | **p-Value** | **Multivariate analysis** OR (95% CI) | p-Value |
|---|---|---|---|---|---|
| Gender | | | 0.064 | - | - |
| Male | 92 | 140 | | - | - |
| Female | 80 | 54 | | - | - |
| Age | 55.77±8.73 | 56.32±9.24 | 0.772 | - | - |
| Liver SWV (kPa) | 8.78±5.4 | 10.86±5.52 | 0.075 | - | - |
| Spleen SWV (kPa) | 16.19±11.93 | 36.99±18.62 | **<0.001** | 1.098(1.041-1.157) | **0.001** |
| AST (IU/L) | 47.91±55.66 | 49.66±25.42 | 0.846 | - | - |
| ALT (IU/L) | 25.47±22.28 | 20.55±6.79 | 0.153 | - | - |
| AST/ALT (AAR) | 1.92±0.76 | 2.5±1.14 | **0.006** | 1.696(0.79-3.641) | 0.175 |
| PLT (x 103) | 166.65±62.05 | 123.68±94.22 | **0.013** | 0.98(0.949-1.011) | 0.208 |
| AST/PLT (APRI) | 0.36±0.52 | 0.79±0.98 | **0.012** | 0.805(0.167-3.868) | 0.786 |
| Spleen diameter (cm) | 9.68±1.53 | 11.7±2.61 | **<0.001** | 1.867(0.894-3.897) | 0.096 |
| ALB (g/dL) | 4.35±0.39 | 3.99±0.69 | **0.004** | 0.472(0.09-2.46) | 0.372 |
| PLT/SD | 17.78±7.56 | 11.24±7.71 | **<0.001** | 1.257(0.888-1.78) | 0.198 |

The values are presented as the mean ± standard deviation; CI- confidence interval, SWV- shear wave velocity, AST- aspartate aminotransferase, ALT- alanine aminotransferase, AAR- AST/ALT ratio, PLT- platelet count, APRI- AST/PLT ratio index, ALB- albumin, SD- spleen diameter

Spearman correlation coefficients were used to assess the correlation between the EVs and elastography values. The Spearman correlation coefficient, Rho(ρ), is a value that ranges between +1 to -1. The closer the ρ is to 1, the more correlated the factors are likely to be. Similarly, the closer the ρ is to -1, the less correlated the factors are likely to be.

The diagnostic performance of the spleen elastography in the distinction of the EVs was assessed by receiver operating characteristic (ROC) analysis to determine the best cut-off values. The best cut-off value was determined while balancing the best sensitivity with the lowest false-positive rate. The area under the ROC curve (AUC) was also calculated.

## Results

In 122 of 488 patients (25%) with valid ARFI measurements, the technical parameters were unsatisfactory (IQR>30%). Of these individuals who could not be further evaluated, 117 cases were unreliable cases regarding splenic stiffness and 43 cases were unreliable cases regarding liver stiffness. Additionally, 38 of these cases were unreliable regarding both organs. These figures exceed 100%;, however, cases could exist in multiple categories. The final study population of evaluated cases with good quality technical parameters obtained consisted of 366 patients (232 men, 134 women), 192 of whom had HBV-related cirrhosis, 74 with HCV-related cirrhosis, and 100 with alcohol-related cirrhosis. The mean age of study participants was 55.92±12.8 years.

Among the 366 patients with valid measurements, 172 patients (47%) had no EVs at EGD. On univariate analysis, spleen shear wave velocity (SWV), spleen diameter, PLT, albumin, AAR, PLT/SD and APRI score were independently associated with EVs. On multivariate analysis, spleen SWV was independently associated with EVs (p<0.001; Table I). According to these results, spleen SWV was the most reliable test that could be used to predict EVs not only on univariate, but also on multivariate analysis.

The AUC of spleen elastography and the presence of EVs was 0.859 (CI: 0.781-0.938). With the Youndeen index, a cut-off value for detecting the presence of EVs using spleen elastography was determined. By setting the spleen elastography cut off value as 29.9 kPa, the sensitivity, specificity, positive predictive value, and negative predictive value were 85.1%, 79.1%, 81.6% (67.98-91.25%), and 82.94% (67.96-92.85%), respectively.

### *Liver and Spleen stiffness Measurements for Predicting EVs according to different etiologies*

Among the 192 cirrhotic patients with HBV, EVs were found in 100 patients. On univariate analysis a statistically significant correlation between liver stiffness and the presence EVs was established (p=0.022). However, on multivariate analysis, statistical differences were not observed between the mean liver stiffness values in patients with and without EVs (p=0.495). Unlike liver stiffness, a significant correlation was observed between spleen stiffness and EVs on univariate (p<0.001) and multivariate analyses (p=0.022; Table II). If the cutoff value applied to hepatitis B virus induced liver cirrho-

Table II. Analysis of non-invasive measurements for predicting EVs in HBV patients.

| **HBV** (n=192) | **Varices (-)** (n=92) | **Varices (+)** (n=100) | **p-Value** | **Multivariate analysis** OR (95% CI) | p-Value |
|---|---|---|---|---|---|
| Gender | | | 0.077 | - | - |
| Male | 48 | 74 | | - | - |
| Female | 44 | 26 | | - | - |
| Age | 53.04±8.22 | 56.44±8.3 | 0.162 | - | - |
| Liver SWV (kPa) | 7.53±3.79 | 11.28±5.55 | **0.009** | 0.89(0.637-1.244) | 0.495 |
| Spleen SWV (kPa) | 16.46±9.4 | 40±15.59 | **<0.001** | 1.22(1.029-1.447) | **0.022** |
| AST (IU/L) | 31.43±9.96 | 40.88±11.91 | **0.005** | 0.684(0.457-1.025) | 0.066 |
| ALT (IU/L) | 20.43±9.85 | 20.2±6.96 | 0.924 | - | - |
| AST/ALT (AAR) | 1.72±0.65 | 2.15±0.67 | 0.03 | 1.158(0.077-17.483) | 0.915 |
| PLT (x $10^3$) | 170.87±56.89 | 128.08±112.77 | 0.108 | - | - |
| AST/PLT (APRI) | 0.2±0.09 | 0.54±0.47 | **0.001** | - | 0.066 |
| Spleen diameter (cm) | 9.78±1.55 | 12.7±2.74 | **<0.001** | 2.615(0.952-7.183) | 0.062 |
| ALB (g/dL) | 4.45±0.22 | 4.11±0.45 | **0.002** | 14.952(0.02-11440.378) | 0.425 |
| PLT/SD | 17.6±5.21 | 10.16±6.86 | **<0.001** | 1.568(0.912-2.696) | 0.104 |

*The values are presented as the mean ± standard deviation; HBV – hepatitis B virus, CI – confidence interval, SWV – shear wave velocity, AST – aspartate aminotransferase, ALT – alanine aminotransferase, AAR – AST/ALT ratio, PLT – platelet count, APRI – AST/PLT ratio index, ALB – albumin, SD – spleen diameter

sis, the sensitivity, specificity, positive predictive value, negative predictive value and AUC were 96.0%, 82.6%, 64.8%(39.0%-85.5%), 98.4%(85.7%-10.0%), 0.920 (CI: .805-.979), respectively.

Among the 74 cirrhotic patients with HCV, EVs were found in 34 patients. No correlation between liver stiffness and EVs on univariate or multivariate analyses was found (all p≥0.05). However, a significant direct correlation (p=0.015) was found between spleen stiffness and EVs on univariate analysis, although this correlation was lost on multivariate analysis (p=0.288; Table III).

Among the 100 patients with alcoholic cirrhosis, EVs were found in 60 patients. No correlation between spleen stiffness and the presence of EVs was found (Table IV)

***Association between splenic diameter and EVs***

No correlation between the spleen diameter and EV on multivariate analysis was obtained. On univariate analysis, only the patients of HBV related liver cirrhosis showed significant correlation between spleen diameter and EV (p<0.001).

***Association between other non-invasive measurement and EVs***

Significant correlations between EVs and albumin (p=0.004) and PLT (p=0.013) were detected on univariate analysis. However, the correlations were not significant on multivariate analysis with alcoholic cirrhosis.

ALT and AST levels were not statistically different between the groups with and without EVs. The AAR ratio (p=0.006) and APRI score (p=0.012) were significantly higher in patients with EVs when compared with the group without EVs on univariate analysis, with the exception of alcoholic liver cirrhosis patients)

The PLT/SD ratio was a relatively good predictive factor for EVs (p<0.001) in HBV-related cirrhosis on univariate analysis, but no significant relationships were found on multivariate analysis or with other origin-related cirrhosis.

## Discussions

Increased resistance to portal blood flow is the key factor for portal hypertension (PTH) in liver cirrhosis. There are many PTH-related complications, and EVs is one of the most severe. As hepatic fibrosis progresses, hemodynamic and pathologic changes can be concomitantly found in the spleen, especially in the stages of hepatic fibrosis. The results of a previous study demonstrated that the size of the spleen increased as liver fibrosis progressed and was more apparent in the late stages. The density of the spleen changes in patients with splenomegaly due to tissue hyperplasia, angiogenesis, and fibrogenesis, as well as portal and splenic congestion [20]. Such changes of spleen stiffness are mechanical properties that can be quantified by ARFI elastography.

Recently, several reports have been published regarding the use of spleen ARFI elastography as a noninvasive diagnostic tool for the detection of EVs. Ye et al have reported a significant correlation between spleen elastography and EVs in patients with chronic HBV (sensitivity 84.1%, specificity 81%) [10]. Colecchia et al found significant correlation between spleen elastography and EV in patients with chronic hepatitis C related liver cirrhosis (sensitivity 98.5%, specificity 60.1%, negative predictive value 98.4%) [11]. Bota et al detected a positive associa-

Table III. Analysis of non-invasive measurements for predicting EVs in HCV patients.

| **HCV** (n=74) | **Varices (-)** (n=40) | **Varices (+)** (n=34) | **p-Value** | **Multivariate analysis** OR (95% CI) | p-Value |
|---|---|---|---|---|---|
| Gender | | | 0.419 | - | - |
| Male | 16 | 20 | | - | - |
| Female | 24 | 14 | | - | - |
| Age | 60.4±5.66 | 57.14±14.75 | 0.531 | - | - |
| Liver SWV (kPa) | 8.18±5.39 | 10.98±6.06 | 0.331 | - | - |
| Spleen SWV (kPa) | 12.1±8.08 | 34.08±23.82 | **0.015** | 1.299(0.801-2.107) | 0.288 |
| AST (IU/L) | 43.5±22.73 | 69.86±33.6 | 0.072 | - | - |
| ALT (IU/L) | 21±8.42 | 19.86±5.27 | 0.756 | - | - |
| AST/ALT (AAR) | 2.06±0.68 | 3.48±1.25 | **0.009** | - | 0.368 |
| PLT (x $10^3$) | 156.7±43.64 | 104.43±72.22 | 0.082 | - | - |
| AST/PLT (APRI) | 0.31±0.21 | 1.21±1.31 | 0.046 | - | 0.388 |
| Spleen diameter (cm) | 9.17±1.48 | 10.84±2.21 | 0.073 | - | - |
| ALB (g/dL) | 4.41±0.2 | 3.63±1.06 | **0.036** | - | 0.217 |
| PLT/SD | 18.12±8.34 | 10.8±9.18 | 0.107 | - | - |

The values are presented as the mean ± standard deviation; HCV – hepatitis C virus, CI – confidence interval, SWV – shear wave velocity, AST – aspartate aminotransferase, ALT – alanine aminotransferase, AAR – AST/ALT ratio, PLT – platelet count, APRI – AST/PLT ratio index, ALB – albumin, SD – spleen diameter

Table IV. Analysis of non-invasive measurements for predicting EVs in alcholic cirrhosis.

| **Alcohol** (n=100) | **Varices (-)** (n=40) | **Varices (+)** (n=60) | **p-Value** |
|---|---|---|---|
| Gender | | | 0.601 |
| Male | 28 | 44 | |
| Female | 12 | 16 | |
| Age | 57.4±10.62 | 55.73±8.28 | 0.664 |
| Liver SWV(kPa) | 12.27±7.34 | 10.1±5.52 | 0.408 |
| Spleen SWV(kPa) | 19.67±18.73 | 33.34±21.08 | 0.111 |
| AST(IU/L) | 90.2±104.86 | 54.87±32.03 | 0.23 |
| ALT(IU/L) | 41.5±40.46 | 21.47±7.43 | 0.071 |
| AST/ALT(AAR) | 2.23±0.97 | 2.63±1.45 | 0.454 |
| PLT(x $10^3$) | 166.9±89.41 | 125.33±70.08 | 0.206 |
| AST/PLT(APRI) | 0.78±0.96 | 1.02±1.34 | 0.635 |
| Spleen diameter(cm) | 9.94±1.55 | 10.45±1.93 | 0.497 |
| ALB(g/dL) | 4.07±0.65 | 3.97±0.81 | 0.756 |
| PLT/SD | 17.85±11.44 | 13.26±8.49 | 0.261 |

The values are presented as the mean ± standard deviation; SWV – shear wave velocity, AST – aspartate aminotransferase, ALT – alanine aminotransferase, AAR – AST/ALT ratio, PLT – platelet count, APRI – AST/PLT ratio index, ALB – albumin, SD – spleen diameter

tion between grade 2-3 EV and spleen elastography in patients with various etiologies (sensitivity 96.7%, specificity 47.6%) [12]. However, there was not any reports assessing diagnostic performance according to the differences of the etiologies resulting in cirrhosis.

The results from the current study indicated a significant correlation between spleen stiffness detected by ARFI and the presence of EVs, especially in cirrhosis resulting from HBV. However, spleen stiffness and other non-invasive tests were not reliable for prediction of EVs in cases of alcoholic-induced liver cirrhosis. Therefore, application of spleen elastography for detecting EVs should be avoided in patients with alcohol induced liver cirrhosis.

We have no explanation for the lack of correlation between spleen stiffness and EV in alcoholic liver cirrhosis. There are reports about various spleen sizes in cirrhosis of different etiologies. In alcoholic cirrhosis, the mean spleen size was significantly smaller than in the hepatitis C and nonalcoholic steatohepatitis [21]. In addition, splenomegaly resulted more in primary biliary cirrhosis, in HBV-related cirrhosis and in cryptogenic cirrhosis than in the alcoholic form [22]. These results show that pathophysiological features of spleen in liver cirrhosis may differ according to its varied etiology. Further studies may be necessary.

The data from the current study demonstrated that other noninvasive tests for detecting EVs (AAR, APRI

test, PLT count, spleen diameter, albumin, and PLT/SD ratio) were independently related to the presence of EVs on univariate analysis. These results corresponded well with the results of previous published studies [5,6,18,19]. However, in multivariate analysis, only spleen elastography remained as a reliable predictor for EVs.

There are several limitations to the current study. Firstly, for comparison purposes, we assessed only singular etiology among HBV, HCV, and alcohol-induced liver cirrhosis, meaning that those with multiple viral infections or combined causes for liver cirrhosis were not assessed. Secondly, there may have been other possible related causes resulting in EVs which were not excluded from our study. Therefore, the results may not be generalizable. Thirdly, among the 488 patients, spleen elastography was not reliable in 117 patients (24%) due to their interquartile range (>30%). This could result in poor reliability in a subsequent follow-up study. Additionally, its unreliable rate is relatively higher, as compared with Fibroscan, in which the inconclusive measurement rates were reported to be 14.3% [23] and 13% [24].

## Conclusions

Spleen stiffness as measured by ARFI may have the potential for use as a non-invasive method for determining the presence of EVs. However, the evidence supporting a similar role for replacing endoscopy is lacking. Furthermore, it is not an appropriate predictor for EVs in alcoholic cirrhosis. A larger study with an increased number of prospective cohort members with different cirrhosis etiologies will be necessary for a more accurate evaluation of the true utility of this method in clinical practice.

**Acknowledgement:** This work was supported by the Dong-A University research fund.

**Conflict of interest:** none

## References

1. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743-752.
2. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol 2007; 102: 2086–2102.
3. Lackner C, Struber G, Liegl B, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology 2005; 41: 1376-1382.
4. Schepis F, Cammà C, Niceforo D, et al. Which patients with cirrhosis should undergo endoscopic screening for esophageal varices detection? Hepatology 2001; 33: 333-338.
5. Giannini E, Botta F, Borro P, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003; 52: 1200-1205.
6. Giannini EG, Zaman A, Kreil A, et al. Platelet count/spleen diameter ratio for the noninvasive diagnosis of esophageal varices: results of a multicenter, prospective, validation study. Am J Gastroenterol 2006; 101: 2511-2519.
7. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV related cirrhosis. Hepatology 2007; 45: 1290-1297.
8. Kazemi F, Kettaneh A, N'kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large esophageal varices. J Hepatol 2006; 45: 230-235.
9. Lupsor M, Badea R, Stefanescu H, et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. J Gastrointestin Liver Dis 2009; 3: 303-310.
10. Ye XP, Ran HT, Cheng J, et al. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. J Ultrasound Med 2012; 31: 1245-1253.
11. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012; 143: 646-654.
12. Bota S, Sporea I, Sirli R, et al. Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients. Ann Hepatol 2012; 11: 519-525.
13. Friedrich-Rust M, Wunder K, Kriener S, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 2009; 252: 595-604.
14. Takahashi H, Ono N, Eguchi Y, et al. Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: a pilot study. Liver Int 2010; 30: 538-545.
15. Bota S, Sporea I, Sirli R, Popescu A, Dănilă M, Sendroiu M. Factors that influence the correlation of acoustic radiation force impulse (ARFI) elastography with liver fibrosis. Med Ultrson 2011; 13: 135-140.
16. Paquet KJ, Oberhammer E. Sclerotherapy of bleeding oesophageal varices by means of endoscopy. Endoscopy 1978; 10: 7-12.
17. Ishibashi H, Higuchi N, Shimamura R, Hirata Y, Kudo J, Niho Y. Sonographic assessment and grading of spleen size. J Clin Ultraound 1991; 19: 21-25.
18. Su CW, Chan CC, Hung HH, et al. Predictive value of aspartate aminotransferase to alanine aminotransferase ratio for hepatic fibrosis and clinical adverse outcomes in pa-

tients with primary biliary cirrhosis. J Clin Gastroenterol 2009; 43: 876-883.
19. Borsoi Viana MS, Takei K, Collarile Yamaguti DC, Guz B, Strauss E. Use of AST platelet ratio index (APRI Score) as an alternative to liver biopsy for treatment indication in chronic hepatitis C. Ann Hepatol 2009; 8: 26-31.
20. Li YJ, Qian LX, He W. A study on the relationship between liver fibrosis staging and spleen volume by computed tomography in patients with chronic hepatitis B. Chin J Misdiagnostics 2009; 9: 7561-7562.
21. Kashani A, Salehi B, Anghesom D, Kawayeh AM, Rouse GA, Runyon BA. Spleen size in cirrhosis of different etiologies. J Ultrasound Med 2015; 34: 233-238.
22. Bolondi L, Zironi G, Gaiani S, Li Bassi S, Benzi G, Barbara L. Caliber of splenic and hepatic arteries and spleen size in cirrhosis of different etiology. Liver 1991; 11: 198-205.
23. Calvaruso V, Bronte F, Conte E, Simone F, Craxì A, Di Marco V. Modified spleen stiffness measurement by transient elastography is associated with presence of large esophageal varices in patients with compensated hepatitis C virus cirrhosis. J Viral Hepat 2013; 20: 867-874.
24. Sharma P, Kirnake V, Tyagi P, et al. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. Am J Gastroenterol 2013; 108: 1101-1107.