The role of spleen stiffness using ARFI in predicting esophageal varices in patients with Hepatitis B and C virus-related cirrhosis

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Introduction. Current guidelines recommend that all patients with cirrhosis undergo upper gastrointestinal endoscopy (UGE) screening for esophageal varices (EV). Unfortunately, UGE has a lot of disadvantages, consequently various non-invasive methods of diagnosing EV have been proposed. We evaluated if spleen stiffness (SS) measured by Acoustic Radiation Force Impulse (ARFI) is a viable technique in diagnosing EV.

Methods. We recruited 178 patients with cirrhosis caused by Hepatitis B and C who underwent biochemical tests, abdominal ultrasound, UGE, LS and SS measurements using ARFI elastography. Based on the endoscopic results the patients were divided in 3 groups: without EV, with small EV (<5 mm) and with large EV (>5 mm).

Results. ARFI SS was the only non-invasive parameter associated with the presence of EV (2.7 ± 0.30 vs. 3.4 ± 0.52 , $p < 0.001$) and large EV (2.91 ± 0.36 vs. 3.86 ± 0.37 , $p = 0.001$) after multivariate logistic regression ($p < 0.001$). ARFI SS for predicting EV showed an AUROC of 0.872 (CI 95%: 0.799–0.944), for a cut-off value of 2.89 m/s: Sensitivity (Se) 91.4% (CI 95%: 81–97%), Specificity (Sp) 67.7% (CI 95%: 51–85%). ARFI SS for diagnosing large EV (>5mm) had better results with an AUROC 0.969 (CI 95%: 0.935–0.99), and for a cut-off of 3.30 m/s: Se 96.4% (CI 95%: 82–99.9%), Sp 88.5% (CI 95%: 78–95%).

Conclusions. SS measured using ARFI is a good method of detecting EV and is an excellent method of diagnosing large EV in patients with virus-related cirrhosis.

Key words: acoustic radiation force impulse, cirrhosis, esophageal varices, spleen stiffness, liver stiffness.

INTRODUCTION

Virus-related chronic hepatitis infection represents an important healthcare issue with a global prevalence for hepatitis C virus (HCV) estimated at 1%, while for hepatitis B virus (HBV) the prevalence is estimated at 3.5% [1].

Portal hypertension (PH) is a crucial consequence of cirrhosis, because it leads to serious complications such as the formation of esophageal varices (EV) and subsequently variceal bleeding. Variceal bleeding is correlated with an increase mortality rate, so the need to screen patients for PH is critical [2]. Hepatic vein pressure gradient is the best way of evaluating PH, but it rarely available in most hospitals and it is used primarily for research purposes [3]. Because of the high mortality rate associated with bleeding varices, current guidelines advocate that patients diagnosed with cirrhosis for the first time go through upper gastrointestinal endoscopy (UGE) screening [4]. UGE is invasive, expensive, not well tolerated by patients and requires highly trained individuals with experience; it remains a gold standard screening

method with many drawbacks [5]. Consequently, various non-invasive methods of diagnosing EV have been proposed involving either laboratory tests, ultrasound parameters and more recently liver stiffness (LS) [6–8]. The data obtained from recent research prompted the Baveno VI Consensus Workshop to conceive guidelines for patients who can avoid screening UGE using non-invasive tests: patients with a liver stiffness <20 kPa measured by transient elastography (Fibroscan) and a platelet count of over 150,000 carry a modest risk of possessing varices that demand treatment and can circumvent UGE [3]. Transient elastography (TE) has a high sensitivity and specificity in determining significant PH, but is not as accurate in predicting EV [6]. As a result with the new Baveno VI criteria around 20% of UGE are avoided, unfortunately a significant number of unnecessary UGE are still performed [9].

PH causes splenomegaly not only by portal congestion as previously thought, other factors such as overactivation of the splenic lymphoid tissue, increased angiogenesis and development of fibrosis appear to have a significant role [10, 11]. This increase

in fibrogenesis or spleen stiffness (SS) can be measured using various noninvasive techniques and has been shown to be directly correlated to hepatic vein pressure gradient [12, 13].

Elastography utilizing acoustic radiation force impulse (ARFI) is an easy to perform, fast, reproducible, noninvasive investigation that monitors the speed of shear wave propagation distant from the area of excitation in order to quantify tissue stiffness. Liver stiffness evaluated by ARFI elastography has already proven to possess excellent diagnostic accuracy in diagnosing liver cirrhosis [14]. The ARFI technique used to measure SS appears to be efficient in predicting EV when compared with upper endoscopy in a small number of studies and it is also accurate in diagnosing clinically significant PH when compared with invasive hepatic vein pressure gradient [12, 15–18]. Consequently we assessed the capability of SS using ARFI in predicting esophageal varices (EV) in patients with cirrhosis caused by Hepatitis B and C.

MATERIALS AND METHODS

We conducted a prospective study from January 2017 until May 2018. The study was achieved in conformity with the Declaration of Helsinki and was authorized by the local ethics committee. Patients in the study provided informed consent prior to study enrollment. We included patients over the age of 18 with cirrhosis diagnosed by clinical examination corroborated with laboratory and imaging. Serum biomarkers of fibrosis, elastography or liver biopsy were utilized for diagnosing uncertain cases of compensated cirrhosis. The viral etiology of cirrhosis was established by specific serologic markers. The exclusion criteria consisted of any additional cause for cirrhosis (autoimmune hepatic diseases, hepatitis D co-infection, heavy alcohol consumption, severe right heart failure, etc), hepatic carcinoma, portal vein thrombosis and patients who refused to undergo endoscopy. We also excluded patients with previous treatment for EV (endoscopic or β -blocker treatment).

All the patients who fulfilled the inclusion criteria underwent clinical, biological, echography and elastography measurements along with UGE. All tests were done within 7 days. Ultrasonography evaluation of the abdomen was performed in all patients utilizing the Siemens Acuson S2000™ ultrasound system (Siemens Medical Solutions, Inc.).

Spleen and liver stiffness measurements by ARFI were performed after an overnight fast. SS was measured with the left arm in abduction while the patients were in the right lateral decubitus position,

the LS was assessed with the right arm in abduction with the patient in left lateral decubitus position, the transducer was perpendicular to the longitudinal axis of the spleen or liver, placed intercostal; the area of interest encompassed 3.8–5.5 mm depth and 5 mm width and was located about 1–2 cm from the liver or spleen capsule, avoiding major vascular structures. During measurements patients were instructed to hold their breath. Five valid measurements expressed as propagation velocity (m/s) were obtained from each organ, with the final value expressed as the median of the total measurements. We also measured longitudinal splenic diameter and portal vein diameter. One single physician, blinded to other data, performed all the measurements.

All patients underwent UGE that were performed by 2 gastroenterologists who had no prior knowledge of the results of the ARFI measurements or of the biological or clinical data. Based on the endoscopic results the patients were separated in 3 groups: without EV, with small EV (<5 mm) and with large EV (>5 mm) [19].

Microsoft Office Excel and IBM SPSS 23 (Statistical Package for the Social Sciences Inc, Chicago, IL) were used to analyze the data. The results are shown as the mean plus minus the standard deviation. The Kolmogorov–Smirnov test was applied to establish which variables had symmetrical distribution and which had asymmetrical distribution. Univariate analysis using the independent t-test was performed for symmetrical distribution while the Mann Whitney U test was used for asymmetrical ones. Afterwards, variables found to be associated with the presence of EV on univariate analysis were incorporated into multivariate logistic regression analysis.

The diagnostic performance of variables for predicting EV was assessed using the area under the receiver operating characteristic (AUROC), the best cut-off values for predicting EV were determined using ROC curve. Diagnostic value was ascertained by using sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR). For all analyses, a p value of <0.05 was treated as statistically significant.

RESULTS

Patient characteristics

The clinical, biochemical, endoscopic and ultrasound characteristics of the study population

(178 patients) are presented in Table 1. The prevalence of females was higher reaching 55 percent. The etiology of cirrhosis was composed of 130 patients

with HCV (73%) and 48 patients with HBV (27%). 60 patients had no EV (33.7%), 62 patients had small EV (34.8%) and 56 possessed large EV (31.5%).

Table 1

Characteristics of patients (n = 178)

Variable	
Age (years)	60.3 ± 8.5
Sex	Male = 98 Female = 80
Etiology	Hepatitis B Virus = 48 Hepatitis C Virus = 130
Aspartate aminotransferase (IU/L)	49.0 ± 24.1
Alanine aminotransferase (IU/L)	51.1 ± 30.8
Platelets(*10 ³ /μL)	157.4 ± 77.6
Portal vein (mm)	10.3 ± 2
Spleen diameter (mm)	121.5 ± 25
International normalized ratio (INR)	1.05 ± 0.13
Hemoglobin (g/dl)	13.1 ± 1.3
Liver Stiffness (m/s)	2.20 ± 0.51
Spleen Stiffness (m/s)	3.20 ± 0.57
Esophageal Varices	No EV = 60
	Small EV = 62
	Large EV = 56

Performance of noninvasive tests in predicting esophageal varices

Table 2 illustrates in juxtaposition the variables of patients without EV and patients with EV. There were no significant differences concerning ages, aspartate aminotransferase, alanine aminotransferase,

international normalized ratio or hemoglobin. Patients with EV had lower platelets ($p = 0.005$), higher values for spleen diameter ($p = 0.001$), portal vein ($p = 0.003$), LS ($p = 0.006$) and SS ($p < 0.001$). On multivariate logistic regression analysis only SS was correlated with the existence of EV ($p < 0.001$).

Table 2

Comparison of variables between patients without esophageal varices and patients with esophageal varices

	No Esophageal Varices n = 62	Esophageal Varices n = 116	Univariate analysis	Multivariate analysis	
			p value	OR (95% CI)	p value
Age (years)	61 ± 10	60.3 ± 8.5	0.45	—	—
Aspartate aminotransferase (IU/L)	44.0 ± 24	51 ± 24	0.20	—	—
Alanine aminotransferase (IU/L)	46.1 ± 26	53 ± 32	0.26	—	—
Platelets(*10 ³ /μL)	189.1 ± 73.2	140 ± 75.1	0.005	0.001 (0.99–1.01)	0.832
Portal vein (mm)	9.7 ± 1.79	10.7 ± 2.0	0.003	0.75 (0.77–1.5)	0.659
Spleen diameter (mm)	106 ± 17.5	129 ± 24	0.001	0.32 (0.99–1.01)	0.64
International normalized ratio (INR)	1.04 ± 0.12	1.05 ± 0.14	0.766	—	—
Hemoglobin (g/dl)	13.1 ± 1.2	13.1 ± 1.3	0.820	—	—
Liver Stiffness(m/s)	2 ± 0.48	2.3 ± 0.5	0.006	0.3(0.19–2.77)	0.64
Spleen Stiffness(m/s)	2.7 ± 0.30	3.4 ± 0.52	<0.001	3.77(5.6–339)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

The ROC curve was applied to ascertain the efficiency of SS for predicting EV and is presented in Figure 1. The AUROC value was 0.872 (95% CI, 0.799–0.944). The cut-off value of 2.89 m/s was capable of revealing the presence of EV with a

91.4% Se (CI 95%: 81–97%), 67.7% Sp (CI 95%: 51–85%), 84.13% PPV (CI 95%: 78–91%), 80.77% NPV (CI 95%: 64–91%), 2.82 PLR (CI 95%: 1.76–5.30), and NLR of 0.127 (CI 95%: 0.05–0.29).

Figure 1. Receiver operating characteristic (ROC) curve of spleen stiffness for the prediction of esophageal varices.

Performance of various noninvasive tests in predicting large esophageal varices (>5mm)

A comparison between variables of patients with large EV (>5mm) and patients without large EV is presented in Table 3. On univariate analysis, patients

with large EV had lower platelets, higher values for aminotransferases, international normalized ratio, spleen diameter, portal vein, LS and SS, but SS was the single parameter correlated with the presence of large EV on multivariate logistic regression ($p < 0.001$).

Table 3

Comparison of variables between patients with large esophageal varices and patients without large esophageal varices

	Large varices (> 5mm)		Univariate analysis	Multivariate analysis	
	Absent n = 122	Present n = 56		OR(95% CI)	p value
Age (years)	59.5 ± 9.0	62 ± 7.1	0.206	–	–
Aspartate aminotransferase (IU/L)	44 ± 22.2	56.6 ± 25	0.004	0.979(0.94–1.020)	0.94
Alanine aminotransferase (IU/L)	45 ± 24.5	64.0 ± 38.9	0.007	1.01(0.976–1.047)	0.99
Platelets(*10 ³ /μL)	177.2 ± 81.0	114.2 ± 47.0	0.001	0.99(0.98–1.01)	0.92
Portal vein (mm)	10.0 ± 1.95	11.1 ± 1.92	0.004	1.20(0.78–1.66)	0.32
Spleen diameter(mm)	115.4 ± 21.7	134.9 ± 26.9	0.002	1.03(0.99–1.07)	0.07
International normalized ratio (INR)	1.02 ± 0.12	1.09 ± 0.14	0.02	4.1(0.35–550)	0.55
Hemoglobin(g/dl)	13.1 ± 1.23	13.0 ± 1.46	0.69	–	–
Liver Stiffness(m/s)	2.10 ± 0.50	2.39 ± 0.49	0.017	0.54(0.13–2.26)	0.40
Spleen Stiffness(m/s)	2.91 ± 0.36	3.86 ± 0.37	0.001	62.3(7.16–541.9)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.

The ROC curve was used to ascertain the performance of SS in the prediction of large EV and is presented in Figure 2. The AUROC was 0.969 (95% CI, 0.935–0.99). The cut-off value of 3.30 m/s was capable to rule out EV with a

Se 96.4% (CI 95%: 82–99.9%), Sp 88.5% (CI 95%: 78–95%), PPV 79.41% (CI 95%: 66–89%), NPV 98.18% (CI 95%: 89–99.7%), PLR 8.38 (CI 95%: 4.17–16.3), NLR 0.04 (CI 95%: 0.01–0.28).

Figure 2. Receiver operating characteristic (ROC) curve of spleen stiffness for the prediction of large esophageal varices.

DISCUSSION

Our study showed that SS measured using ARFI is a good method of predicting EV (AUROC = 0.87, CI 95%: 0.799–0.944) and is excellent at identifying large EV (AUROC = 0.969, CI 95%: 0.935–0.99) while LS was not associated with the presence of EV or large EV. A SS cut-off value of 2.89 m/s could exclude EV with a 91.4% Se (CI 95%: 81–97%), 67.7% Sp (CI 95%: 51–85%), with a good NPV 80.77% (CI 95%: 64–91%), unfortunately it has a wide confidence interval, probably because of the small sample size. The SS cut-off value of 3.3 m/s could be used to exclude large EV with a Se 96.4% (CI 95%: 82–99.9%), Sp 88.5% (CI 95%: 78–95%) with an excellent NPV 98.18% (CI 95%: 89–99.7%).

Studies published over the years showed that stiffness of spleen using various techniques such as TE, ARFI/Point Shear Wave Elastography, 2D-Shear Wave Elastography, Magnetic Resonance Elastography was a viable method in predicting EV [20]. However, most of the studies involving SS have used TE and it is necessary to take into account a few ways in which ARFI is superior to TE. ARFI allows the examiner to accurately select the area being measured for stiffness and a single ARFI probe can be used in both obese and non-obese patients. Furthermore, upper SS values measured by TE are limited to 75 kPa, SS often reaching values above that, while ARFI does not have this problem [14].

A number of studies have evaluated SS measured by ARFI as a noninvasive method of predicting EV [12, 15–18, 21, 22]. Similar to our study, Takuma et al. found that a cut-off of 3.3 m/s could exclude the presence of EV in compensated cirrhosis (AUROC 0.921, Se 98.9, Sp 62.9, PLR 2.661, NLR 0.018) [16]. In the same study the performance of predicting EV (AUROC 0.934) was better than in our study, while using a the larger cut-off value 3.18 m/s [16].

An important issue is the fact that the correlation between splenic stiffness and the presence of EV depends on the etiology of cirrhosis; for example in alcoholic cirrhosis SS seems not to be associated with the presence of EV, while SS in virus-related cirrhosis is associated [17]. Furthermore, in a study where the prevalence of alcoholic cirrhosis was 31%, the accuracy of SS in predicting EV had an AUROC of only 0.578 [23]. Similarly, Kim et al. who included in their study cirrhotic patients with multiple etiologies where 32.8% were of alcoholic etiology the performance of SS using ARFI for the prediction of EV was fair with an AUROC of 0.785 and an even lower accuracy for the detection of large EV (AUROC 0.762) [22].

In contrast, studies performed on patients with only hepatitis B virus cirrhosis using ARFI showed a higher accuracy for predicting EV [17, 18]. Likewise in patients with hepatitis C virus cirrhosis Rizzo et al. discovered that a SS cut-off

value of 3.1 m/s measured by ARFI was excellent for diagnosing EV (AUROC 0.959); interestingly in their study the researches divided the spleen into 3 regions and obtained stiffness measurement from each region, thus by uniformly covering of the spleen their result were significantly improved [15].

We admit that our study has a number of limitations, firstly the small number of patients included, secondly we only evaluated patients with virus-related cirrhosis, and further research should separate patients by etiology in order to choose

appropriate cutoff values for each etiology. Lastly, the study was performed in a single center and had no external validation or extensive internal validation. Further studies need to be conducted in order to assess the viability of ARFI in predicting EV taking into account the etiology.

In conclusion, SS measured by ARFI is a good method of revealing the presence of EV (AUROC 0.869) and it is an excellent method of identifying the presence of large EV (>5 mm) with an AUROC 0.969 in patients with virus-related cirrhosis.

Introducere. Ghidurile actuale recomandă ca toți pacienții cu ciroză să efectueze endoscopie digestivă superioară (EDS) pentru screening-ul varicelor esofagiene (VE). Însă EDS prezintă numeroase dezavantaje, drept pentru care au fost studiate metode non-invazive pentru diagnosticul VE. Am evaluat dacă elasticitatea splinei folosind Acoustic Radiation Force Impulse (ARFI) este o tehnică bună de diagnostic a VE.

Metode. Am recrutat 178 de pacienți cu ciroză cauzată de hepatita B și C care au efectuat teste biochimice, ecografie abdominală, EDS, elasticitatea ficatului (LS) și elasticitatea splinei (SS) utilizând elastografia ARFI. Pe baza rezultatului endoscopic, pacienții au fost împărțiți în 3 grupe: fără VE, cu VE mici (<5mm) și cu VE mari (>5mm).

Rezultate. ARFI SS a fost singurul parametru non-invaziv care s-a asociat cu prezența de VE (2.7 ± 0.30 vs. 3.4 ± 0.52 , $p < 0.001$) și VE mari (2.91 ± 0.36 vs. 3.86 ± 0.37 , $p = 0.001$) după regresia logistică multivariată ($p < 0.001$). ARFI SS în predicția VE a arătat AUROC de 0.872 (CI 95%: 0.799–0.944), pentru o valoare cut-off de 2.89m/s: Sensibilitate (Se) 91.4% (CI 95%: 81–97%), Specificitate (Sp) 67.7% (CI 95%: 51–85%). ARFI SS pentru diagnosticarea VE mari (>5mm) a avut rezultate mai bune cu AUROC 0.969 (CI 95%: 0.935–0.99) pentru un cut-off de 3.30 m/s: Se 96.4% (CI 95%: 82–99.9%), Sp 88.5% (CI 95%: 78–95%).

Concluzii. SS măsurată folosind ARFI este o metodă bună de diagnostic a VE și este o metodă excelentă de diagnostic a VE mari la pacienții cu ciroză virală.

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