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Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients?

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ABSTRACT

Aim. To establish an algorithm which includes the liver stiffness (LS) and/or spleen stiffness (SS) assessed by ARFI for the prediction of significant esophageal varices-EV (at least grade 2). **Material and methods.** Our study included 145 newly diagnosed cirrhotic patients admitted in our Department between September 2009-August 2011. 62 patients (42.7%) had significant EV. We performed 10 ARFI measurements in each patient, both in the liver and in the spleen; median values were calculated, expressed in meters/second. In 24 consecutive newly diagnosed cirrhotic patients admitted between September 2011-December 2011, we prospectively analyzed the value of the new score for predicting significant EV. **Results.** The LS and SS assessed by ARFI elastography, and the percentage of patients with ascites were stastically significant higher in patients with significant EV as compared with those without EV or grade 1 EV. By multiple regression analysis we obtained the following formula for predicting significant EV: prediction of significant EV (Pred EV_{2-3}) score: -0.572 + 0.041 x LS (m/s) + 0.122 x SS (m/s) + 0.325 x ascites (1-absent, 2-present). The best Pred EV_{2-3} cut-off value for predicting significant EV was > 0.395 (AUROC = 0.721, accuracy = 69.6%). The accuracy in the group of patients in which the value of this score was prospectively analyzed was similar with that obtained in the first cohort of patients (70.8 vs. 69.6%). In conclusion, the proposed Pred EV_{2-3} score had a enough good value for predicting significant EV.

Key words. Spleen stiffness. Liver stiffness. Liver cirrhosis. Portal hypertension. Acoustic Radiation Force Impulse Elastography.

INTRODUCTION

Liver cirrhosis is the final stage of chronic hepatopathies and this disease had lots of complication: portal hypertension, hepatocellular carcinoma, hepato-renal syndrome, etc. Development of esophageal varices (EV) due to portal hypertension is an important complication. Variceal bleeding is a life-threatening event with mortality per bleeding episode of approximately 10-20%,[1-3] and one year survival is only 63%.[4] According to the Baveno consensuses[5] the screening for EV in cirrhotic patients by upper gastrointestinal endoscopy is a strong recommendation and the primary prevention of variceal bleeding applies in patients with previously diagnosed significant EV detected by periodical gastroscopy.[5,6]

In the last years several studies showed that Transient Elastography (TE) could enough accurate to predict the presence of significant EV.[7-10]

ARFI (acoustic radiation force impulse) elastography is a new method used for the evaluation of liver fibrosis.

ARFI imaging technology involves the mechanical excitation of tissue using short-duration acoustic pulses (push pulses) in a region of interest chosen by the examiner, producing shear waves that spread away from the region of interest, generating localized, micron-scale displacements into the tissue.[11-12] Simultaneously, detection waves of lower intensity than that of the push pulse are generated. The push pulse uses a few hundred cycles

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and different voltage compared to the short cycle B-mode pulse. The moment of interaction between the shear waves and the detection waves marks the period of time elapsed between the generating of shear waves and their entire crossing of the region of interest. By recording the shear wave front at several locations and correlating these measurements with the elapsed time, the shear wave velocity (meters/second-m/s) can be quantified; generally, the stiffer a region in the tissue, the greater the shear wave velocity as it travels through this region.[13-16]

Since transient elastography (TE) showed encouraging results for the evaluation of portal hypertension,[7-10] we tried to find if ARFI elastography, is able or not to predict the presence of significant esophageal varices.

OBJECTIVE

The aim of this paper was to establish an algorithm which includes the liver stiffness (LS) and/or spleen stiffness (SS) assessed by ARFI for the prediction of significant esophageal varices-EV (at least grade 2).

MATERIAL AND METHODS

Patients

Our study included 145 consecutive newly diagnosed cirrhotic patients admitted in our Department between September 2009-August 2011. The diagnosis of liver cirrhosis was established by clinical, histological, ultrasound, endoscopic and/or laparoscopic criteria. All the patients signed the informed consent, the study was in accordance with the Helsinki Declaration of 1975 and was approved by the local Ethics Committee.

In 14 patients (9.6%) the diagnosis of liver cirrhosis was establish when the patients presented to the hospital with esophageal bleeding.

No patient was treated with beta-blockers before ARFI measurements and also, no patients had portal thrombosis on ultrasound examination.

The data from this 145 patients were used to create a new score (which included LS and SS) for predicting significant EV.

In 24 consecutive newly diagnosed cirrhotic patients admitted in our Department between September 2011-December 2011, we prospectively analyzed the value of the new score for predicting significant EV.

Spleen and liver stiffness evaluation by means of ARFI

In each patient was measured LS by means of ARFI in the right liver lobe, 1-2 cm below the liver capsule, by intercostal approach, with the patient laying in left lateral decubitus (Figure 1). SS was also assessed by means of ARFI, 1-2 cm under de spleen capsule, by intercostal approach, with the patient laying in right lateral decubitus (Figure 2). Scanning by means of ARFI was performed with minimal scanning pressure applied by the operator, while the patients were asked to stop breathing for a moment, in order to minimize breathing motion. ARFI measurements were performed with a Siemens Acuson

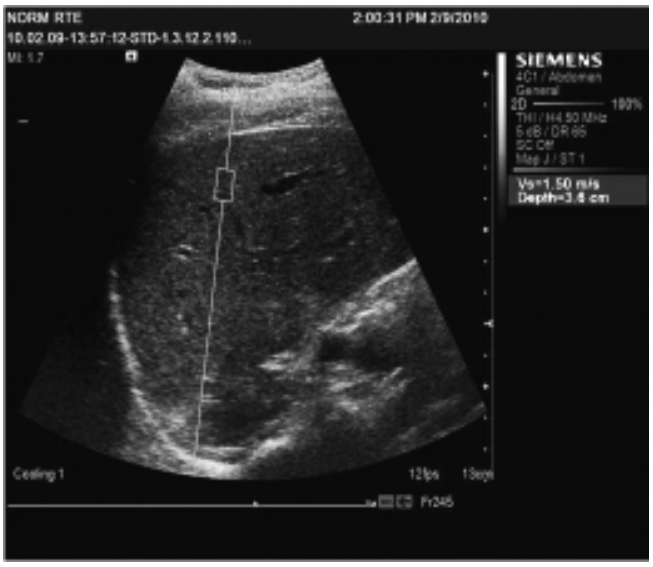

Figure 1. *ARFI measurement in the liver.*

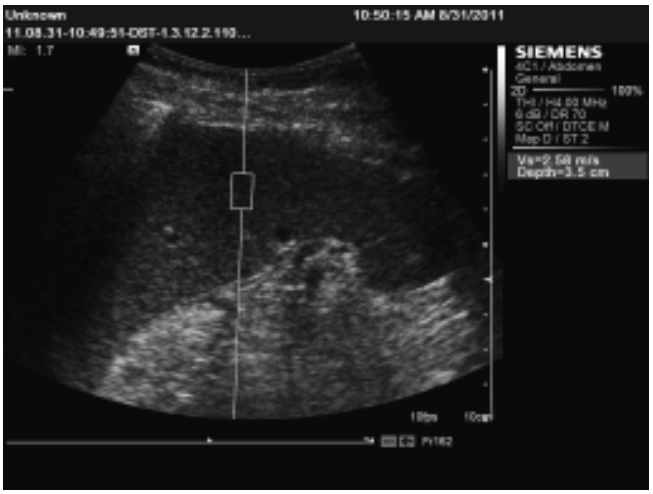

Figure 2. *ARFI measurement in the spleen.*

S2000™ ultrasound system. In each patient 10 valid ARFI measurements were performed both in the liver and in the spleen and median values were calculated, the results being expressed in m/s.

ARFI measurements were performed blind to the endoscopy data. In case of patients with focal liver lesions, ARFI measurements were performed outside of the tumor.

Upper gastrointestinal endoscopy

All cirrhotic patients included in our study underwent upper endoscopy, using a flexible EVIS EXERA video gastroscope (Olympus Europe Medical Systems, Hamburg, Germany).

EV were classified as:

- **Small (grade 1).** Small straight varices.
- **Medium (grade 2).** Enlarged tortuous varices occupying less than one third of the lumen.
- **Large (grade 3).** Large coil-shaped varices occupying more than one third of the lumen.

We classified the patients in 2 groups: without varices or small EV and the other group with significant EV (grade 2 and 3).

The interval between ARFI measurements and the upper gastrointestinal endoscopy was between 0-30 days.

The operators who performed the gastroscopy were blinded to elastographic measurements.

Ultrasound examination

The ultrasound examination was performed in each patient in the same session with ARFI measurements using a Siemens Acuson S2000™ ultrasound system, with a convex array probe of 4-9 MHz. The antero-posterior diameter of the spleen was measured and considered to be indicative of the spleen size. The patients were evaluated also for focal liver lesions, portal vein thrombosis, presence of ascites.

Statistical analysis

The data obtained from our patients were collected in a Microsoft Excel file, the statistical analysis being performed using the MedCalc Software (MedCalc program, Belgium) and WINK Statistical Data Analysis Research Software (Texasoft, Cedar Hill, Texas, USA). ARFI measurements, age, laboratory data were numeric variables, so the mean and standard variation were calculated.

Differences between numerical variables were analyzed by nonparametric tests (Mann-Whitney or Kruskal-Wallis tests). The Chi-square (χ^2) test (with Yates' correction for continuity) was used for the comparison of two proportions expressed as a percentage (n designates the total number of patients included in a particular subgroup).

Multiple regression analysis was used to calculate the new score for prediction of significant based on LS and SS assessed by ARFI elastography, and the presence or history of ascites.

The diagnostic performances of LS and SS assessed by means of ARFI elastography, and the new score which includes LS and SS were assessed by using receiver operating characteristics (ROC) curves that were built for the detection of significant EV. Optimal cut-off values were chosen so that the sum of sensitivity (Se) and specificity (Sp) would be the highest. DeLong test was used to compare AUROC curves. 95% confidence interval were calculated for each predictive test. A p-value < 0.05 was regarded as significant for each statistic test.

RESULTS

The main characteristics of the patients included in this study are presented in table 1.

Valid ARFI measurements in the liver in 143/145 patients (98.6%) and in the spleen in 142/145 patients (97.9%).

The patients were divided in 2 groups: without or with grade I EV (EV_{0-1}) and patients with significant (at least grade 2 EV) - EV_{2-3}. The LS and SS assessed by ARFI elastography and the percentage of patients with ascites were significantly higher in patients with EV_{2-3} as compared with those with EV_{0-1} (Table 2).

The best LS cut-off value for predicting significant EV was > 2.25 m/s [AUROC 0.596, p = 0.04, with 93.4% Se, 28.9% Sp, 49.5% positive predictive value (PPV), 85.7% negative predictive value (NPV) and 56.5% accuracy].

The best SS cut-off value for predicting significant EV was > 2.55 m/s (AUROC 0.578, p = 0.004, with 96.7% Se, 21% Sp, 47.6% PPV, 89.4% NPV and 53.1% accuracy).

We considered the LS, SS assessed by means of ARFI, and the presence of ascites to calculate a new score to predict the presence of significant EV using multiple regression analysis.

The following formula was obtained:

Prediction of significant EV (Pred EV_{2-3}) score: -0.572 + 0.041 x LS (m/s) + 0.122 x SS (m/s) + 0.325 x ascites (1-absent, 2-present).

The mean Pred EV_{2-3} value was statistically significant higher in the group of patients with significant EV *vs.* those without or grade 1 EV (Figure 3):

• (0.508 ± 0.158) *vs.* (0.358 ± 0.191), p < 0.0001.

The best Pred EV_{2-3} cut-off value for predicting significant EV was > 0.395 (AUROC 0.721, p = 0.0001, with 75 % Se, 61.8 % Sp, 61.4% PPV, 78.2% NPV and 69.6% accuracy) (Figure 4).

The Pred EV_{2-3} score had a better predictive value for the presence of significant EV that LS and SS assessed by means of ARFI (Table 3).

In a cohort of 24 patients, the value of PredEV_{2-3} score for predicting significant EV was prospectively

Table 1. The main characteristics of the patients.

Parameter	Number of patients
• Number of patients	145
• Mean age (years)	59.1 ± 10.3
• Gender	
Male	n = 87 (60%)
Female	n = 58 (40%)
• Mean body mass index (kg/m²)	26.7 ± 4.3
• Etiology of liver cirrhosis	
Hepatitis C virus	n = 49 (33.8%)
Hepatitis B virus	n = 17 (11.7%)
Hepatitis B+D virus	n = 4 (2.7%)
Hepatitis B+C virus	n = 3 (2.1%)
Alcoholic	n = 45 (31.1%)
Nonviral, nonalcholic	n = 27 (18.6%)
• Esophageal varices:	
Absent	n = 59 (40.7%)
Grade I	n = 24 (16.6%)
Grade II	n = 42 (28.9%)
Grade III	n = 20 (13.8%)
• Patients with esophageal bleeding	n = 14 (9.6%)
• Ascites	
No	n = 82 (56.5%)
Yes	n = 63 (43.5%)
• Hepatocellular carcinoma	
No	n = 134 (92.4%)
Yes	n = 11 (7.6%)
• Child-Pugh class	
A	n = 66 (45.5%)
B	n = 63 (43.4%)
C	n = 16 (11.1%)
• Mean MELD score	12.4 ± 5.1
• Mean aspartat aminotransferase value (U/L)	96.2 ± 98.3
• Mean alanine aminotransferase value (U/L)	65.2 ± 62.3
• Mean alkaline phosphatase value (U/L)	149.6 ± 114.7
• Mean gama-glutamyl transpeptidase value (U/L)	160.2 ± 184.1
• Mean total bilirubin value (mg/dL)	2.8 ± 2.6

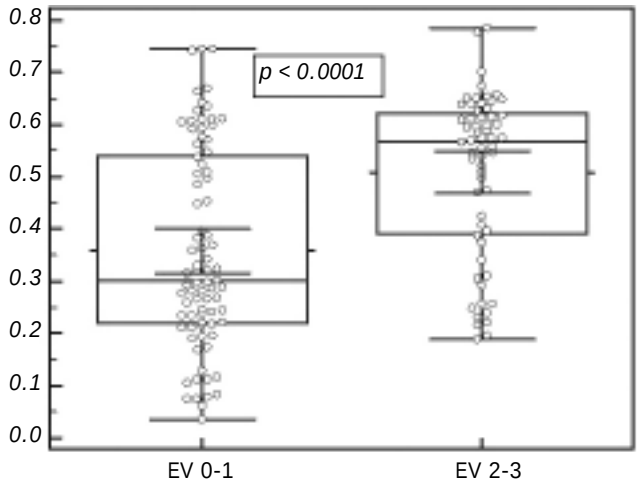

Figure 3. *The mean Pred EV_{2-3} in cirrhotic patients with EV_{0-1} and EV_{2-3}.*

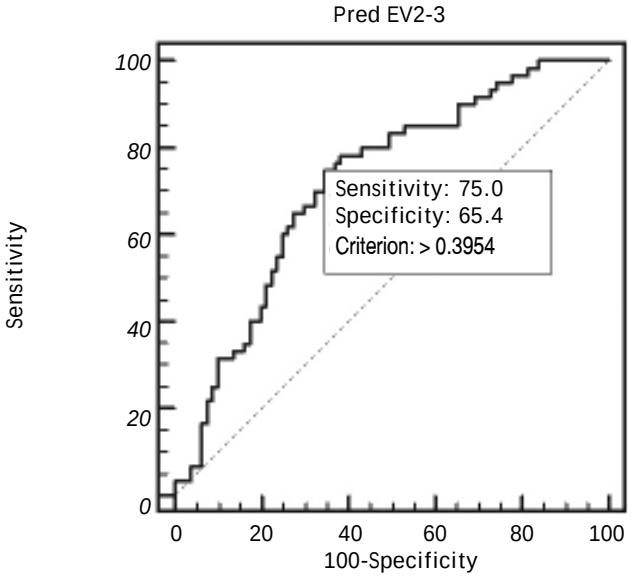

Figure 4. *AUROC curve for predicting significant EV.*

Table 2. The differences between cirrhotic patients with EV_{0-1} vs. those with EV_{2-3}.

Parameter	EV_{0-1} (83 patients)	EV_{2-3} (62 patients)	p
Mean LS (m/s)	2.81 ± 0.80	3.06 ± 0.67	0.03
Mean SS (m/s)	3.08 ± 0.61	3.28 ± 0.50	0.04
Mean spleen size (mm)	132.1 ± 26.2	138.4 ± 25.3	0.07
Percentage of patients with ascites (%)	34.9	70.9	0.0001

Table 3. Comparison between AUROC curves for Pred EV_{2-3} score, LS and SS assessed by ARFI.

		Difference between areas	Standard error	95% Confidence Interval	p
AUROC Pred EV_{2-3} (0.721)	AUROC SS (0.578)	0.143	0.047	0.042 to 0.230	0.004
AUROC Pred EV_{2-3} (0.721)	AUROC LS (0.596)	0.125	0.053	0.030 to 0.241	0.01

analyzed. The distribution of EV, in this cohort of patients was: 9 patients (37.5%) did not have EV, 3 patients (12.5%) had grade 1 EV, 6 patients (24%) had grade 2 EV and, 6 patients (24%) had grade 3 EV. PredEV_{2-3} score had 66.7% Se, 75% Sp, 72.7% PPV, 69.2% NPV and 70.8% accuracy to predict significant EV.

DISCUSSION

Several studies were published regarding the predictive value of LS and SS assessed by means of TE for the presence of significant EV.[7-10,17] For detection of significant EV, AUROC curves ranged between 0.72-0.78 for LS assessed by TE[8-10,17] and between 0.78-0.84 for SS.[7,17] Starting from this results, in the last time several studies analyzed the values of ARFI elastography for predicting significant portal hypertension.[18-21]

Salzl, *et al.*[18] presented the only data regarding the correlation of ARFI measurements with hepatic venous pressure gradient measurements. They obtained a good correlation of LS measurements assessed by ARFI with hepatic venous pressure gradient measurements (r = 0.709), and the AUROC curve for predicting clinically significant portal hypertension was 0.874.

Vermehren, *et al.*[19] assessed the predictive value of LS and SS assessed by ARFI for predicting significant EV and the AUROC curves were similar with those obtained in our present study.

Rifai, *et al.*[20] obtained a significantly better performance of LS as compared with SS for predicting significant portal hypertension (AUROC 0.90 *vs.* 0.68), but in that study were included only 30 patients with cirrhosis and significant portal hypertension, while 70 patients had chronic hepatopathies with various stages of fibrosis and 25 subjects were the control group. Also, the LS cut-off value proposed by Rifai, *et al.,* for predicting significant portal hypertension (1.67 m/s), is lower than the ARFI cut-off values proposed by the most published studies for diagnosing liver cirrhosis.[13,22-25]

In a previous study published by our group,[21] which included 57 cirrhotic patients, no significant differences regarding SS were observed between patients with and without EV, also between those with and without a history of variceal bleeding.

In our present study, were included only newly diagnosed cirrhotic patients who did not received beta-blockers before ARFI measurements, while in other studies[19-21] were included patients with history of variceal bleeding, or implantation of transjugular intrahepatic portosystemic shunt, so most probably some patients received beta-blockers before elastographic measurements. This is important, because was demonstrated that LS assessed by TE is influenced by the use of beta-blockers.[26] Also, in our study, the period of time between ARFI measurements and gastroscopy was 0-30 days, while in the others studies was until 12 months.

Also, our study is the first which combine the LS and SS in order to increase the value of ARFI elastography for predicting significant EV. Pred EV_{2-3} score, based on LS and SS measurements by means of ARFI elastography, and the presence of ascites, had a enough good value for predicting significant EV (AUROC = 0.721, 69.6% accuracy), comparable with the value of LS and SS assessed by means of TE showed by the other studies,[7-10,17] and much

better than LS and SS alone. The accuracy in the group of patients in which the value of this score was prospectively analyzed was similar with that obtained in the first cohort of patients.

In conclusion, the Pred EV_{2-3} score, which includes LS and SS assessed by means of ARFI, and the presence of ascites had a enough good value for predicting significant EV, but at this moment the noninvasive methods cannot replace the upper gastrointestinal endoscopy for the screening of EV in cirrhotic patients.

ABBREVIATIONS

- **ARFI:** acoustic radiation force impulse.
- **LS:** liver stiffness.
- **SS:** spleen stiffness.
- **EV:** esophageal varices.
- **AUROC:** aria under a receiver operating curve.
- **TE:** transient elastography.
- **m/s:** meters/second.
- **n:** the total number of patients included in a particular subgroup.
- **Se:** sensitivity.
- **Sp:** specificity.
- **PPV:** positive predictive value.
- **NPV:** negative predictive value.

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