The influence of liver residual mass on the values of Acoustic Radiation Force Impulse Elastography (ARFI) in cirrhotic patients

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Aim: The aim of our study was to assess the influence of liver residual mass in cirrhotic patients on the liver stiffness (LS), measured by ARFI elastography. Methods: Two hundreds eleven cirrhotic patients were enrolled. To evaluate the liver residual mass, the Child-Pugh and MELD scores were used and 10 valid ARFI measurements were performed. The correlation between Child-Pugh, MELD scores and the LS were evaluated. Results: Valid ARFI measurements were not obtained in 3 patients. A direct, very low correlation between the LS values and the Child-Pugh (r=0.264, p<0.001) and MELD scores (r=0.194, p=0.005) was found. A direct, low correlation between LS measurements and total bilirubin (r=0.271, p<0.001) and an inverse, low correlation with albumin (r=-0.270, p<0.001), prothrombin time (r=-0.196, p=0.006), cholinesterase (r=-0.241, p=0.003) was obtained. The LS mean values were statistically significant higher in patients with Child-Pugh class B vs. A (p=0.002) and in Child-Pugh C vs. A (p<0.001). The values were not significantly different in patients with Child-Pugh B vs. C (p=0.06). Conclusions: Higher values of LS measurements by means of ARFI could be an indicator of decreased liver functional reserve, evaluated by means of Child Pugh or Meld scores.

Keywords: Child-Pugh, MELD, liver cirrhosis, liver stiffness, ARFI Elastography

Rezumat
Scop: Evaluarea influenței rezervei funcționale hepatice la pacienții cu ciroză hepatică asupra valorilor durității hepatice determinată prin elastografia ARFI. Material și metodă: S-au studiat 211 pacienți cu ciroză. S-a folosit scorurile Child-Pugh și MELD pentru evaluarea rezervei funcționale hepatice. S-au efectuat efectuat 10 măsurători ARFI valide la fiecare pacient. S-a studiat correlația între scorurile Child-Pugh si MELD și duritatea hepatică. Rezultate: La 3 pacienți nu s-au obținut măsurători ARFI valide. S-a găsit o corelație directă, foarte slabă între valorile ARFI scorul Child-Pugh (r=0.264, p<0.001) și MELD (r=0.194, p=0.005). S-a obținut o corelație directă, slabă între valorile ARFI și bilirubina totală (r=0.271; p<0.001) și o corelație inversă, slabă cu albumina (r=-0.270; p<0.001), timpul de protrombină (r=-0.196; p=0.006), colinesteraza (r=-0.241; p=0.003). Valorile ARFI au semnificativ statistic mai mari la pacienții cu clasă Child-Pugh B vs. A (p=0.002) și cei cu Child-Pugh C vs. A (p<0.001). Nu au fost diferențe semnificative la pacienții cu clasă Child-Pugh B vs. C (p=0.06). Concluzii: Valorile mai mari ale durității hepatice determinate prin ARFI, pot fi un indicator a scăderii rezervei funcționale hepatice, evaluată prin scorul Child-Pugh sau MELD.

Cuvinte cheie: Child-Pugh, MELD, ciroza hepatică, duritatea hepatică, elatografia ARFI

Introduction
Noninvasive methods for the assessment of liver fibrosis have become very popular in the latter period. They can be serological tests (such as FibroTest, ELF score-Enhanced liver fibrosis score) or elastographic methods (such as FibroScan, Real-Time Elastography or Acoustic Radiation Force Impulse Elastography).

Acoustic Radiation Force Impulse elastography (ARFI) is a new method used for the assessment of liver
fibrosis [1-5], offered by Siemens and integrated into an ACUSON S2000 ultrasound system.

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 in the tissue [6-7]. Simultaneously, detection waves of lower intensity than that of the push pulse are generated. The push pulse uses a few hundred cycles and different voltage compared to the short cycle B-mode pulse. The moment of interaction between the shear waves and 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 [2, 8-10].

An advantage of the elastographic methods as compared to the serological ones seems to be that they can stratify the severity of liver cirrhosis (serological tests evaluate only the severity of fibrosis).

The aim of this study was to assess, in cirrhotic patients, the influence of liver residual mass on liver stiffness (LS), measured by ARFI elastography.

Patients and methods

The study included 211 cirrhotic patients (hospitalized in our Clinic), 68 women and 143 men with a mean age 59.3±10.5 years. The diagnosis of liver cirrhosis was established prior to the study by clinical, histological, ultrasound, endoscopic and/or laparoscopic criteria. The study was approved by the local Ethics Committee and all the patients signed the informed consent.

From the 211 cirrhotic patients, 129 (61.1%) had esophageal varices, 34 (16.1%) history of variceal bleeding, 54 (25.5%) hepatocellular carcinoma and 94 patients (44.5%) ascites in the moment of ARFI evaluation.

Regarding the etiology of liver cirrhosis, 83 patients (39.3%) had HCV infection, 64 patients (30.3%) alcoholic liver cirrhosis, 28 patients (13.3%) HBV infection, 4 patients (1.9%) HBV+HDV infection, 4 patients (1.9%) HBV infection + alcohol abuse, 3 patients (1.4%) HCV + alcohol abuse, 2 patients (0.9%) HBV+HCV infection, 1 patient (0.4%) haemochromatosis and in 22 patients (10.5%) the etiology of liver cirrhosis could not be established (cryptogenic cirrhosis).

For the evaluation of liver functional reserve we used the Child-Pugh [11-12] and MELD scores [13-14], calculated according to the well known formulas.

ARFI was performed in all the patients in left lateral decubitus, with the right arm in maximum abduction. Scanning was performed between the ribs in the right liver lobe, 1 cm under the capsule, 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 (fig 1). In every patients 10 measurements and a median value was calculated.

The data obtained from our patients were collected in a Microsoft Excel file, the statistical analysis being performed using the MedCalc program and WINK Statistical Data Analysis Research Software. ARFI measurements were numeric variables, so the mean and standard variations were calculated. For statistical analysis we used the Spearman rank correlation coefficient (r) (used for the correlation between LS evaluated by means of ARFI and various parameters), the t test and respectively the 2-way ANOVA (used to compare mean LS values among various subgroups of patients).

We built a receiver operating characteristics (ROC) curve for predicting the presence of at least B class Child-Pugh cirrhosis. Optimal cut-off values were chosen to maximize the sum of Sensitivity (Se) and Specificity (Sp). Se and Sp were calculated according to standard methods.

The results were analyzed also according to IQR (interquartile range interval= the difference between the 75th and the 25th percentile, essentially the range of middle 50% of the data) and/or SR (success rate).

Results

The characteristics of the cirrhotic patients included in the study are presented in table I.
In 3 patients we did not obtain valid 10 ARFI measurements (1.4%).

A direct, very low, linear correlation between the LS values and the Child-Pugh (r=0.264, p<0.001) and MELD scores (r=0.194, p=0.005) was found.

The LS measurements by means of ARFI were correlated with biological parameters which explore the liver functional reserve, as shown in table II.

In the present study 16 patients (7.5%) were incorrectly classified using a cut-off value of 1.8 m/s of LS measurements for predicting cirrhosis, obtained in one of our previous studies [3].

In the study group, 14 patients (6.6%) had an IQR ≥30% and/or SR <60%. In the group of incorrectly classified patients by means of ARFI, the number of patients with unreliable measurements (IQR≥30% and/or SR<60%) was statistically significantly higher than in the group of patients correctly classified (25% vs. 5.1%, p=0.01).

Regarding the Child-Pugh classification, 96 patients (45.5%) were Child-Pugh class A, 71 (33.6%) were class B and 44 (20.9%) were class Child-Pugh class C.

The mean values of ARFI measurements (m/s), according to the Child-Pugh class were: class A - 2.59±0.68, class B - 2.93±0.72 and class C - 3.18±0.63.

The 2-way ANOVA test showed a statistically significant difference between the mean values of ARFI measurements of the 3 Child-Pugh class (p<0.001).

The mean values of ARFI measurements were statistically significant higher in patients with Child-Pugh B
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The study performed by our group [3], in which we included 22 patients with chronic hepatopathies, in which liver biopsy was performed and 23 with clinical, ultrasonographic and/or endoscopic signs of cirrhosis, investigated by means of ARFI had 50% sensitivity (Se), 75% specificity (Sp), 70% positive predictive value (PPV), 56.2% negative predictive value (NPV), with 61.5% accuracy (AUROC - 0.65) for predicting the presence of at least B class Child-Pugh cirrhosis (fig 3).

The predictive value of ARFI elastography for the presence of cirrhosis was also excellent, for a cut-off value of 1.8 m/s the AUROC was 0.92.

In a study performed by Lupşor et al [2], 112 patients with chronic HCV hepatitis were evaluated by means of liver biopsy (the stage of fibrosis was assessed according to the Metavir scoring system), ARFI and TE (FibroScan). For a cut-off value of >2m/s for the prediction of cirrhosis, ARFI had 80% Se, 95.4% Sp, 90.3% PPV and 90% NPV (AUROC=0.93).

A study published by Goertz et al [4] included 57 patients with chronic viral hepatitis B and C that underwent ARFI and consecutively liver biopsy. The area under the receiver operating characteristic (ROC) curve for the accuracy of ARFI imaging was 87% for prediction of cirrhosis.

A study published by Haque et al in 2010 [15] included 22 patients with chronic hepatopathies, in which LB and ARFI were performed in the same session. ARFI values were compared with both Batts-Ludwing score (F0 to F4) and modified Ishak score (F0 to F4). For the prediction of liver cirrhosis, the AUROC was 0.85 for both Ishak and Batts-Ludwing scores.

In the Kim et al [16] study, 521 subjects were evaluated (293 with clinically proven chronic liver disease, 95 with fatty liver and 133 with normal liver). B-mode liver ultrasonography and ARFI elastography were performed in all patients. The mean ARFI value was compared with US-based scores obtained from two radiologists (calculated, based on liver surface nodularity, parenchyma echotexture and hepatic vein contour), Child-Pugh scores and liver function tests. The mean ARFI value was better correlated with Child-Pugh scores and all liver function tests (except total proteins) than the ultrasonography based scores.

In a recent paper of Iijima et al [17], 293 patients with chronic hepatopathies were evaluated by ARFI and liver biopsy: 42 with B hepatitis, 156 with C hepatitis, 6 with hepatitis B+C, and 49 with non-B non-C hepatitis. The area under the receiver operating characteristic curve (AUROC) for distinguishing cirrhosis was 0.870. The cut-off value for predicting cirrhosis was 1.64 m/s (sensitivity 82%, specificity 88%). A correlation between the ARFI values and biochemical analysis was found in hyaluronic acid (Spearman coefficient r=0.54) and slight correlations with aspartate aminotransferase, platelet count, total bilirubin, albumin and prothrombin time.

Şirli et al [18] evaluated the value of ARFI Elastography for prediction of the occurrence of complications in 157 patients with liver cirrhosis. The mean value of ARFI measurements in patients with large esophageal varices (at least grade 2) was not statistically significantly different from the one in patients with no or small esophageal varices: 2.73±0.71 vs. 2.8±0.71 m/s (p=0.49), also in patients with or without a history of variceal bleeding: 2.78±0.81 vs. 2.77±0.7 m/s (p=0.99). The mean value of ARFI measurements in patients with hepatocellular carcinoma was not statistically significantly different from the one in patients with no hepatocellular carcinoma: 2.7±0.64 vs. 2.88±0.81 m/s (p=0.19), but the mean value of ARFI measurements in patients with compensated liver cirrhosis was statistically significantly lower than the one in patients with decompensated liver cirrhosis (Child B and C): 2.67±0.73 vs. 3.05±0.8 m/s (p=0.021). A cutoff of ARFI value > 3.31 m/s, 45% Se, 86% Sp, 71% PPV and 67% NPV was obtained for predicting decompensated cirrhosis (AUROC 0.641, p=0.007).

In our study we found a direct, very low, linear correlation between Child-Pugh score (r=0.264), MELD score (r=0.194) and ARFI values (p<0.001 and p=0.005).

Regarding the correlation with biological parameters that explore the liver functional reserve, a direct, low correlation between LS measurements and total bilirubin (r=0.271, p<0.001) and an inverse, low correlation with albumin (r=-0.270, p<0.001), prothrombin time (r=0.196, p=0.006) and cholinesterase (r=-0.241, p=0.003) were found. Similar to the Kim et al [16] study, we did not find a correlation between LS measurements by means of ARFI and the total proteins (r=-0.051, p=0.559).

Regarding the correct diagnosis of liver cirrhosis, the ARFI technique correctly classified 92.5% of the patients. In the group of the patients incorrectly classified, an important number of ARFI measurements did not fulfill the quality criteria, having an IQR≥30% and/
or SR<60%. So, an explanation of incorrect diagnosis of liver cirrhosis by means of ARFI elastography may be the inappropriate technical parameters (IQR and/or SR).

Regarding the Child-Pugh classification, the mean LS measurements were statistically significant higher in patients with Child-Pugh class B vs. A (p=0.002) and in Child-Pugh C vs. A (p<0.001). For a cut-off value higher than 3.11 m/s, ARFI had 50% Se, 75% Sp, 70 % PPV, and 56.2% NPV with 61.5% accuracy (AUROC - 0.65) for predicting at least B class of liver cirrhosis in Child-Pugh classification.

One explanation for the existing correlation between cirrhosis scores and LS measurements by means of ARFI can be that this elastographic method explores the liver stiffness. An increase in the liver stiffness as a marker of fibrosis means a decrease of the liver function, scars replacing liver functional parenchyma. Repeated liver stiffness measurements by means of TE or ARFI (the last one having the advantage that it can also be performed in patients with ascites) can be an indicator of the evolution of liver cirrhosis (especially in cases in which specific treatment is administered, such as viral hepatitis, primary biliary cirrhosis or alcoholic cirrhosis).

**Conclusion**

LS measurements by means of ARFI could be performed in 98.6% of the cirrhotic patients (with compensated or decompensated disease). Higher values of LS measurements on ARFI can be an indicator of decreased liver functional reserve, so that repeated stiffness measurements can be used for the follow-up of these patients.

**Conflict of interest:** none

**References**