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

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Abstract

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 influenţei rezervei funcţionale hepatice la pacienţii cu ciroză hepatică asupra valorilor durităţii hepatice determinată prin elastografia ARFI. **Material şi metodă:** S-au studiat 211 pacienţi cu ciroză. S-a folosit scorurile Child-Pugh şi MELD pentru evaluarea rezervei funcţionale hepatice. S-au efectuat efectuat 10 măsurători ARFI valide la fiecare pacient. S-a studiat corelaţia între scorurile Child-Pugh si MELD şi duritatea hepatică. **Rezultate:** La 3 pacienţi nu s-au obţinut măsurători ARFI valide. S-a găsit o corelaţie directă, foarte slabă între valorile ARFI scorul Child-Pugh (r=0,264, p<0,001) şi MELD (r=0,194, p=0,005) . S-a obţinut o corelaţie directă, slabă între valorile ARFI şi bilirubina totală (r=0,271; p<0,001) şi o corelaţie 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 pacienţii cu clasă Child-Pugh B vs. A (p=0,002) şi cei cu Child-Pugh C vs. A (p<0,001). Nu au fost diferenţe semnificative la pacienţii cu clasă Child-Pugh B vs. C (p=0,06). **Concluzii:** Valorile mai mari ale durităţii hepatice determinate prin ARFI, pot fi un indicator a scăderii rezervei funcţionale hepatice, evaluată prin scorurul Child-Pugh sau MELD.

Cuvinte cheie: Child-Pugh, MELD, ciroza hepatică, duritatea hepatică, elastografia 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

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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 diagnosed 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.



Fig 1. ARFI determination

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.

Table I. Patients characteristics in the study group

Parameter	
Mean age (years)	59.3±10.5
Gender	-female: 68 (32.2%) -male: 143 (67.8%)
Mean LS values (m/s)	2.83±0.72 range between 1.05-4.6 m/s
AST (NV=5-34 U/L)	88.42±79
ALT (NV=10-35 U/L)	62.42±53.53
Total bilirubin (NV=0.2-1 mg/dl)	2.88±5.56
Total proteins (NV=6-8 g/dl)	6.95±1.25
Albumin (NV=3.5-5 g/dl)	3.51±0.91
Prothrombin index time (NV>75%)	75.09±20.47
Pseudocholinesterase value (NV=4500-8000 U/L)	4050.99±2391.71
Child-Pugh score (points)	7.18±2.13
Meld score (points)	10.71±5.64

NV- Normal values, AST- Aspartataminotransferase, ALT- alaninaminotransferase

Table II. The correlation between ARFI values and biological parameters

Biological parameter	Spearman rank correlation coefficient (r)	p
Total bilirubin	0.271	<0.001
Total proteins	-0.051	0.559
Albumin	-0.270	<0.001
Prothrombin time	-0.196	0.006
Cholinesterase	-0.241	0.003

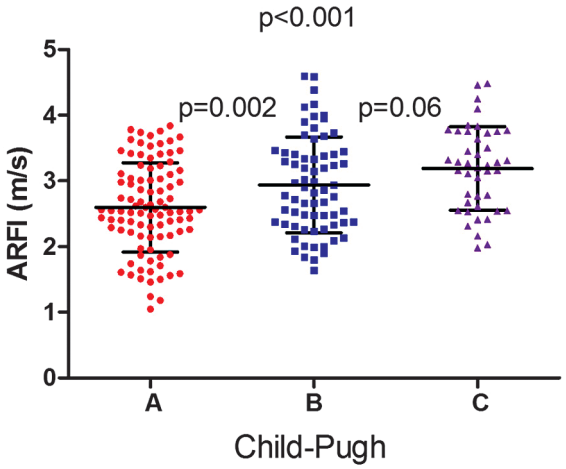


Fig 2. Distribution of ARFI values for various Child-Pugh class

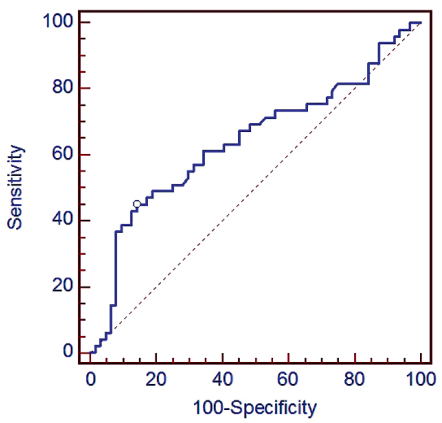


Fig 3. AUROC curve for predicting at least class B liver cirrhosis (according to the Child-Pugh classification)

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

vs. A (p=0.002) and in Child-Pugh C vs. A (p<0.001), but the values were not significantly different in patients with Child-Pugh B vs. C (p=0.06) (fig 2).

For a cut-off value of 3.11 m/s, LS measurements 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).

Discussions

Several previous studies demonstrated the value of ARFI elastography for the prediction of liver cirrhosis. In a study performed by our group [3], in which we included 114 patients (38 healthy volunteers, 76 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 TE and ARFI, a direct, strong, linear correlation (Spearman rho=0.869) was found between ARFI measurements and fibrosis (Spearman rho = 0.675). 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=0.543) 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±0.71m/s (p=0.49), also in patients with or without a history of variceal bleeding: 2.78±0.81 vs. 2.77±0.7m/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: 2.70±0.64 vs. 2.88±0.81m/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±0.8m/s (p=0.021). A cut-off 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 fulfil 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

1. 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.
2. Lupşor 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; 18: 303-311.
3. Sporea I, Sirli RL, Deleanu A, et al. Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. Ultraschal Med 2011; 32 Suppl 1: S46-52.
4. Goertz RS, Zopf Y, Jugl V, et al. Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. Ultraschall Med 2010; 31: 151-155.
5. Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G. Acoustic radiation force imaging for noninvasive staging of liver sonoelastography fibrosis. World J Gastroenterol 2009, 15: 5525-5532.
6. Madsen EL, Sathoff HJ, Zagzebski JA. Ultrasonic shear wave properties of soft tissues and tissuelike materials. J Acoust Soc Am 1983; 74: 1346-1355.
7. Frizzell LA, Carstensen EL. Shear properties of mammalian tissues at low megahertz frequencies. J Acoust Soc Am 1976; 60: 1409-1411.
8. Zhai L, Palmeri ML, Bouchard RR, Nightingale RW, Nightingale KR. An integrated indenter-ARFI imaging system for tissue stiffness quantification. Ultrason Imaging 2008; 30: 95-111.
9. Nightingale K, Soo MS, Nightingale R, Trahey G. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. Ultrasound Med Biol 2002; 28: 227-235.
10. Mauldin FW Jr, Zhu HT, Behler RH, Nichols TC, Gallippi CM. Robust principal component analysis and clustering methods for automated classification of tissue response to ARFI excitation. Ultrasound Med Biol 2008; 34: 309-325.
11. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
12. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg 1997; 3: 628-637.
13. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007; 45: 797-805.
14. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000; 31: 864-871.
15. Haque M, Robinson C, Owen D, Yoshida EM, Harris A. Comparison of acoustic radiation force impulse imaging (ARFI) to liver biopsy histologic scores in the evaluation of chronic liver disease: A pilot study. Ann Hepatol 2010; 9: 289-293.
16. Kim JE, Lee JY, Kim YJ, et al. Acoustic radiation force impulse elastography for chronic liver disease: comparison with ultrasound-based scores of experienced radiologists, Child-Pugh scores and liver function tests. Ultrasound Med Biol 2010; 36: 1637-1643.
17. Iijima H, Tanaka H, Aizawa N, et al. Usefulness of VTTQ (Virtual Touch Tissue Quantification) to diagnose fibrosis and inflammation in chronic hepatitis. Hepatology 2010; 52 (Suppl): 960A.
18. Şirli R, Sporea I, Bota S, Ciof O, Popescu A, Danilă M. Can Acoustic Radiation Force Impulse Elastography (ARFI) predict the complications of liver cirrhosis? Rom J Intern Med 2010; 5: 15-20.