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Quantitative ARFI elastography predicts short-term decompensation in HCV-related cirrhosis

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ABSTRACT:

— ***Background:*** In early-stage cirrhosis, the liver functional reserve may be preserved or rapidly deteriorated. This unpredictable progression of cirrhosis is caused by the heterogeneous distribution of hepatic fibrosis, that can be assessed by Quantitative Acoustic Radiation Force Impulse (ARFI) Elastography. In our study, we evaluated if Quantitative ARFI could be predictive of the short-term clinical outcome of patients with compensated HCV-related Child-Pugh A liver cirrhosis.

— ***Patients and Methods:*** 46 patients with HCV-related Child A cirrhosis were submitted to Quantitative ARFI sampling on the right liver and underwent a 24-month clinical follow-up. The velocity of the shear waves (in m/s) in the liver tissue was collected and recorded from 20 different sites, and the median and interquartile range were calculated. We compared the clinical progression of patients whose first quartile (q1) of ARFI values was >2 m/s vs. <2 m/s.

— ***Results:*** At baseline, all patients had median liver stiffness >2 m/s. 27 patients (59%) had q1 values <2 m/s. Short-term clinical progression of cirrhosis was significantly associated with higher q1 values (OR 45.6, p=0.042). The number of patients who clinically progressed was higher in the group with q1 >2 m/s (63.2% vs. 11.1%, p=0.0003). In fact, 7.4% of patients with q1 <2 m/s progressed to Child-Pugh class B; in the group of subjects with q1 >2 m/s, 31.6% progressed from Child-Pugh class A to B and 5.7% from Child-Pugh class A to C. None of the patients with q1 <2 m/s died during the course of the 24-month follow-up vs. 15.8% of patients with q1 >2 m/s (p=0.032).

— ***Conclusions:*** A q1 value >2 m/s by quantitative ARFI may help to identify patients with compensated cirrhosis with reduced functional reserve and at higher risk for short-term clinical progression.

— ***Keywords:*** ARFI, Cirrhosis, Decompensation, Elastography, Fibrosis, HCV.

INTRODUCTION

Chronic hepatitis C is characterized by necro-inflammatory damage and fibrotic scarring of the liver. This pathway is known to induce a progressive disruption of liver functional units leading to full-blown cirrhosis[1]. Fibrosis is randomly distributed within the liver[2]. This heterogeneity seems higher in more advanced fibrosis stages: in fact, both imaging[3-5] and histopathological studies[6] have reported the variability of liver fibrosis to be much more in the setting of cirrhosis in comparison with lower fibrosis stages. As a consequence, the natural history and the clinical progression of liver disease might result highly variable too[7]. In the so-called compensated or early cirrhosis, liver parenchyma results heavily scarred though still functionally efficient: patients exhibit few signs or symptoms of hepatic insufficiency and their biochemical parameters are only mildly impaired[8]. This clinical condition can be stable for a long time or show a nonlinear progression towards decompensation. Decompensation may result from an extensive liver scarring, with heavy reduction of its functional reserve, or may be accelerated by precipitating

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events, such as rupture of esophageal varices, hepatocellular carcinoma, portal thrombosis, and sepsis. In patients with chronic hepatitis C, the hepatic functional reserve is closely related with residual hepatic mass and with the extent of anatomic preservation of lobular structures[9]. The transition from a compensated to a decompensated stage has a dramatic impact on the natural history of cirrhosis, as decompensated cirrhosis is associated with a significantly higher morbidity and mortality[8].

Liver function in cirrhosis can be assessed by clinical scores, such as the Child-Pugh score[10] or by quantitative tests, such as galactose and indocyanine green clearance[11]. Child scoring system[12] modified by Pugh[13] is the most widely used index and includes biochemical parameters (plasma bilirubin, albumin and prothrombin time) and clinical parameters (presence of encephalopathy and ascites). Although Child-Pugh score represents the most widely used prognostic index to assess liver function in cirrhotic patients, it suffers from several limitations[10] and may not be able to identify the subgroup of patients with compensated cirrhosis at higher risk of developing prompt decompensation. In a recent prospective study of Wang et al[14], 36% of patients with Child A class cirrhosis died during the first year of follow-up.

In the last years, ultrasound-based elastographic methods, including Transient Elastography (TE)[15,16] and Acoustic Radiation Force Impulse Elastography (ARFI)[5], have been developed for the quantitative evaluation of liver fibrosis in chronic hepatitis C. ARFI uses a standard ultrasonographic probe and offers elastography with a flexible metering box of 1 cm at variable depths. An acoustic push pulse transmitted by the transducer (3.5 MHz) induces an elastic shear wave that propagates through the tissue. The propagation of the shear wave is followed by detection pulses that are used to measure the velocity of shear wave propagation, which is directly related to tissue stiffness. Speed increases with stiffness; therefore, it is higher in the presence of fibrosis[5]. The evaluation of liver stiffness by ARFI relies not only on a central tendency measure, such as the median stiffness value, but also on a measure of heterogeneity, i.e. the interquartile range (IQR). In a cohort of 139 patients with CHC, Rizzo et al[5] have shown that IQR increased alongside fibrosis stage. It may be hypothesized that patients showing a lower IQR may have a more homogeneous distribution of hepatic fibrosis, whereas a wider IQR may reflect a spotty and heterogeneous spread of fibrosis within the liver. From a functional point of view, this hypothesis implies that patients with higher IQR may have more spared liver areas, with a subsequent higher functional reserve in comparison with those having lower IQR of liver stiffness. In the aforementioned study of Rizzo et al[5], a median ARFI value >2 m/s was the best cutoff for predicting cirrhosis. We hypothesized that a first quartile (q1) of ARFI values higher than 2 m/s could be associated a more extensive alteration of liver structure and a subsequent higher risk of liver decompensation and a worse short-term prognosis in comparison with a q1 <2 m/s. In the present pilot prospective study, we enrolled a cohort of patients with newly diagnosed Hepatitis C Virus (HCV)-related Child A class cirrhosis and we evaluated whether the q1 of ARFI values was able to predict the short-term clinical outcome.

PATIENTS AND METHODS

Study population

Between January 2010 and January 2012, 58 consecutive patients presenting at the Outpatient Clinic of Infectious Diseases (Garibaldi Nesima Hospital of Catania, Italy) were newly diagnosed as affected with HCV-related liver cirrhosis and considered for enrolment in the present study. The diagnosis of cirrhosis was based on a clinical and histological evaluation.

Subsequently, throughout a 6-month clinical follow-up, 12 patients were excluded from the study: 5 who developed severe cirrhosis-related complications (3 hepatocellular carcinoma, 2 spontaneous bacterial peritonitis), 3 because of severe comorbidities (2 cases of severe sepsis and one case of colonic cancer), 3 because of endoscopic evidence of esophageal varices and 1 because of refusal to enter the study. Thus, 46 patients with Child-Pugh class A cirrhosis were finally enrolled. None of the patients had a concomitant HBV and/or HIV coinfection. None had either autoimmune or metabolic disease or excessive alcohol consumption. No patient had evidence of cardiac or renal failure. Patients were not under treatment with beta-blockers, diuretics, antibiotics, interferon or ribavirin by the time of study onset.

All patients signed a written informed consent before study inclusion, in accordance with the Declaration of Helsinki.

At baseline, each patient underwent a consecutive 2-day protocol: on the first day, a complete clinical and biochemical evaluation was performed. Then, patients were examined with Quantitative ARFI by a single well-experienced operator (L.R.), blinded to biochemical and clinical data, at the private Outpatient Clinic "Ultrasuoni" in Catania.

METHODS

Patients were regularly visited every six months until the end of the 24 month-follow-up. Cirrhosis clinical progression was defined as an increase in Child-Pugh score of at least one point during follow-up.

Quantitative Acoustic radiation force impulse elastography

B-mode standard ultrasonography scanning and Quantitative ARFI elastography were performed using a Siemens Acuson S2000 (Siemens AG, Erlangen, Germany) with a 4Cl transducer, as described in details elsewhere[5].

The velocity of the shear wave (in m/s) in the liver tissue was collected and recorded from 20 different sites, 5 sites for each segment (V, VI, VII, and VIII)

within the right lobe according to a random sampling method described elsewhere[5]. The patient was in the supine position for segment V and VIII measurement and in left lateral position for segment VI and VII measurement. A median and interquartile range (IQR) of the 20 results was calculated. The shear wave velocity was measured within a rectangular region of interest (10 mm long X 5 mm wide) chosen by the observer.

STATISTICAL ANALYSIS

Data are expressed as mean±standard deviation (SD), median (IQR), or n (%), as appropriate. Baseline characteristics of patients with or without q1 >2 m/s were compared using Mann-Whitney U test and Fisher's exact test, when appropriate.

To identify predictors of clinical progression, univariate and subsequent logistic regression analysis were used. Odds ratio (OR) was also calculated.

Statistical analysis was performed using statistical computing software R.

Table 1. Baseline characteristics of the 46 patients with HCV-related cirrhosis enrolled in the study.

Variables	No.=46
Age (years)**	60 (57-63)
Sex, male*	22 (47.8)
HCV RNA*10^5 (IU/ml)●	3.93 ±2.41
HCV Genotype 1/2/3/4*	32 (69.6)/3 (6.5)/ 11 (23.9)/0 (0)
Total bilirubin (mg/dl)**	1.1 (0.9-1.7)
AST (IU/l)**	54 (25-117)
ALT (IU/l)**	69 (35-129)
Albumin (g/dl)**	3.7 (3.4-4.3)
Platelet count*10^3/µl**	97 (105-125)
INR**	1.21 (1.1-1.57)
BMI (kg/m^2)**	27 (24-30)

*Data presented as N (%) **Data presented as median (IQR) ● Data presented as mean±standard deviation (SD)
ARFI: Acoustic Radiation Force Impulse Elastography; AST: aspartate aminotransferase; ALT: alanine aminostransferase; BMI: body mass index; INR: International Normalized Ratio; IQR: interquartile range; TE: transient elastography.

RESULTS

Study Population Characteristics

The characteristics of the 46 patients enrolled in the present study are summarized in Table 1. There were 22 male patients (47.8%). Median age was 60 (57-63) years. Mean HCV-RNA plasma level was 3.93±2.41*10^5 IU/ml. HCV genotype was 1a/b in 32 patients (69.6%), 2 in 3 patients (6.5%) and 3 in 11 (23.9%).

Clinical progression of cirrhosis and mortality rates: comparison between patients with q1 ARFI liver values <2 m/s and >2 m/s

At baseline, all patients had median liver stiffness >2 m/s. 27 patients (59%) had q1 values <2 m/s (Table 2).

The number of patients who clinically progressed (i.e. with an increase in Child-Pugh score of at least one point at follow-up) was significantly higher in the group with q1 >2 m/s (63.2% *vs.* 11.1%, p=0.0003) (Figure 1). In fact, 7.4% of patients with q1 <2 m/s progressed to Child-Pugh class B, whereas in the group of subjects with q1 >2 m/s, 31.6% progressed from Child-Pugh class A to B and 5.7% from Child-Pugh class A to C.

None of the patients with q1 <2 m/s died during the 24-month follow-up. In the group with q1 >2 m/s, 3/19 patients (15.8%) died, 2 due to hepatocellular carcinoma and one due to hepatic decompensation (p=0.032).

In a logistic regression model evaluating the predictors of clinical progression, we found that short-term clinical progression of cirrhosis was significantly associated only with higher q1 (OR 45.6, p=0.042) but not with higher median ARFI value or other clinical predictors of decompensation.

Table 2. Characteristics of cirrhotic patients with the first quartile (q1) of ARFI liver values >2 m/s vs. q1 <2 m/s.

	Cirrhotics with q1 <2 m/s (No.=27)	Cirrhotics with q1 >2 m/s (No.=19)
Age (years)**	63 (59-66)	59 (56-61)
Sex, male*	13 (44)	9 (47.3)
HCV RNA*10^5 (IU/ml)●	3.63±2.18	3.89±1.97
HCV Genotype 1/2/3/4*	18 (66.7)/2 (7.4)/7 (25.9)/0 (0)	14 (73.6)/1 (5.2)/4 (21.2)/0 (0)
Total bilirubin (mg/dl)**	0.95 (0.8-1.1)	1.22 (0.93-1.6)
AST (IU/l)**	56 (37-113)	62 (35-129)
ALT (IU/l)**	61 (41-124)	72 (44-133)
Albumin (g/dl)**	3.7 (3.4-4.2)	3.5 (3.3-4.1)
Platelet count*10^3/µl **	105 (95-125)	120 (98-128)
INR**	1.18 (1-1.45)	1.25 (1.14-1.58)
BMI (kg/m^2)**	28 (24-31)	27 (23-29)

*Data presented as N (%) **Data presented as median (IQR) ● Data presented as mean±standard deviation (SD)
ARFI: Acoustic Radiation Force Impulse Elastography; AST: aspartate aminotransferase; ALT: alanine aminostransferase; BMI: body mass index; INR: International Normalized Ratio; IQR: interquartile range; TE: transient elastography.

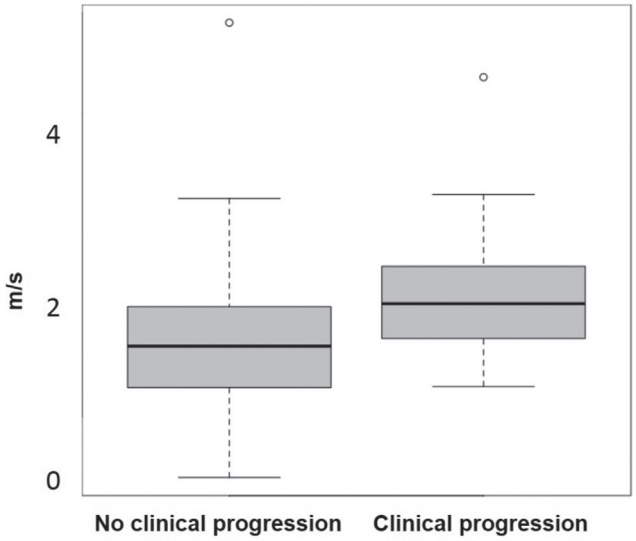

Figure 1. First quartile (q1) of ARFI liver values among patients with or without short-term clinical progression of cirrhosis. Q1 was significantly higher in the group of subjects experiencing clinical progression of cirrhosis (2.06 (1.8-2.29) vs. 1.85 (1.64-2.04), p=0.024).

DISCUSSION

Liver fibrosis is known to be heterogeneously distributed within the liver of patients with chronic hepatic disease[2]. In a study evaluating the sensitivity and specificity of magnetic resonance elastography for staging hepatic fibrosis, Huwart et al[3] observed that the heterogeneity of liver elasticity and viscosity increased with increasing fibrosis stage. In particular, it was higher among subjects with cirrhosis when compared to those with less severe fibrosis stages. Similar findings were reported by Rizzo et al[5] with ARFI elastography and by Romero-Gomez et al[4] using Fibro-Computed Tomography.

In the present study, we found that the evaluation of the variability of fibrosis distribution by ARFI elastography can predict the short-term clinical progression of HCV-related cirrhosis. We hypothesized that patients with a first quartile of ARFI liver measurements greater than 2 m/s (identified as the best cut-off for predicting cirrhosis[5]) might have a more homogeneous fibrotic impairment of liver parenchyma; in our study, we found a significantly higher rate of clinical progression of liver cirrhosis, as well as mortality, among patients with q1 >2 m/s. Considering that the severity of liver fibrosis is closely related to the risk of hepatic decompensation[17], it is not surprising to find out that patients with a more homogeneous distribution of liver fibrosis have a reduced hepatic functional reserve and an increased risk of clinical progression of liver disease. Recent studies have suggested that hepatic venous pressure gradient (HPVG) in an independent predictor of decompensation in patients with compensated cirrhosis[18,19]. However, measurement of HPVG is invasive and not routinely available in many centers. Therefore, noninvasive methods, such as ARFI elastography[5,20], may represent a more accessible and acceptable way to risk stratify patients and define the most appropriate timing of follow-up.

In previous studies of Bota et al[21,22], the authors evaluated the influence of several technical parameters, including IQR, on the correlation between ARFI elastography and histological liver fibrosis. They found that the correlation was stronger when the IQR was less than 30% of the median value, whereas ARFI liver values did not correlate with fibrosis among patients with IQR ≥30%. They concluded that the IQR should be <30% to obtain the best correlation between ARFI values and liver fibrosis. However, we think that this is a misinterpretation of ARFI methodology, suffering from TE approach for validating liver stiffness measures. Differently from TE, ARFI is set to perform nine consecutive measurements for each "push" within the ROI and the final value has to fall in the confidence interval established at 95% to be considered reliable and represented on the screen in m/s. As a consequence, every ARFI measure is intrinsically validated and the IQR variability should not be considered as a quality parameter but as an indicator of the heterogeneity in fibrosis distribution throughout the liver.

Our study has several limitations: we present data from a small cohort of patients, which may have limited the statistical power of our analysis. We did not include subjects with chronic hepatitis of different etiology and we were not able to measure HPVG. Also, we could not reassess patients with ARFI elastography at the end of the follow-up or at the time of clinical worsening.

CONCLUSIONS

Our results provide evidence that the evaluation of the heterogeneity of liver fibrosis by ARFI elastography may help identifying patients with compensated cirrhosis at higher risk for short-term clinical progression. As the prognosis of this subgroup of patients is poor, we believe that a prompt identification of high-risk individuals can help defining more appropriate strategies for follow-up. Further investigation on larger cohorts is warranted to confirm the results of our preliminary study.

Informed consent statement:
All study participants provided informed written consent prior to study enrollment.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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