Performance of a New Elastographic Method (ARFI technology) Compared to Unidimensional Transient Elastography in the Noninvasive Assessment of Chronic Hepatitis C. Preliminary Results

Monica Lupsor[1], Radu Badea[1], Horia Stefanescu[2], Zeno Sparchez[2], Horaţiu Branda[1], Alexandru Serban[3], Anca Maniu[1]

1) Department of Ultrasonography; 2) Department of Hepatology; 3) Department of Pathology, 3rd Medical Clinic, University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Background and aims: The current study aims to evaluate the performance of a new elastographic method (ARFI) in noninvasive fibrosis assessment and to compare it to another validated technology (transient elastography, TE). **Method**: 112 consecutive chronic hepatitis C patients (histologically proven according to the Metavir scoring system: 12.5% F0, 26.6% F1, 16.1% F2, 7.1% F3, 37.5% F4) were prospectively included in this study. They were examined on the same day, using both ARFI (with shear wave velocity – SWV- quantification) and TE (with liver stiffness quantification). **Results**: SWV is correlated only with fibrosis ($r=0.717$, $p<0.0001$) and necroinflammatory activity ($r=0.328$, $p=0.014$), but not with steatosis ($r=0.122$, $p=0.321$). There is a significant increase of SWV in parallel with the increase in the fibrosis stage: 1.079±0.150 (F0-F1), 1.504±0.895 (F2), 1.520±0.575 (F3), 2.552±0.782 (F4), $p<0.0001$, but there is a certain degree of overlap between the consecutive stages F1-F2 ($p=0.072$), F2-F3 ($p=0.965$). SWV cut-off values (m/s) that were predictive for each fibrosis stage were: 1.19 ($F\geq1$), 1.34 ($F\geq2$), 1.61 ($F\geq3$) and 2.00 (F4). AUROC for ARFI vs TE were: 0.709 vs 0.902, $p=0.006$ ($F\geq1$), 0.851 vs 0.941, $p=0.022$ ($F\geq2$), 0.869 vs 0.926, $p=0.153$ ($F\geq3$) and 0.911 vs 0.945, $p=0.331$ (F4). **Conclusions**: ARFI allows SWV quantification, in strong correlation with the fibrosis stage. Steatosis does not influence SWV. The maximal performance of the method consists of the prediction in severe fibrosis and cirrhosis. The diagnostic accuracy is strongly comparable to TE only for the prediction of severe fibrosis and cirrhosis, whereas for earlier stages, TE performs better.

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Address for correspondence: Dr. Monica Lupşor
Ultrasonography Dept.
3rd Medical Clinic
19 – 21 Croitorilor Str
Cluj-Napoca, Romania
E-mail: monica.lupsor@umfcluj.ro

Key-words

Chronic hepatitis C – noninvasive – fibrosis – ARFI – transient elastography.

Introduction

Chronic liver diseases, especially C virus hepatitis, are an important public health issue. For the time being, the golden standard in the assessment of these patients is liver biopsy (LB), an invasive procedure, possibly encumbered with secondary effects [1, 2].

Nowadays, there is an increasing interest in finding new non-invasive methods for the evaluation of chronic hepatitis C (CHC) patients, as an alternative to needle biopsy, with focus on the elastographic methods. Some technologies (unidimensional transient elastography - TE) have been validated on CHC patients in numerous studies [3-9]. ARFI (Acoustic Radiation Force Impulse Imaging) technology is increasingly studied for its use in different clinical applications, including tumors of the breast, liver, kidney, colon and rectum, the characterizing of atherosclerotic plaques, as well as for the monitoring of radiofrequency ablation [10-19]. As for the assessment of diffuse liver diseases, studies are now in progress and, to our knowledge, there are only preliminary results available at the time, which have been communicated in different specialized conferences [20-23].

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, perpendicularly to the acoustic push pulse, generating localized, micron-scale displacements in the tissue [24, 25]. Simultaneously, detection waves of lower intensity than that of the push pulse (1:100) are generated. The push pulse uses a few hundreds 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 wavefront at several locations and correlating these measurements with the elapsed time, the shear wave velocity – SWV (m/s) can be quantified; generally, the stiffer a region in the tissue, the greater the SWV as it travels through this region. Thus, the measured SWV is an intrinsic and reproducible property of the tissue [13, 14, 18].

The equipment lists the SWV as well as the depth at which the measurement was performed. A single transducer on a diagnostic scanner is used both to generate radiation force and to track the resulting displacement. Since this technique is implemented via additional software imaging control and detection algorithms, the method can provide co-registered B-mode, color Doppler and ARFI images [10].

This study aims to evaluate the performance of a new elastographic method (ARFI technology) in the assessment of fibrosis in a group of CHC patients who have undergone LB and to compare it to another validated technology (unidimensional TE).

Method

Patients

We prospectively included in this study 112 CHC patients examined in the 3rd Medical Clinic, Cluj-Napoca, between October and December 2008. All patients had positive HCV-RNA and were scheduled for a LB, in order to stage and grade their condition (except cirrhotic patients, in whom diagnosis had been confirmed through LB no more than 6 months before).

The exclusion criteria were: presence of ascites at clinical or ultrasound examination (ascites is a physical limitation to the TE because elastic waves do not propagate through fluids), co-infection with HBV and/or HIV, other active infectious diseases, and pregnancy.

Alongside the epidemiological data, certain biological parameters were determined on a blood sample taken 12 hours after overnight fasting: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gama-glutamyl transferase (GGT), total cholesterol, triglycerides, total bilirubin, glycemia (Konelab 20i – Thermo Electron Corp., Finland).

The study was approved by the local Ethical Committee of the University of Medicine and Pharmacy Cluj-Napoca. The patients provided written informed consent before the beginning of the study, in accordance to the principles of the Declaration of Helsinki (revision of Edinburgh, 2000).

Elastography examination

A single examiner observed all the patients using both ARFI and TE one day before LB. The patient was lying in a dorsal decubitus position, with the right arm extended above the head and the SWV and liver stiffness (LS) measurements were performed on the same area of liver parenchyma (intercostally, in the right lobe, in an area free from large vascular structures belonging to the 8th segment).

Unidimensional transient elastography

Transient elastography was performed using a FibroScan® device (Echosens, Paris, France), consisting of a 5-MHz ultrasound transducer mounted on the axis of a vibrator. The vibrator generates a painless vibration (frequency 50 Hz and amplitude 2 mm) similar to a „flick", generating a shear wave that propagates through the skin and the subcutaneous tissue into the liver. The velocity of the wave is directly related to the LS [3].

During the acquisition, patients were lying in a dorsal decubitus position, with the right arm in maximum abduction. The Fibroscan transducer, covered with a drop of coupling gel, was placed perpendicularly in the intercostal space. Under TM and A-mode control, the operator would choose a liver portion within the right lobe, free from any large vascular structure or the gallbladder. Then the operator would press the probe button to commence the measurements. Transient elastography measures the stiffness in an area located 25 to 45 mm beneath the skin. The median value of 10 successful acquisitions, expressed in kilopascals (kPa), was recorded as representative of LS. As previously described [3] and as suggested by the provider of the equipment, we considered as representative 10 successful acquisitions with a success rate of at least 60% (the ratio of the number of successful measurements to the total number of acquisitions) and with an interquartile range (IQR) lower than 30% of the median value.

ARFI technology

The second type of elastographic examination was performed by means of an ultrasound device ACUSON S2000 (Siemens), equipped with a 4 MHz frequency transducer, with the ARFI technology implemented via additional software imaging control and detection algorithms. For fibrosis quantification, the "Virtual Touch (VT) tissue quantification" application was used, allowing for the measurement of SWV (m/s) within the interest area chosen by the examiner, according to the principles described in the Introduction section. The higher the tissue stiffness, the higher the SWV.

The transducer is placed on the patient's skin, on the right upper quadrant, in the same intercostal spaces used for the LS measurement through TE. The region of interest for measuring the SWV was chosen 4 cm below the skin level, because TE also measures the stiffness in an area located 25 to 45 mm beneath the skin. We avoided the subcapsular regions that usually hold a larger fibrosis content. When scanning between ribs, no pressure was applied to the liver and the patient was asked to stop breathing for a moment (instead of deep inspiration and breath hold).

When VT tissue quantification was enabled on the S2000 system, the feature was in a setup mode. Whenever the operator pressed the update key, one VT tissue quantification measurement was acquired.

The equipment listed the SWV (m/s) in the region of interest as well as the depth at which the measurement was performed (Fig. 1). When no valid measurement could be acquired, the monitor would display the "X-X-X-X" symbol, meaning that the confidence level internally determined by the shear velocity estimation algorithm was below 0.8

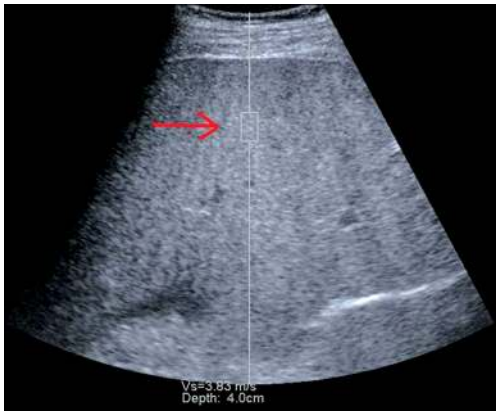

Fig 1. The ultrasound image used to quantify the shear wave velocity 4 cm below the skin level.

on a 0 to 1 scale. This means that the individual velocity estimates between tracking beams varies too much to provide a reliable reading. This is a safety feature to ensure invalid measurements are not misinterpreted, a "quality factor"- like feature that has a minimum threshold to provide a reliable reading.

As for TE, the median of the 10 SWV measurements was used for the statistical analysis.

Histopathological analysis

A LB specimen was prelevated by using the TruCut technique with an 1.8 mm (14G) diameter automatic needle device - Biopty Gun (Bard GMBH, Karlsruhe, Germany). The LB specimens were fixed in formalin and embedded in paraffin. The slides were evaluated by a single expert pathologist unaware of the clinical data. Only biopsy specimens with more than 6 intact portal tracts were eligible for evaluation [26]. The liver fibrosis and necroinflammatory activity were evaluated semi quantitatively according to the Metavir scoring system [27].

Fibrosis was staged on a 0-4 scale as follows: F0 – no fibrosis; F1 – portal fibrosis without septa; F2 - portal fibrosis and few septa; F3 – numerous septa without cirrhosis; F4 – cirrhosis. The necroinflammatory activity was graded as A0 – none; A1 – mild; A2 – moderate; A3 – severe. Steatosis was classified by visual assessment as: 0 - none; 1 – steatosis in <33% of hepatocytes; 2 - steatosis in 33% to 66% of hepatocytes; and 3 - steatosis in > 66% of hepatocytes.

Statistical analysis

The statistical analysis was performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean value and standard deviation, while the categorical variables – as percentages. The distribution of the SWV for each class of histopathological parameters analyzed was studied with the "box plot" diagrams. The difference of means was tested with the Anova analysis of variance and the Kruskal-Wallis test, while the relationship between different parameters – through Spearman correlation coefficients.

The accuracy of SWV and LS measurement for assessment of the fibrosis stage was evaluated by calculating sensitivity (Se), specificity (Sp), positive and negative predictive value (PPV, NPV) and the ROC curves ("Receiver-Operating Characteristic curve"). Optimal cut-off values were chosen to maximize the sum of sensitivity and specificity, and positive and negative predictive values were computed for these cut-off values. We also calculated the adjusted AUROC, taking into account the prevalence of each fibrosis stage, using DANA method, as described by Poynard et al [28]. The areas under the ROC curves obtained for both elastographic techniques were compared using the method proposed by Hanley and McNeil [29].

Results

Baseline characteristics of patients

The clinical, biochemical and histopathological characteristics of the patients are summarized in Table I. The average size of the LB specimen was 11.02 mm, with an average number of 11 portal spaces. SWV ranged from 0.75 to 4.15 m/s (median 1.70 m/s) and the LS values ranged from 2.70 to 75 kPa (median 19.28 kPa).

Table I. Clinical, biochemical and histological characteristics of the study group

Patient characteristics	Mean ± SD (interval) or %
Sex (female)	60.4%
Age (years)	48.97 ± 12.28 (21 - 76)
BMI (kg/m^2)	26.06 ± 3.96 (18.07 - 36.30)
AST (UI/l)	65.22 ± 41.55 (13 - 214)
ALT (UI/l)	80.22 ± 51.38 (11 - 201)
GGT (UI/l)	103.86 ± 138.36 (12 - 1018)
Total bilirubin (mg/dl)	1.16 ± 1.16 (0.29 - 3.01)
Alkaline phosphatase (U/l)	225.30 ± 85.89 (115 – 312)
Glycemia (mg/dl)	102.4 ± 30.61 (72.8 - 132.60)
Cholesterol (mg/dl)	177.06 ± 42.47 (101 – 335)
Triglycerides (mg/dl)	111.08 ± 58.81 (19 - 317)
Platelets (10^9/l)	175.15 ± 73.53 (28 - 315)
Fibrosis stage	
F0	12.5 %
F1	26.6 %
F2	16.1 %
F3	7.1 %
F4	37.5 %
Necroinflammatory activity	
A0	2%
A1	23%
A2	41%
A3	34%
Degree of fatty infiltration	
S0 (absent)	56%
S1 (<33%)	30.8%
S2 (33-66%)	7.7%
S3 (>66%)	5.5%

BMI body mass index; AST aspartate aminotransferase; ALT alanine aminotransferase; GGT gamma-glutamyl-transpeptidase

Success rate of ARFI compared to TE

Of the 112 examined patients, 10 (8.92%) did not yield any valid measurement through the ARFI technique. Six of these had a TE success rate of <60%. No patient with examination failure in TE yielded valid measurements in ARFI. The relatively small number of patients who failed examination did not allow for a complex analysis of the factors leading to it; a high BMI is probably not the only factor determining ARFI examination failure (Table II).

Table II. Characteristics of patients with ARFI failure

	ARFI success rate (%)	TE success rate (%)	Age	Sex	BMI (kg/m²)	Fibrosis stage
1	0	91	45	F	26.81	4
2	0	0	44	M	34.19	1
3	0	100	32	F	19.33	2
4	0	56	51	M	31.19	4
5	0	50	38	M	30.39	1
6	0	100	56	F	31.14	4
7	0	25	49	M	30.00	4
8	0	91	56	M	24.61	2
9	0	91	74	M	23.66	4
10	0	50	52	M	32.60	4

The relationship between ARFI-measured velocity and TE-measured LS vs histological parameters

Although LS indicated by TE correlated strongly with fibrosis, moderately with necroinflammatory activity and weakly with steatosis, the SWV measured through the ARFI technique correlated only with fibrosis and necroinflammatory activity, but not with steatosis (Table III). On the whole, there was a significant increase of SWV in parallel with the increase in fibrosis stage ($p<0.0001$). However, there was a certain degree of overlap between consecutive stages and therefore SWV does not change significantly between F0-F1 ($p=0.493$), F1-F2 ($p=0.072$), F2-F3 ($p=0.965$). SWV for each fibrosis stage is illustrated in Table IV, and the SWV box plots in Fig 2.

ARFI performance for the fibrosis assessment in CHC patients. Comparison between ARFI and TE

The SWV cut-off values that were predictive for each fibrosis stage and their performance in quantifying fibrosis are presented in Table V. ARFI overestimated the fibrosis stage in 5 patients, and underestimated it in 33 patients.

Taking into account the prevalence of each fibrosis stage, the adjusted AUROC values using the DANA method were as follows: 0.709 (for F≥1), 0.851 (F≥2), 0.869 (F≥3) and 0.911 (F4) - for ARFI, respectively 0.902 (F≥1), 0.941 (F≥2), 0.926 (F≥3) and 0.945 (F4) for TE. These values did not significantly differ from the observed AUROCs for either ARFI or TE.

Table III. Correlation of the shear wave velocity (ARFI) and liver stiffness (TE) with different histological parameters

Histopathological parameter	SWV, m/s (ARFI)		LS, kPa (TE)	
	Spearman correlation coefficient	p	Spearman correlation coefficient	p
Fibrosis	0.717	<0.0001	0.880	<0.0001
Necroinflammatory activity	0.328	0.014	0.530	<0.0001
Steatosis	0.122	0.321	0.368	<0.0001

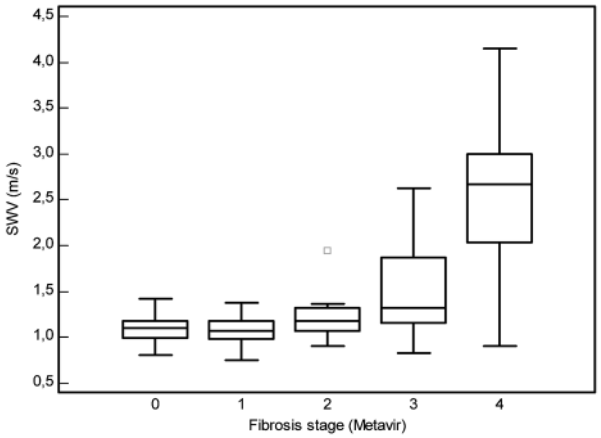

Fig 2. Variation of the SWV depending on the stage of fibrosis, measured through the ARFI technique 4 cm below the skin level. The top of the bottom of the boxes are the first and third quartiles, respectively. The length of the box represents therefore the inter quartile range including 50% of the values. The line through the middle of each box represents the median. The error shows the minimum and maximum values (range).

By comparing the areas under the ROC curves for the prediction of each fibrosis stage in both ARFI and TE techniques, it appears that AUROC does significantly better predict ≥F1 and ≥F2 stages for TE, while in the case of severe fibrosis (F3) and cirrhosis (F4), there is no significant difference between the performances of the two methods (Table V, Fig 3).

Table IV. Shear wave velocity recorded for each fibrosis stage

Fibrosis stage	Mean SWV	Standard deviation	Standard error	Confidence interval 95%	Minimal value	Maximal value
F0	1.103	0.158	0.042	1.011 – 1.195	0.81	1.42
F1	1.067	0.157	0.029	1.006 – 1.128	0.75	1.38
F2	1.504	0.895	0.223	1.027 – 1.198	0.91	4.08
F3	1.520	0.575	0.203	1.039 – 2.000	0.83	2.63
F4	2.552	0.782	0.130	2.288 – 2.817	0.90	4.15

Table V. SWV and LS cut-off values for the diagnosis of different fibrosis stages and their corresponding AUROCs

	≥ F1 F0 vs F1234		≥ F2 F01 vs F234		≥ F3 F012 vs F34		F4 F0123 vs F4	
	SWV (m/s)	LS (kPa)	SWV (m/s)	LS (kPa)	SWV (m/s)	LS (kPa)	SWV (m/s)	LS (kPa)
Cut-off	>1.19	>5.2	>1.34	>8.1	>1.61	>9.6	>2.00	>13.1
Se (%)	62.07	85.26	67.80	84.85	79.07	95.83	80,00	95.12
95% CI	51.0-72.3	76.5-91.7	54.4-79.4	73.9-92.5	61.0-89.9	85.7-99.4	63,1-91,5	83.4-99.3
Sp (%)	85.71	92.86	92.86	95.35	94.83	86.89	95.45	89.17
95% CI	57.2-97.8	66.1-98.8	80.5-98.4	84.2-99.3	85.6-98.9	75.8-94.1	87.3-99.0	79.9-95.7
+LR	4.34	11.94	9.49	18.24	15.29	7.31	17.60	9.24
-LR	0.44	0.16	0,35	0.16	0.22	0.05	0,21	0.05
PPV	96.4	98.8	93.0	96.6	91.9	85.2	90.3	84.8
NPV	26.7	48.1	67.2	80.4	85.9	96.4	90.0	96.8
DA (%)	64.70	86.36	77.45	88.18	89.21	90	90.19	90.90
AUROC	**0.725**	**0.918**	**0.869**	**0.961**	**0.900**	**0.957**	**0.936**	**0.970**
SE	0.064	0.029	0.035	0.018	0,034	0.021	0.030	0.018
95% CI	0.628-0.809	0.849-0.962	0.788-0.928	0905-0.988	0,824-0.951	0.900-0.986	0.869-0.975	0.924-0995
P (Area=0.5)	0.0004	0.0001	0.0001	0.0001	0,0001	0.0001	0.0001	0.0001
Adjusted AUROC	**0.709**	**0.902**	**0.851**	**0.941**	**0.869**	**0.926**	**0.911**	**0.945**
P*	0.859	0.696	0.716	0.432	0.519	0.296	0.557	0.326
P**	0.006		0.022		0.153		0.331	

Se sensitivity; Sp specificity; PPV positive predictive value; NPV negative predictive value; CI confidence interval; +LR Positive likelihood ratio; -LR Negative likelihood ratio; DA diagnosis accuracy; AUROC area under ROC curve; SE standard error. P* significance level between the observed AUROC and the adjusted AUROC for the prediction of each fibrosis stage. P** significance level between the adjusted AUROCs assessed with both ARFI and TE.

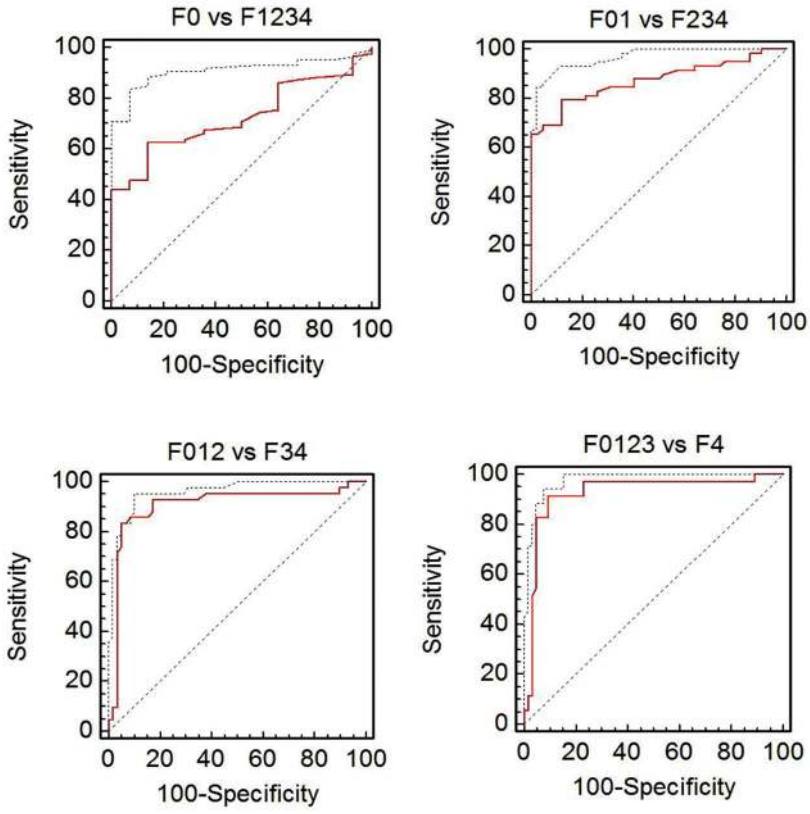

Fig. 3. Comparison of the ROC curves in both ARFI (in red) and TE (in blue) techniques for the prediction of each fibrosis stage.

Discussion

Lately, there has been a growing interest in finding new imaging methods for the noninvasive assessment of liver fibrosis. Transient elastography was validated in CHC patients (3-9). Regarding the ARFI technique, studies are now in progress and there are only preliminary results available at the moment (20–23). Most of them are limited to SWV comparison in different conditions, mainly cirrhosis vs. non-cirrhosis.

In this context, we set out to analyze the histological parameters correlating with the SWV measured through the ARFI technique and its performance for the fibrosis assessment in CHC patients, by comparing it to the "golden standard" (LB), as well as to TE.

SWV correlated strongly with fibrosis, moderately with necroinflammatory activity, and not with steatosis. To our knowledge, there is only one other published study on the subject, also showing that SWV does not correlate with steatosis [23]. For the same group of patients (although only 13.2% had ≥33% steatosis), LS correlated with steatosis as well, not only with fibrosis and necroinflammatory activity. However, this observation must be confirmed on a larger number of patients with different degrees of fatty infiltration on LB.

The necroinflammatory activity remains an interfering factor for both methods. In fact, for TE, the influence of necroinflammatory activity was suggested by a report showing that significant variations in LS occur during a flare in ALT levels in patients with chronic viral hepatitis [30] and was confirmed by results obtained from patients with acute viral hepatitis [31]. However, there was not such an observation for ARFI until now. In our group, ARFI overestimated the fibrosis stage in only 5 patients, too low a number to allow for a rigorous statistical analysis of the possible part played by the transaminase level in altering the results. Further studies are necessary to assess to which extent and from which level of severity the necroinflammatory activity influences the SWV.

Of the histopathological parameters, SWV was strongest correlated with fibrosis. There was a significant increase in SWV alongside the increase in fibrosis stage, but, at the same time, there was a degree of overlap between consecutive stages. For F0-F1 patients, SWV in our study group was 1.079±0.15 m/s, a value comparable to those communicated so far: 1.19±0.25 m/s [20] and 0.96±0.15 m/s [21]. For cirrhotic patients, SWV reached 2.55±0.78 m/s in our study, compared to 2.4 m/s [20], 2.62 ±0.66 m/s [23], and 3.06±0.96 m/s [21].

We tried to define SWV cut-off values for each fibrosis stage. They were chosen so that the sum between sensitivity and specificity was maximal: 1.19 m/s (for the prediction of stages F≥1), 1.34 m/s (F≥2), 1.61 m/s (F≥3) and 2.00 m/s (F4). In comparison to the LS cut-off values as quantified by TE (5.2 kPa, 8.1 kPa, 9.6 kPa and 13.1 kPa), SWV cut-off values are rather close. In addition, as shown in Table V, the best results for ARFI were obtained for the prediction of severe fibrosis and cirrhosis (89.21% - 90.19% diagnostic accuracy), whereas, for the prediction of earlier stages, the diagnostic accuracy only reached 64.70% (≥ F1) and 77.45% (≥ F2), respectively. Therefore, ARFI should not necessarily be seen as a substitute for LB or other invasive procedures in the prediction of each fibrosis stage, but rather as a "differentiation" instrument to quickly establish the clinical priorities when a patient with severe fibrosis is found.

By comparing the areas under the ROC curves in both ARFI and TE, AUROC predicts significantly better the ≥F1 and ≥F2 stages for TE, while, in the case of severe fibrosis (F3) and cirrhosis (F4), the difference between the performances of the two methods is not significant. A preliminary study comparing the performances of the two elastographic methods found an insignificant difference between TE and ARFI in F≥2 stages as well, not only in the F>3 and F4 stages [22]. The performance of TE for significant fibrosis in our population was better than that already reported, with an AUROC of 0.96 as compared with AUROCs around 0.84 in the most recent meta-analysis [32]. Future studies are therefore necessary, involving large groups of patients having undergone LB, to compare the performances of the two methods in the prediction of each fibrosis stage and to establish the factors that may interfere with the prediction.

Poynard et al demonstrated that the prevalence of liver fibrosis stages is a major factor of variability in assessing the diagnostic value of a fibrosis marker [28]. In our study, the adjusted AUROC according to the prevalence of each individual fibrosis stage did not significantly differ from the observed ones, for either ARFI or TE. However, we acknowledge that there is a selection bias in our population with uneven distribution of fibrosis stages and overrepresentation of patients with severe fibrosis-cirrhosis (44.6%), even though AUROCs remain similar after adjustment according to the DANA.

The theoretical advantage of ARFI as compared to TE is its implementation on an ultrasound device, via additional software imaging control and detection algorithms, thus allowing the visualization of B mode, color Doppler mode and ARFI images with the same equipment. Furthermore, the SWV can be measured not only through the intercostal approach in the right lobe, but also through the subcostal approach or even the left lobe. Still, when the measurements are taken in the left lobe, they may be influenced by the heart pulsations transmitted through the liver parenchyma. In the present study, SWV assessment was performed in the upper right quadrant, the same area used for the measurement of the LS by TE, to ensure the most accurate comparison of the two methods and to avoid the errors generated by the potential uneven distribution of fibrosis.

Regarding the ARFI technique failure, no valid measurement was obtained in 10 patients (8.92%). Six of these had a TE success rate of below 60%. There was no patient with examination failure in TE who would yield valid ARFI measurements. The small number of patients with a failed examination did not allow for a complex analysis of

the factors leading to it. In any case, unlike TE (proven to fail only in obese patients) [3-6], the ARFI technology seems to be influenced by more than just an increased BMI. As shown in the user manual, there are a few factors that can cause measurements failure, individually or in combination: excessive tissue motion (such as cardiac pulsations in the tissue that disrupt the SWV estimate); high attenuation of the signal in large patients (making it difficult for the system to identify the shear wave peak consistently as it propagates); and very high stiffness of the tissue impairing the SWV estimate (velocity out of range), thus lowering the confidence interval.

By carefully eliminating the errors generated by excessive tissue motility, it looks like obesity and cirrhosis with high tissue stiffness are possible limiting factors of the examination.

Our study is only a preliminary one, performed on a rather small group of patients and therefore, no analysis of the factors that may independently lead to failure of the examination could be made. Furthermore, given our goal (to compare the two elastographic methods), we excluded from the study the patients having ascites, a known cause of TE failure. In what concerns the ARFI technique, longitudinal waves from the push pulses are transmitted through ascites, whereas shear waves are measured only at the region of interest: therefore, the SWV assessment is still possible in the presence of ascites. Studies on larger groups of patients, including those with ascites, will be able to establish the predictive factors of ARFI failure.

The ARFI technique can be performed as part of a usual ultrasonic examination and it may become integrated in the ultrasonographical protocol in the future. The usefulness of this new diagnostic method, its advantages and limitations and also the intra and inter-observer reproducibility should be evaluated in prospective studies on patients having undergone LB.

We used LB as the reference standard because it is recommended for the pre-treatment assessment of CHC patients in the latest consensus statements [33]. However, its reproducibility is poor, due to the heterogeneity in liver fibrosis and sample size, and also to inter and intra-observer variability. The most important factor leading to erroneous LB interpretation is the inadequate size of the specimen; it has been suggested that specimens below 20 mm in length and 1.4 mm in thickness, including less than 11 portal spaces, may underestimate the fibrosis stage [34]. In a comparative study between percutaneous LB as opposed to liver resection results, the accuracy of the fibrosis assessment varied from 65% (for a 15 mm specimen length) to 90% (for a 40 mm length), indicating that the bioptic specimens should measure at least 25 mm in length to allow a correct assessment of fibrosis [35]. In our patients, the average length of the bioptic specimen was 11.02 mm, with an average of 11 portal spaces; only 20% of our patients had a biopsy specimen over 15 mm, and this is a possible limitation of the study.

Conclusions

ARFI technology allows the quantification of the shear wave velocity, strongly correlated with the fibrosis stage. Steatosis does not influence the shear wave velocity. The maximal usefulness of this method comes in the prediction of severe fibrosis and cirrhosis, for which the diagnostic accuracy is highly comparable to TE, whereas the TE has better performance for the earlier stages of fibrosis.

Conflicts of interest

None to declare.

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