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● *Original Contribution*

ACOUSTIC RADIATION FORCE IMPULSE AND SUPERSONIC SHEAR IMAGING VERSUS TRANSIENT ELASTOGRAPHY FOR LIVER FIBROSIS ASSESSMENT

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Abstract—Our study compared three elastographic methods—transient elastography (TE), acoustic radiation force impulse (ARFI) imaging and supersonic shear imaging (SSI)—with respect to the feasibility of their use in liver fibrosis evaluation. We also compared the performance of ARFI imaging and SSI, with TE as the reference method. The study included 332 patients, with or without hepatopathies, in which liver stiffness was evaluated using TE, ARFI and SSI. Reliable measurements were defined as a median value of 10 (TE, ARFI imaging) or 5 (SSI) liver stiffness measurements with a success rate ≥60% and an interquartile range interval <30%. A significantly higher percentage of reliable measurements were obtained using ARFI than by using TE and SSI: 92.1% versus 72.2% ($p < 0.0001$) and 92.1% versus 71.3% ($p < 0.0001$). Higher body mass index and older age were significantly associated with inability to obtain reliable measurements of liver stiffness using TE and SSI. In 55.4% of patients, reliable liver stiffness measurements were obtained using all three elastographic methods, and ARFI imaging and TE were similarly accurate in diagnosing significant fibrosis and cirrhosis, with TE as the reference method. (E-mail: isporea@umft.ro) © **2013 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Liver stiffness, Liver fibrosis, Transient elastography, Acoustic radiation force impulse elastography, Supersonic shear imaging.**

INTRODUCTION

Chronic liver diseases are quite common in daily practice. In some areas, chronic viral hepatitis B and/or hepatitis C are dominant, and in others, non-viral chronic hepatopathies (alcoholic or non-alcoholic steatohepatitis) are more common. To assess the severity of chronic liver diseases, the hepatologist can use invasive (liver biopsy) or non-invasive techniques.

After its introduction into daily practice, the first liver biopsy being performed in 1923 (Bingel 1923), percutaneous liver biopsy became an indispensable tool for the evaluation of liver diseases. Because liver biopsy offers information regarding fibrosis stage, necro-inflammation and fatty infiltration and reveals specific markers in certain hepatic diseases, this morphologic examination is considered the "gold standard" method for assessment of liver diseases (Grant and Neuberger 1999; Rockey et al. 2009). However, we must consider that after diagnostic liver biopsy, minor or serious complications, including death, may occur in 1–5% of cases (Piccinino et al. 1986), and that liver biopsy has limitations because of the uneven distribution of liver fibrosis (Bedossa et al. 2003), the small size of the specimen (approximately 1/50,000th of the total volume of the liver) (Afdhal 2006) and inter- and intra-observer diagnostic discrepancies in biopsy assessments of liver fibrosis (Bedossa et al. 1994). For these reasons, several non-invasive methods for liver fibrosis assessment have been developed in the last 10–15 y.

Serologic tests were the first ones to be developed; they can be used evaluate liver fibrosis (Guha et al. 2008) and activity and fibrosis (Poynard et al. 2004). Subsequently, transient elastography (TE), commercialized as the FibroScan, a shear wave ultrasound elastographic method, began to be used for liver fibrosis assessment. Several published studies and meta-analyses (Friedrich-Rust et al. 2008; Sandrin et al. 2003; Tsochatzis et al. 2011) have reported that TE is a reliable diagnostic tool for the non-invasive evaluation of liver fibrosis, especially in patients with chronic

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hepatitis C (Castera et al. 2005; Tsochatzis et al. 2011), but also in those with chronic hepatitis B (Chon et al. 2012; Marcellin et al. 2009) and non-alcoholic steatohepatitis (Wong et al. 2010) and in post-transplant patients (Adebajo et al. 2012). TE also has some limitations: it is hampered by the presence of ascites because TE waves cannot penetrate into ascites; obesity significantly decreases the rate of reliable measurements (Castera et al. 2010); aminotransferases flares are associated with falsely elevated TE values (Coco et al. 2007, Viganò et al. 2010); and extra-hepatic cholestasis (Millonig et al. 2008) and high central venous pressure (Millonig et al. 2010) falsely increase the liver stiffness values assessed by TE. Also, the FibroScan device is quite expensive and, thus, in some countries, the number of available systems is limited.

In the last 3 y, several real-time elastographic methods have been used for the non-invasive assessment of liver fibrosis. They can be classified into two categories: *train methods*, such as real-time tissue elastography (Havre et al. 2008), and *shear wave methods*, such as acoustic radiation force impulse (ARFI) elastography (Friedrich-Rust et al. 2007) and supersonic shear imaging (SSI) (Bavu et al. 2011). Unlike TE, real-time elastographic methods are included in standard ultrasound systems that can be used for many other purposes (standard ultrasound examination, Doppler evaluation, contrast-enhanced ultrasound), so that these devices are more cost effective. Another advantage is that patients with ascites can also be evaluated by means of real-time techniques.

Among the real-time elastographic methods, ARFI has been studied the most. A recently published meta-analysis (Friedrich-Rust et al. 2012) indicated that it is a good method for liver fibrosis evaluation, with accuracies of 0.87 in predicting significant fibrosis ($F \geq 2$), 0.91 in predicting severe fibrosis ($F \geq 3$) and 0.93 in predicting liver cirrhosis. SSI is the latest to appear on the market, and there are few, although promising, published studies regarding this technique (Bavu et al. 2011, Ferraioli et al. 2012).

The main aim of this study was to compare the feasibility of using the three elastographic methods involving ultrasound shear waves (TE, ARFI and SSI). The secondary aim was to compare ARFI elastography and SSI with respect to performance in the assessment of liver fibrosis assessment, with TE as the reference method, because TE has already been validated for the evaluation of liver fibrosis (Adebajo et al. 2012; Castera et al. 2005; Chon et al. 2012; European Association for the Study of the Liver 2011, 2012; Marcellin et al. 2009; Tsochatzis et al. 2011; Wong et al. 2010).

METHODS

Patients

Our study included 332 consecutive patients for whom liver stiffness (LS) was evaluated in the same session using three elastographic methods: TE, ARFI and SSI. The subjects were: healthy volunteers (medical students, nurses and medical doctors from our hospital: none had a history of liver disease, but additional tests, such as biological tests and viral markers, were not performed, with the exception of an ultrasound examination, which was normal); patients with chronic hepatitis B and C; patients with chronic non-viral hepatitis (such as alcoholic or non-alcoholic steatohepatitis, autoimmune hepatitis, primary biliary cirrhosis); and patients previously diagnosed with liver cirrhosis on the basis of clinical, biologic, ultrasonographic, morphologic and/or laparoscopic criteria.

All patients included in our study had a homogeneous liver structure (without focal liver lesions) and no ascites on abdominal ultrasound examination.

All patients signed an informed consent before elastographic measurements; the study was approved by the local ethics committee and was performed in accordance with the Helsinki Declaration of 1975.

Transient elastography

Liver stiffness was measured by means of TE using the FibroScan device (EchoSens, Paris, France), which incorporates a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. The vibrator generates a completely painless vibration (50-Hz frequency and 2-mm amplitude), which induces an elastic shear wave propagating through the skin and the subcutaneous tissue to the liver, which is tracked using the coaxial ultrasound transducer. The wave velocity is directly related to tissue stiffness, which is calculated by the device and expressed in kilopascals (Sandrin et al. 2003).

For each patient, 10 valid TE measurements were performed under fasting conditions. The patient was in the supine position, by the intercostal approach, with the right arm in maximum abduction. A standard M-probe was used. The median value was calculated and expressed in kilopascals. A reliable measurement was defined as the median of 10 valid LS measurements with a success rate (SR = ratio of number of successful acquisitions to total number of acquisitions) $\geq$60% and an interquartile range (IQR = difference between 75th and 25th percentiles, essentially the range of the middle 50% of the data) $<$30% (Fig. 1). The median of 10 valid measurements was considered as indicative of the severity of fibrosis.

Fig. 1. Transient elastography measurement. On the screen are displayed the liver stiffness expressed in kilopascals (kPa), the interquartile range (IQR) and the success rate.

Transient elastography measurement was defined as failed if no valid measurement was obtained after at least 10 attempts; a measurement was considered unreliable if fewer than 10 valid attempts were made; SR $<$ 60% and/or IQR $\geq$ 30% (Castera et al. 2010). In TE, the system automatically displays on the screen the median, IQR and SR.

Transient elastography measurements were performed by four experienced operators who had performed more than 1000 examinations each (one operator per patient) and who were blinded to all clinical and other elastographic data.

Because TE is a validated method for liver fibrosis evaluation (Adebajo et al. 2012; Castera et al. 2005; Chon et al. 2012; European Association for the Study of the Liver 2011, 2012; Marcellin et al. 2009; Tsochatzis et al. 2011; Wong et al. 2010), it was considered the reference method against which the performance of ARFI and SSI elastography was assessed. To discriminate between the various stages of fibrosis with TE, we used the latest published LS cutoffs proposed in the Tsochatzis meta-analysis (Tsochatzis et al. 2011): 7.2 kPa for significant fibrosis ($F \geq 2$) and 14.5 kPa for liver cirrhosis ($F = 4$) (Tsochatzis et al. 2011).

Acoustic radiation force impulse elastography

Acoustic radiation force impulse elastography was performed with a Siemens Acuson S2000 Virtual Touch ultrasound system (Siemens AG, Erlangen, Germany) with a 4CI transducer. The principle underlying ARFI elastography is that shearing of the examined tissue induces a strain in the tissues. An acoustic "push" pulse is automatically produced by the ultrasound probe and directed to the side of a region of interest (ROI), which is where the speed of the shear wave is measured. This ROI has a predefined size, provided by the system (10 mm long and 5 mm wide). The acoustic "push" pulse generates shear waves that propagate into the tissue, perpendicular to the "push" axis. Detection waves are also generated by the transducer to measure the propagation speed of these shear waves, which increases with fibrosis severity (Palmeri et al. 2008). The speed of the shear waves, measured in meters per second, as well as measurement depth, is displayed by the system.

For each patient, 10 valid ARFI measurements were performed under fasting conditions, with the patient in supine position with the right arm in maximum abduction, by the intercostal approach in the right liver lobe, 1–2 cm under the liver capsule. Minimal scanning pressure was applied by the operator; the patient was asked to stop normal breathing for a moment to minimize breathing motion (Fig. 2). The median of 10 valid measurements was calculated and considered indicative of the severity of fibrosis.

Acoustic radiation force impulse measurements were performed by one of three operators, each of whom had at least 2 y of experience in conventional ultrasound examination and had performed more than 150 ARFI measurements. The operators were blinded to any clinical or elastographic data.

In contrast to TE, the manufacturer of the ARFI device initially did not recommend use of the technical parameters IQR and SR, but a previous study published by our group (Bota et al. 2011) indicated that the correlation of LS assessed by ARFI with fibrosis was significantly better in patients in whom ARFI measurements had good technical parameters, compared with those with high IQR and/or low SR. Currently, the manufacturer specifies that the IQR parameter seems to improve

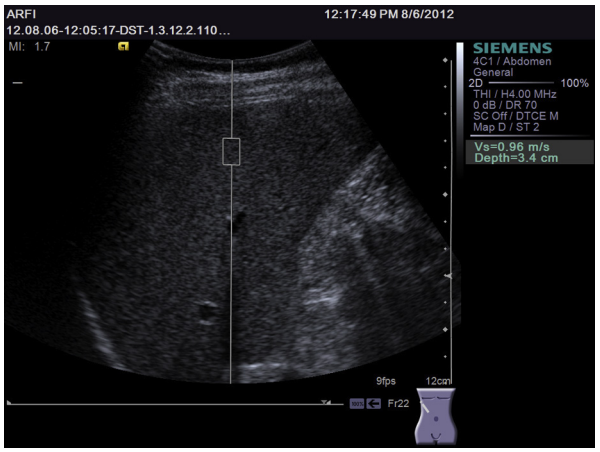

Fig. 2. Acoustic radiation force impulse measurement. The measurement is performed in the area enclosed by the box. On the screen are displayed the velocity (in m/s) and depth of the measurement.

the performance of this technique, but it is not considered a fixed manufacturer-recommended protocol. For these reasons, in this study, we decided to use the same criteria for defining failed, unreliable and valid measurements as used for TE.

To discriminate between the various stages of fibrosis using ARFI results, we employed the LS cutoffs proposed in a recently published meta-analysis (Friedrich-Rust et al. 2012): 1.34 m/s for significant fibrosis ($F \geq 2$) and 1.8 m/s for liver cirrhosis ($F = 4$).

Supersonic shear imaging

Supersonic shear imaging was performed with an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France), using a SC6–1 convex probe. The principle underlying SSI involves the combination of a radiation force induced in tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence able to capture the propagation of resulting shear waves in real time. The ultrasound system captures the generated shear waves. To capture them in sufficient detail, frame rates of a few thousands of images per second are needed. This ultrafast imaging mode acquires raw radiofrequency data at a very high frame rate, up to 5000 frames/s. Shear wave speed is then estimated by a Doppler-like acquisition over a region of interest. The shear wave speed is used to calculate tissue stiffness. Elasticity is displayed using a color-coded image superimposed on a B-mode image: where stiffer tissues appear red and softer tissues appear blue. At the same time, LS is quantitatively estimated; the mean LS value in the region of interest, as well as the standard deviation of the measured elasticity, is displayed on the screen, expressed in kilopascals (Bercoff et al. 2004, Muller et al. 2009) or, if the operator chooses, meters per second.

For each patient, five valid SSI measurements were performed under fasting conditions, with the patient in supine position, with the right arm in maximum abduction, by the intercostal approach, in the right liver lobe, 2 cm under the liver capsule, in an area of parenchyma free of large vessels, using a box of 3.5 × 2.5 cm in which a 1-cm-diameter circular region of interest was selected (Fig. 3). The median value of five valid SSI measurements was calculated (expressed in kilopascals) and considered indicative of the severity of fibrosis.

As for ARFI elastography, the manufacturer of the SSI device did not recommend any technical parameter for quality assessment of the measurements. Because it has been reported that in ARFI elastography, the correlation of LS measurements with fibrosis is significantly better in cases with measurements with good technical parameters (Bota et al. 2011), we decided to use IQR and SR to assess the quality of SSI measurements.

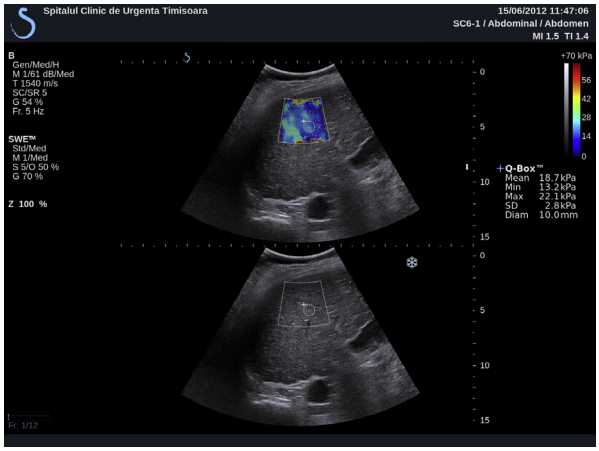

Fig. 3. Supersonic shear imaging measurement. The measurement is performed inside of the circle which is positioned in an area of homogeneous color. On the screen are displayed the mean, minimum, maximum and standard deviation of the measurement, as well as the diameter of the circle.

Thus, for defining failed, unreliable and reliable LS measurements, respectively, the same criteria used for TE and ARFI were used for SSI.

The SSI measurements were performed by the same operators who performed ARFI measurements. During one working day, each operator performed either SSI or ARFI measurements, in different rooms, so that they were blinded to all clinical and elastographic data. Also, the operators who performed SSI and ARFI measurements did not perform TE measurements.

To estimate fibrosis by means of SSI, we used the cutoffs proposed in the largest published study that compared SSI measurements with liver biopsy results (Ferraioli et al. 2012): 7.1 kPa for significant fibrosis ($F \geq 2$) and 10.4 kPa for liver cirrhosis ($F = 4$).

We decided to perform only five SSI measurements because in the other published studies, such as Ferraioli et al. (2012) and Bavu et al. (2011), only four or five SSI measurements were performed, and we used these studies to evaluate our results. It should also be specified that SSI measurements are more time consuming than ARFI or TE measurements.

Statistical analysis

Statistical analysis was performed using MedCalc Software (MedCalc Software bvba, Ostend, Belgium). The Kolmogrov-Smirnov test was used for testing the distribution of numerical variables. Means and standard deviations were calculated for numerical variables with a normal distribution, whereas for variables with a non-normal distribution, medians and ranges were calculated. Qualitative variables are expressed as numbers and percentages. A parametric test (*t*-test) was used to assess differences between numerical variables with a normal

distribution; and a nonparametric test (Mann–Whitney or Kruskal–Wallis test) was used for variables with a non-normal distribution. The χ^2 test (with Yates' correction for continuity) was used to compare proportions expressed as percentages (n = total number of patients included in a particular subgroup). Ninety-five percent confidence intervals were calculated for each predictive test. A p-value <0.05 was considered as indicating significance for each statistic test.

RESULTS

The main characteristics of the patients included in the study are summarized in Table 1.

Reliable LS measurements were obtained in a significantly higher percentage of patients by ARFI elastography compared with TE and SSI: 92.1% versus 72.2% ($p < 0.0001$) and 92.1% versus 71.3% ($p < 0.0001$), respectively. The rates of reliable LS measurements for TE and SSI were similar: 72.2% and 71.3% ($p = 0.86$).

In only 4 patients (1.2%) reliable LS measurements could not be obtained with any of the three elastographic methods.

Higher body mass index (BMI) and older age were significantly associated with inability to obtain reliable LS measurements for both TE and SSI. In SSI measurements, the presence of chronic hepatopathies was also associated with failed and unreliable measurements. No factors were identified as significantly associated with the inability to obtain reliable LS measurements by ARFI elastography (Table 2).

In obese patients also (BMI ≥ 30 kg/m^2, 21% of all patients included in study), reliable LS measurements were obtained in a significantly higher percentage of patients by ARFI elastography compared with TE and SSI: 87.1% versus 30.4 % ($p < 0.0001$) and 87.1% versus 40% ($p < 0.0001$), respectively; TE and SSI had similar rates of reliable measurements in obese patients: 30.4% and 40% ($p = 0.31$).

Reliable LS measurements by all three shear wave ultrasound elastographic methods were obtained in 184 of 332 patients (55.4%). We used this cohort to study the performance of ARFI and SSI in the diagnosis of significant fibrosis ($F \geq 2$) and cirrhosis ($F = 4$), with TE as the reference method, because it is a validated method for liver fibrosis assessment.

Significant fibrosis was diagnosed in 46% of cases by TE, with 7.2 kPa as the cutoff LS value. As we mentioned under Methods, we considered the following LS values as cutoffs for significant fibrosis ($F \geq 2$): 1.34 m/s for ARFI and 7.1 kPa for SSI elastography. The sensitivity, specificity and accuracy of ARFI and SSI in the diagnosis of significant fibrosis were similar (Table 3).

Liver cirrhosis was diagnosed in 12.5% of cases by TE, using 14.5 kPa as the cutoff LS value. For ARFI and SSI elastography, we used the following cutoff values: 1.8 m/s and 10.4 kPa, respectively. The sensitivity, positive predictive value (PPV) and accuracy of ARFI and SSI were similar for the diagnosis of cirrhosis, whereas the specificity and negative predictive value (NPV) were significantly better for SSI (Table 3).

Supersonic shear imaging was significantly more accurate in the diagnosis of cirrhosis than in the diagnosis of significant fibrosis: accuracy = 85.8 versus 74.4% ($p = 0.01$). ARFI elastography diagnosed cirrhosis and significant fibrosis with similar accuracy: 78.2% versus 72.2% ($p = 0.22$).

Table 1. Main characteristics of patients[†]

Age, y	53 (18–79)
Gender	
Male	144 (43.4%)*
Female	188 (56.6%)
Body mass index (kg/m^2)	26.4 ± 5.3
Diagnosis (n)	
Healthy volunteers	56 (16.9%)
Chronic hepatitis B	63 (18.9%)
Chronic hepatitis C	86 (25.9%)
Chronic non-viral hepatitis	91 (27.4%)
Cirrhosis	36 (10.9%)
Alanine aminotransferase (U/L)	57 (18–650)
Aspartate aminotransferase (U/L)	60 (25–685)

* Variables with a normal distribution are expressed as the mean ± standard deviation; variables with a non-normal distribution are expressed as the median and range.

† Number (%) of patients.

DISCUSSION

At this time, there is an ongoing debate over the invasive or non-invasive assessment of liver fibrosis. In some European countries, such as France, non-invasive methods for evaluation of liver fibrosis are used extensively, but in other countries, such as the United States (US), mainly liver biopsy is used in daily practice for hepatic fibrosis assessment. It should be noted that TE is not used in the United States because of the lack of Food and Drug Administration approval.

To our best knowledge, this study is the first to compare the three most frequently used shear wave elastographic methods (TE, ARFI and SSI) for LS assessment.

The main aim of the study was to assess the "intent-to-diagnose" value of the three elastographic methods, because before analysis of any method's accuracy, reliable measurements should be obtained. A significantly higher percentage of reliable LS measurements were made with ARFI, compared with TE and SSI, whereas similar rates of reliable measurements were made with

Table 2. Factors associated with the inability to obtain reliable liver stiffness measurements by all three elastographic methods*

Transient elastography (TE)			
Parameter	Reliable LS measurements n = 240 (72.2%)	Failed or unreliable LS measurements n = 92 (27.8%)	*p*
Age (y)	52 (18–78)	57 (21–79)	**0.0002**
Gender			
Male	103 (42.9%)†	41 (44.5%)	0.88
Female	137 (57.1%)	51 (55.5%)	0.88
Body mass index (kg/m^2)	25.1 ± 4.1	30.1 ± 6.2	**<0.0001**
Alanine aminotransferase (U/L)	67 (18–650)	53 (25–145)	0.10
Chronic hepatopathies			
Yes	194 (80.8%)	82 (89.1%)	0.10
No	46 (19.2%)	10 (10.9%)	0.10
Cirrhosis			
Yes	23 (9.6%)	13 (14.1%)	0.32
No	217 (90.4%)	79 (85.9%)	0.32
ARFI elastography			
Parameter	Reliable LS measurements n = 306 (92.1%)	Failed or unreliable LS measurements n = 26 (7.9%)	*p*
Age (y)	54 (18–79)	47 (24–67)	0.15
Gender			
Male	134 (43.8%)	10 (38.4%)	0.74
Female	172 (56.2%)	16 (61.6%)	0.74
Body mass index (kg/m^2)	26.3 ± 5.2	28.2 ± 6.5	0.07
Alanine aminotransferase (U/L)	65 (18–650)	54 (28–95)	0.24
Chronic hepatopathies			
Yes	258 (84.3%)	19 (73.1%)	0.23
No	48 (15.7%)	7 (26.9%)	0.23
Cirrhosis			
Yes	34 (11.1%)	2 (7.7%)	0.83
No	272 (88.9%)	24 (92.3%)	0.83
Supersonic shear imaging (SSI)			
Parameter	Reliable LS measurements n = 237 (71.3%)	Failed or unreliable LS measurements n = 95 (27.8%)	*p* value
Age (y)	52 (18–78)	57 (22–79)	**<0.0001**
Gender			
Male	109 (45.9%)	35 (36.8%)	0.16
Female	128 (54.1%)	60 (63.2%)	0.16
BMI (kg/m^2)	24.9 ± 4.4	30.3 ± 5.5	**<0.0001**
Alanine aminotransferase (U/L)	53 (18–650)	70 (22–350)	0.23
Chronic hepatopathies			
Yes	191 (80.5%)	86 (90.5%)	**0.04**
No	46 (19.5%)	9 (9.5%)	**0.04**
Cirrhosis			
Yes	25 (10.5%)	11 (11.6%)	0.92
No	212 (89.5%)	84 (88.4%)	0.92

LS = liver stiffness.
In bold are differences statistically significant.
* Numerical variables with a normal distribution are expressed as the mean ± standard deviation, whereas variables with a non-normal distribution are expressed as the median value and range.
† Number (%) of patients.

SSI and TE. The percentage of reliable TE measurements in our study was lower that in Castera et al. (2010) (72.2% vs. 83%–84%), probably because of the higher BMI of our patients. Similarly to the study of Castera et al. (2010), higher BMI and older age were associated with failed and unreliable measurements. The same factors, in addition to the presence of chronic hepatopathies, were associated with the inability to obtain reliable LS measurements using SSI.

The percentage of reliable SSI measurements was much lower than that in Ferraioli et al. (2012), who evaluated 121 patients with chronic hepatitis C (71.3% vs. 97.5%). Possible explanations for this difference are the higher BMI, older age and heterogeneity of our cohort.

Table 3. Performance of ARFI and SSI in diagnosis of significant fibrosis and cirrhosis, with TE as the reference method for liver fibrosis assessment

	Sensitivity (%)			Specificity (%)			Positive predictive value (%)			Negative predictive value (%)			Accuracy (%)		
	ARFI	SSI	*p*	ARFI	SSI	*p*	ARFI	SSI	*p*	ARFI	SSI	*p*	ARFI	SSI	*p*
Significant fibrosis ($F \geq 2$)	75.5	79.1	0.48	69.3	70.4	0.90	68.4	70.1	0.81	76.4	79.3	0.58	72.2	74.4	0.71
Liver cirrhosis ($F = 4$)	86.9	82.6	0.31	77	86.3	0.03	35.1	46.3	0.03	97.6	97.2	0.93	78.2	85.8	0.07

ARFI = acoustic radiation force impulse; SSI = supersonic shear imaging.

It should also be mentioned that Ferraioli et al. (2012) did not use the quality technical parameters IQR and SR for SSI measurements, but even if we had not used these quality parameters, the rate of valid LS measurements would still have been much lower in our study: 77.1% versus 97.5%. When only obese patients were analyzed, the percentage of reliable LS measurements was approximately 40% for TE and SSI and more than double that for ARFI. The obesity problem was partially solved for TE by the recent development of a more sensitive ultrasound sensor (XL probe), which also has the ability to non-invasively quantify liver steatosis (de Lédinghen et al. 2010; Myers et al. 2012), but greatly increases the device's cost.

As opposed to the other two elastographic methods, in ARFI elastography, even though BMI was higher in patients with failed and unreliable LS measurements compared with those with reliable measurements, the difference did not reach statistical significance, probably because of the relatively small number of cases in which reliable LS measurements could not be obtained. Also, no other factors were identified as significantly associated with failed and unreliable ARFI measurements.

Our secondary aim was to compare the performance of ARFI elastography and SSI in liver fibrosis assessment, with TE as the reference method. We chose TE as the reference method because it is the only ultrasound-based elastographic method recognized for non-invasive liver fibrosis assessment, being included in the guidelines of the European Association for the Study of the Liver (EASL) as a tool for liver fibrosis assessment in patients with chronic hepatopathies, especially chronic hepatitis C (European Association for the Study of the Liver 2011, 2012). According to the meta-analysis of Tsochatzis et al. (2011), which included 40 studies, TE performed well in predicting liver cirrhosis, considering liver biopsy as the "gold standard," with a summary sensitivity of 0.83 (95% confidence interval [CI]: 0.79–0.86) and a summary specificity of 0.89 (95% CI: 0.87–0.91). TE performed less well in predicting significant fibrosis, but the performance was still good, with a summary sensitivity of 0.79 (95% CI: 0.74–0.82) and a summary specificity of 0.78 (95% CI: 0.72–0.83). In our study, liver biopsy, still considered the "gold standard" for liver fibrosis assessment, was not available. But it should be specified that liver biopsy is not perfect. To be accurately interpreted by the pathologist, the liver biopsy specimen should be at least 1.5 cm long (Friedman 2004), ideally 4 cm (Bedossa et al. 2003), and include at least 8 (Grant and Neuberger 1999) or 11 (Guido and Rugge 2004) portal tracts, in the opinion of other authors. Published studies indicate that up to 20% of liver biopsy specimens are not large enough to be interpreted by the pathologist (Beaugrand 2006). Also, the inter- and intra-observer diagnostic discrepancies in biopsy assessment of liver fibrosis are important (Bedossa et al. 1994; Rousselet et al. 2005), whereas TE measurements have very good intra- and inter-observer agreement (Fraquelli et al. 2007). Last, but not least, liver biopsy is an invasive method and is not acceptable to all patients, especially if repeated evaluations are needed.

Even if SSI and TE values are reported as Young's modulus values, the cutoff values are not equal if different elastographic methods are used. If all cutoff values were to be reported in meters per second, the cutoff values for predicting significant fibrosis and liver cirrhosis would be 1.34 and 1.80 m/s for ARFI elastography, 1.55 and 2.20 m/s for TE and for 1.54 and 1.86 m/s for SSI. An explanation for the divergent values is the different technical principles underlying these techniques.

Several published studies have compared different elastographic methods for assessment of liver fibrosis. Most of the published studies that compared the value of TE and ARFI elastography in liver fibrosis evaluation, with liver biopsy as the reference method, reported similar performance in predicting significant fibrosis and cirrhosis (Colombo et al. 2012; Ebinuma et al. 2011; Friedrich-Rust et al. 2009a, 2009b; Kircheis et al. 2012; Sporea et al. 2010), but some studies did indicate that TE (Lupsor et al. 2009) or ARFI elastography (Rizzo et al. 2011) was significantly better. In the meta-analysis by Friedrich-Rust et al. (2012), which included 312 patients from four studies in which LS was evaluated using ARFI and TE, the statistical analysis revealed that TE performed significantly better.

Recently, in another meta-analysis (presented so far only as an abstract), including 840 patients from eight studies who were evaluated with ARFI, TE and liver biopsy (Bota et al. 2012), the odds ratios for ARFI and TE for the detection of significant fibrosis and cirrhosis were similar.

Until now, only two published studies (Bavu et al. 2011; Ferraioli et al. 2012) have compared TE with SSI in evaluation of liver fibrosis. Both reported that SSI performed significantly better in diagnosing significant fibrosis, whereas TE and SSI performed similarly in predicting liver cirrhosis. Our study is the first to compare SSI with ARFI elastography, with TE as the reference method, for liver fibrosis assessment. To decrease the risk of bias, we decided to use, for TE and ARFI, the cutoff values proposed by the latest published meta-analysis (Friedrich-Rust et al. 2012; Tsochatzis et al. 2011) and, for SSI, the cutoff values published by the largest study to compare SSI with liver biopsy (Ferraioli et al. 2012). The accuracy rates of ARFI and SSI were similar for the diagnosis of significant fibrosis and cirrhosis. Similar to published data (Fierbinteanu-Braticevici et al. 2009; Friedrich-Rust et al. 2009a, 2009b; Sporea et al. 2011), in our study SSI had better accuracy in the diagnosis of liver cirrhosis than in the diagnosis of significant fibrosis, whereas for ARFI elastography, the accuracy rates were similar.

In daily practice, seldom more than one non-invasive elastographic method for liver fibrosis assessment is available at any center. Thus, the hepatologist must choose the most cost-effective one. According to our results, ARFI elastography could be this method, as it has a significantly higher rate of reliable LS measurements, compared with TE or SSI, and is similar in accuracy to SSI in diagnosing significant fibrosis and liver cirrhosis. Also, as previously noted, most of the published studies (Bota et al. 2012; Colombo et al. 2012; Ebinuma et al. 2011; Friedrich-Rust et al. 2009a, 2009b; Kircheis et al. 2012; Sporea et al. 2010) have reported similar accuracy for ARFI and TE in the evaluation of liver fibrosis. ARFI has another advantage compared with TE: It can be integrated into a standard ultrasound system (which can also be used for standard ultrasound evaluation, contrast-enhanced ultrasound and/or Doppler examinations).

CONCLUSIONS

Acoustic radiation force impulse elastography is the most feasible shear wave elastographic method for assessment of liver fibrosis, especially in obese patients, whereas TE and SSI are similar with respect to rate of reliable LS measurements. With TE as the reference method for liver fibrosis evaluation, ARFI and SSI had similar rates accuracy in diagnosing significant fibrosis and liver cirrhosis.

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