Liver Fibrosis in Viral Hepatitis: Noninvasive Assessment with Acoustic Radiation Force Impulse Imaging versus Transient Elastography[1]

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Purpose: To compare, in a pilot study, acoustic radiation force impulse (ARFI) imaging technology integrated into a conventional ultrasonography (US) system with both transient elastography (TE) and serologic fibrosis marker testing for the noninvasive assessment of liver fibrosis.

Materials and Methods: Informed consent was obtained from all subjects, and the local ethics committee approved the study. ARFI imaging involved the mechanical excitation of tissue with use of short-duration acoustic pulses to generate localized displacements in tissue. The displacements resulted in shear-wave propagation, which was tracked by using US correlation-based methods and recorded in meters per second. Eighty-six patients with chronic viral hepatitis underwent TE, ARFI imaging, and serum fibrosis marker testing. Results were compared with liver biopsy findings, which served as the reference standard.

Results: ARFI imaging ($\rho = 0.71$), TE ($\rho = 0.73$), and serum fibrosis marker test ($\rho = 0.66$) results correlated significantly with histologic fibrosis stage ($P < .001$). Median ARFI velocities ranged from 0.84 to 3.83 m/sec. Areas under the receiver operating characteristic curve for the accuracy of ARFI imaging, TE, and serum fibrosis marker testing were 0.82, 0.84, and 0.82, respectively, for the diagnosis of moderate fibrosis (histologic fibrosis stage, ≥2) and 0.91, 0.91, and 0.82, respectively, for the diagnosis of cirrhosis.

Conclusion: ARFI imaging is a promising US-based method for assessing liver fibrosis in chronic viral hepatitis, with diagnostic accuracy comparable to that of TE in this preliminary study.

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Chronic infection with a hepatitis virus is an important cause of liver cirrhosis and associated sequelae (1). Precise estimation of the degree of liver fibrosis is important for determining the prognosis, surveillance, and treatment (2). Liver biopsy is still the procedure most commonly used as the reference standard for assessing liver fibrosis. However, it is invasive and associated with patient discomfort and, in rare cases, serious complications (3). In addition, the accuracy of liver biopsy is limited owing to intra- and interobserver variability and sampling errors (4,5). Therefore, research has been focused on the evaluation of noninvasive methods for assessing liver fibrosis. To date, most study investigators have evaluated transient elastography (TE) (6,7), as well as serologic fibrosis marker tests—specifically, FibroTest (Biopredictive, Paris, France) (based on several blood biomarker values) and aspartate aminotransferase–to-platelet ratio index (APRI) examinations (8,9).

Preliminary quantitative in vivo results indicate that acoustic radiation force impulse (ARFI) imaging technology can be applied for the diagnosis of liver fibrosis and cirrhosis (10). ARFI imaging has been incorporated into a conventional ultrasonographic (US) device (Acuson S2000; Siemens Medical Solutions, Mountain View, Calif). Our purpose was to compare, in a pilot study, the ARFI imaging technology integrated into a conventional US system with both TE and serologic fibrosis marker testing for the noninvasive assessment of liver fibrosis.

Materials and Methods

No financial support was received for the present study. One of the authors (T.P.) has a capital interest in Biopredictive, the company that markets FibroTest. The patent for this system is owned by a public organization, Assistance Publique Hôpitaux de Paris (Paris, France).

Subjects

Informed consent was obtained from all participating subjects, and the ethics committee of J. W. Goethe University approved our study. All patients with chronic viral hepatitis who had undergone liver biopsy within the past 15 months at J. W. Goethe University Hospital were contacted and invited to participate in the study, which was conducted from May to June 2008. Of 113 consecutive patients who met these inclusion criteria, 43 declined to give consent. Therefore, 70 patients with chronic viral hepatitis and current liver biopsy data were included. In addition, 16 patients with viral hepatitis and proved liver cirrhosis who presented to our outpatient hepatology clinic during the study period but had not recently (within past 15 months) undergone liver biopsy were invited to participate as well. None of these patients declined to give consent.

Thus, a total of 86 patients (mean age, 48 years ± 14 [standard deviation]; age range, 19–80 years) were included in the study. Mean ages were 47.3 years ± 15.9 (median age, 48 years; age range, 19–80 years) for female patients and 48.6 years ± 12.5 (median age, 50 years; age range, 26–70 years) for male patients. As the mean rate of liver fibrosis progression per year in the untreated patients, expressed in stage-specific transition probability values, was estimated to be 0.085–0.120 for fibrosis stages derived according to the Metavir scoring system (11), an interval of up to 15 months between liver biopsy and study inclusion was accepted for enrollment in our study. The interval between liver biopsy and study inclusion ranged from 1 to 15 months (mean, 9 months), and no patients received a course of antiviral therapy between liver biopsy and noninvasive estimation of liver fibrosis degree.

Chronic viral hepatitis was diagnosed when either hepatitis C virus (HCV) antibodies and HCV-RNA, or hepatitis B surface antigen and hepatitis B virus–DNA were present in the serum. Liver biopsy was indicated to determine the histologic fibrosis stage and the degree of liver tissue inflammation. In the 16 patients with chronic viral hepatitis and liver cirrhosis who had not undergone liver biopsy within the past 15 months, the diagnosis of liver cirrhosis was based on the results of US or magnetic resonance (MR) imaging (liver surface nodularity, liver segment I hypertrophy, splenomegaly, hepatofugal portal venous flow, enlargement and tortuosity of the hepatic artery, and portosystemic vascular shunts). Patients with ascites were excluded from the study because TE can be performed successfully only when the probe is in close contact to the liver.

In addition, 20 healthy adult volunteers (12 women, eight men) who were matched in sex distribution with the patient group and did not have a history of relevant concomitant illness (heart, lung, or liver disease or neoplasia) were examined with ARFI imaging and served as a reference group in which to obtain benchmark median ARFI velocity measure-

Advance in Knowledge

- In this pilot study, acoustic radiation force impulse (ARFI) imaging results were comparable to transient elastography results.

Implication for Patient Care

- ARFI imaging may prove to be an inexpensive noninvasive means of assessing liver fibrosis and cirrhosis and, in some cases, of avoiding biopsy.

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Abbreviations:
ALT = alanine aminotransferase
APRI = aminotransferase–to-platelet ratio index
ARFI = acoustic radiation force impulse
A_z = area under receiver operating characteristic curve
HCV = hepatitis C virus
TE = transient elastography

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Guarantors of integrity of entire study, M.F., K.W., S.Z.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.F., K.W., J.B., E.H., T.P., C.F.D.; clinical studies, M.F., K.W., F.S., J.B., T.P., J.V., S.Z., C.S.; statistical analysis, M.F., K.W., S.R., E.H., T.P.; and manuscript editing, M.F., K.W., F.S., J.B., E.H., T.P., C.F.D., S.Z., C.S.

See Materials and Methods for pertinent disclosures.

ments. The mean age of the volunteers (32 years; age range, 22–55 years) was significantly younger than that of the patient group ($P < .001$). No volunteers had taken any medication or illegal drugs or consumed an excessive amount (>15 g/d) of alcohol at the time of ARFI imaging.

Histologic Liver Analysis

Liver biopsy specimens were fixed in 4% buffered formalin and embedded in paraffin. Two-micrometer-thick sections were stained with hematoxylin-eosin, Perls iron, periodic acid-Schiff (after digestion with diastase), or Masson trichrome stain. All biopsy specimens were analyzed by an experienced pathologist (S.K., 15 years experience) who was blinded to the patients' clinical results. Liver fibrosis stages were evaluated semiquantitatively according to the Metavir scoring system (12). The liver fibrosis stage was determined by using a five-point (F0–F4) scale: Stage F0 indicated no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with a few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Necroinflammatory activity was graded according to the modified histologic activity index grading system: grade A for periportal or periseptal interface hepatitis; B for confluent necrosis; C for focal lytic necrosis, apoptosis, and focal inflammation; and D for portal inflammation with a maximal score of 18 (13). Steatosis was assessed according to the number of hepatocytes with fatty degeneration: Grade S indicated that fewer than 5% of the hepatocytes had fatty degeneration; S1, 5%–33% of the hepatocytes; S2, more than 33% to 66% of the hepatocytes; and S3, more than 66% of the hepatocytes. The biopsy specimen was judged to be adequate if it contained at least six portal tracts and was at least 1 cm in length. The mean length of the included liver biopsy specimens was 22.9 mm ± 9.4 (standard deviation) (median length, 20.0 mm; range, 10–48 mm).

Blood Markers

In all patients, the following blood parameters were measured on the same day that TE was performed, in the same laboratory: aspartate aminotransferase, alanine aminotransferase (ALT), γ-glutamyltransferase, alkaline phosphatase, total bilirubin, platelet count, α2-macroglobulin, apolipoprotein AI, and haptoglobin. Enzymatic activity was measured at 37°C according to International Federation of Clinical Chemistry standards.

The APRI (9) was calculated as follows: APRI = $(AST_{ULN} \cdot 100)/PC$, where AST_{ULN} is the upper limit of the normal aspartate aminotransferase value and PC is the platelet count, in 10^9 cells per liter. The upper limits of the normal aspartate aminotransferase concentrations in female and male patients are 35 and 50 IU/mL, respectively (9). The laboratory staff followed the preanalytical and analytical recommendations required to obtain fibrosis marker (FibroTest) and serum necroinflammatory marker (ActiTest; Biopredictive) (14) scores. Both scores were computed at the Biopredictive Web site *(http://www.biopredictive.com)*. Security algorithms (at the industrial Web site) prompting the exclusion of patients at high risk for false-positive and false-negative results were respected (14,15).

Imaging

In all patients, ARFI imaging (Acuson S2000, Virtual Touch Tissue Quantification mode) and TE (FibroScan; Echosens, Paris, France) were performed on the same day by two physicians (K.W., M.F., 4 and 6 years of experience in US, respectively) who were blinded to the liver biopsy results and to each other's results. A median of 10 measurements obtained in each patient by each examiner were compared for analysis of interexaminer agreement. The median measurements obtained by both examiners for each patient were used for all other analyses in the study. The measurement duration was assessed and documented.

The machine used to perform TE (FibroScan) is equipped with a probe that includes a US transducer mounted on the axis of a vibrator. A vibration transmitted from the vibrator toward the tissue induces an elastic shear wave that propagates through the tissue. These propagations are followed by pulse echo acquisitions, and the measured velocity of the propagations is directly related to tissue stiffness. Results are expressed in kilopascals. Details have been described in previous studies (16). TE was performed in the right lobe of the liver, through the intercostal space. After the area of measurement was located, the examiner pressed the button of the probe to start the acquisition. The measurement depth was between 25 and 65 mm. As suggested by the manufacturer, 10 successful acquisitions were performed in each patient. Only those TE results obtained with 10 valid measurements, with a success rate of at least 60% and an interquartile range of 30% or lower, were considered reliable. TE failure was defined as the acquisition of fewer than 10 valid measurements.

ARFI imaging involves targeting an anatomic region to be interrogated for elastic properties with use of a region-of-interest cursor while performing real-time B-mode imaging. Tissue in the region of interest is mechanically excited by using short-duration (~262 μsec) acoustic pulses with a fixed transmit frequency of 2.67 MHz to generate localized tissue displacements in tissue. The displacements result in shear-wave propagation away from the region of excitation and are tracked by using US correlation-based methods (17). The maximal displacement is estimated for many ultrasound tracking beams that are laterally adjacent to the single push beam and transmitted at a nominal center frequency of 3.08 MHz and a pulse repetition frequency of 4500–9000 Hz. By measuring the time to peak displacement at each lateral location, one can reproduce the shear-wave speed of the tissue (10,18). The shear velocity is estimated in a central window of 5 mm axial by 4 mm width within a region of interest graphically displayed at a size of 1 cm axial by 6 mm width (Fig 1). The shear-wave propagation velocity is proportional to the square root of tissue elasticity (19,20). Results are expressed in meters per sec-

Figure 1

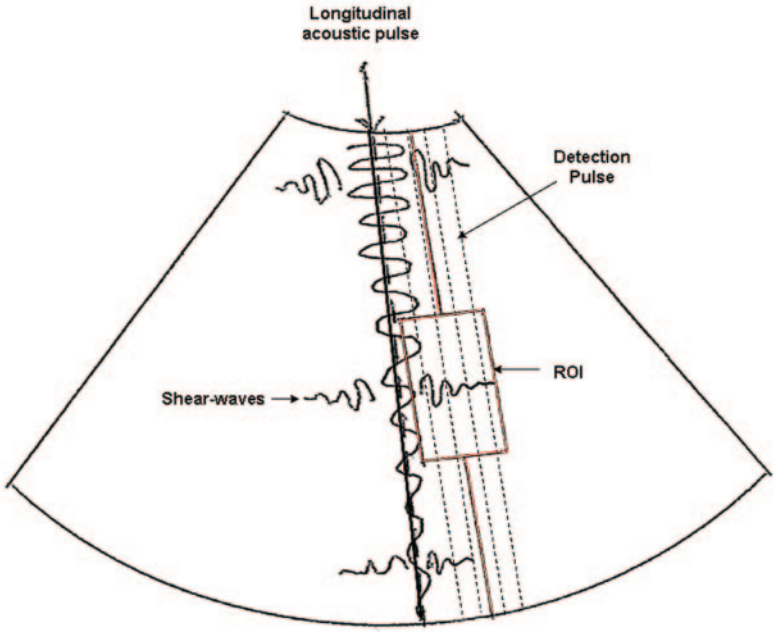

Figure 1: Schematic of principles of ARFI imaging in Virtual Touch Tissue Quantification (Siemens Medical Solutions) mode. Transmission of longitudinal acoustic pulse leads to tissue displacement, which results in a shear-wave propagation away from the region of excitation. The shear-wave velocity is measured within a defined region of interest *(ROI)* (central window of 5 mm axial by 4 mm width) by using ultrasound tracking beams laterally adjacent to the single push beam.

Figure 2

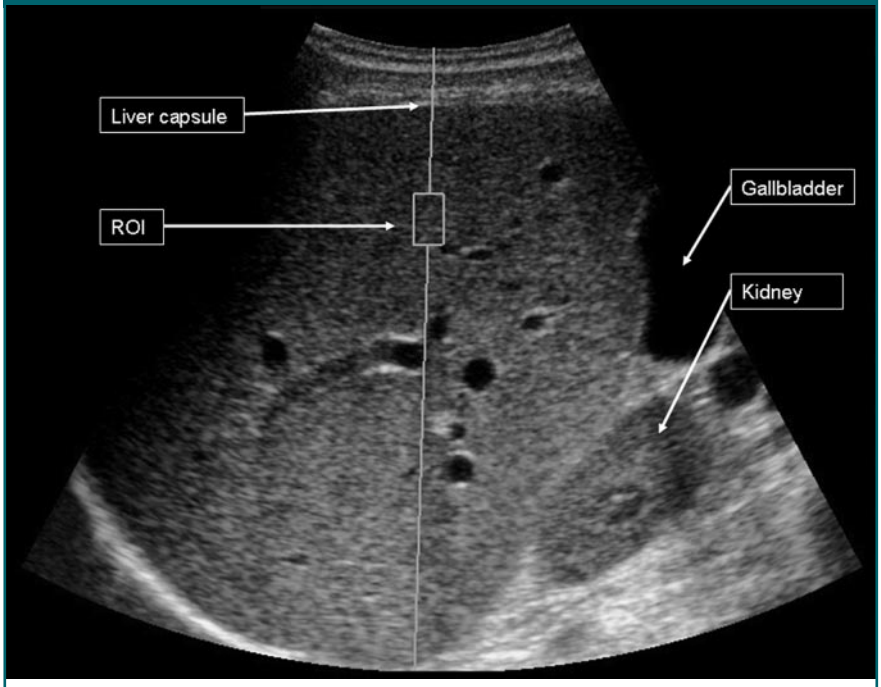

Figure 2: Real-time ARFI imaging measurement in liver of 41-year-old man with fibrosis stage F3. *ROI* = region of interest.

ond (range, 0.5–4.4 m/sec; ±20% accuracy over the range).

In all patients, ARFI imaging was performed with a curved array at 4 MHz for B-mode imaging. The examination was performed in the right lobe of the liver, through the intercostal space, at the same site as the TE measurement. An area where the liver tissue was at least 6 cm thick and free of large blood vessels was chosen. A measurement depth of 2 cm below the liver capsule was chosen to standardize the examination (Fig 2). Consistent with the TE protocol, 10 successful acquisitions were performed in each patient.

Statistical Analyses

For TE and ARFI imaging, the median of the 10 successful measurements obtained in each patient was calculated and used for further analyses. The TE and ARFI imaging values were not normally distributed and were therefore expressed as medians. Because the TE, ARFI imaging, and laboratory values were not normally distributed, we used the nonparametric Jonckheere-Terpstra test to compare these values with the histologic fibrosis stage. Correlations between the different fibrosis assessment approaches and the histologic fibrosis stage were also analyzed by using Spearman correlation coefficients.

We assessed the diagnostic performance of TE, ARFI imaging, and serum fibrosis markers by using receiver operating characteristic curves. The receiver operating characteristic curve represents sensitivity versus (1 − specificity) for all possible cutoff values for the prediction of the different fibrosis stages. Areas under the receiver operating characteristic curve (A_z) and the 95% confidence intervals of the A_z values were calculated by using SPSS, version 15, software (SPSS, Chicago, Ill). A_z values for the different diagnostic criteria for the same data set were compared by using the nonparametric DeLong test. A_z values for the different fibrosis assessment methods were correlated, and use of the DeLong test enabled us

to take these correlations into account. Therefore, this testing may have revealed significant differences in diagnostic accuracy, even when the confidence intervals for single A_z values—which ignored these correlations—were overlapping.

The cutoff values used to define the regions of prediction of each fibrosis stage were determined by using a common optimization step that maximized the Youden index (21) for predicting the advanced stages. After the cutoff levels were optimized, sensitivity, specificity, and positive and negative predictive values were calculated from the same data, without further adjustments (eg, with cross validation). Data for the entire study population were analyzed, with those patients with proved liver cirrhosis assigned to the Metavir stage F4 group. The influences of different factors on the results were analyzed by using Bonferroni correction for multiple tests. In cases involving a diagnosis of fibrosis stage F2 or higher versus a stage lower than F2, we also calculated an A_z value adjusted for differences in mean advanced fibrosis stage versus mean nonadvanced fibrosis stage (DANA) according to the method of Poynard et al (22) to derive a standardized DANA value of 2.5.

To analyze the discordance in results due to the inclusion of patients infected with hepatitis B virus and HCV, we performed a subanalysis involving patients infected with HCV only and compared these results with those for the entire study group. To exclude the influence of biopsy specimens with lengths shorter than 15 mm on the analysis results, we performed a subanalysis in which all patients with biopsy specimens shorter than 15 mm were excluded and compared these results with those for the entire study group. The influence of steatosis was evaluated by comparing the data of patients with steatosis grade S1, S2, or S3 with those of patients with steatosis grade S0 and comparing the data of patients with grade S2 or S3 with those of patients with grade S0 or S1. To evaluate the influence of ALT

Table 1

Patient Characteristics

Characteristic	Value
M/F patients	46/35
Patient age (y)	
Mean*	48 ± 14 (19–80)
Median	49
Body mass index (kg/m^2)	
Mean*	26 ± 4 (17–40)
Median	25
AST level (×ULN)	
Mean*	1.3 ± 1.2 (0.3–10.2)
Median	1.1
ALT level (×ULN)	
Mean*	1.6 ± 1.4 (0.3–10.6)
Median	1.2
GGT level (×ULN)	
Mean*	1.3 ± 1.7 (0.1–9.9)
Median	0.7
Total bilirubin level (mg/dL)	
Mean*	0.73 ± 0.45 (0.2–2.6)
Median	0.6
Platelet count (×10^3/mm^3)	
Mean*	172 ± 71 (2–321)
Median	176
HBV infection	17
HBV-DNA (×10^6 U/L)	
Mean*	5.9 ± 24.2
Median	3.8
HCV infection	64
HCV-RNA (×10^6 U/L)	
Mean*	2.75 ± 4.8
Median	1.2
Genotype 1	46
Genotype 2	5
Genotype 3	13
Histologic fibrosis stage	
F0	8
F1	19
F2	23
F3	9
F4	22†
Histologic steatosis stage‡	
S0	42
S1	8
S2	11
S3	4

Note.—Unless otherwise noted, data are numbers of patients. AST = aspartate aminotransferase, GGT = γ-glutamyltransferase, HBV = hepatitis B virus, ULN = upper limit of normal. Normal ALT and aspartate aminotransferase levels for female and male subjects are less than 35 U/L and less than 50 U/L, respectively. Normal GGT levels for female and male patients are less than 39 U/L and less than 66 U/L, respectively.

* Mean ± standard deviation. Numbers in parentheses, where applicable, are the range.

† Includes six patients with stage F4 fibrosis and 16 patients with clinically proved liver cirrhosis.

‡ Histologic steatosis stages for 65 patients who underwent liver biopsy.

levels, we divided the patients into two groups: patients with normal ALT levels (ALT level/upper limit of normal ALT level, ≤1) and patients with elevated ALT levels (ALT level/upper limit of normal ALT level, >1). To assess the influence of serum necroinflammatory marker (ActiTest) scores, we compared the data of patients with a score of 2 or 3 with the data of patients who had a score of 0 or 1. These groups were compared by using Bonferroni correction for multiple tests. $P < .05$ indicated a significant correlation or difference.

Results

Eighty-six patients met the inclusion criteria. Two patients were excluded because their TE measurements were unreliable: Fewer than 10 valid measurements were obtained. In both of these patients, the distance between the skin and the liver capsule at the sight of TE (thoracic belt) was greater than 2 cm. Three other patients were excluded because the laboratory values needed to calculate their serum fibrosis marker (FibroTest) scores were missing. Therefore, the data of 81 patients were included in the final analysis. Demographic, biochemical, and virologic characteristics are shown in Table 1.

ARFI Imaging

The median velocity measured with ARFI imaging in the 20 healthy volunteers was 1.10 m/sec (mean, 1.13 m/sec ± 0.23; range, 0.85–1.42 m/sec). The velocities measured in the study patients ranged from 0.84 to 3.83 m/sec. According to the different Metavir fibrosis scores, the median velocities in the study patients were 1.13 m/sec (mean, 1.16 m/sec ± 0.17; range, 0.95–1.4 m/sec) for patients with stage F0, 1.17 m/sec (mean, 1.18 m/sec ± 0.18; range, 0.84–1.70 m/sec) for patients with stage F1, 1.22 m/sec (mean, 1.34 m/sec ± 0.34; range, 0.86–2.50 m/sec) for patients with stage F2, 1.64 m/sec (mean, 1.75 m/sec ± 0.51; range, 1.15–2.63 m/sec) for patients with stage F3, and 2.26 m/sec (mean, 2.38 m/sec ± 0.74; range, 1.15–3.83 m/sec) for patients with stage F4. The entire examination lasted 4–10 minutes per patient (median, 6 minutes per patient).

Relationships between Fibrosis Assessment Method and Histologic Liver Analysis Findings

Correlations between the ARFI imaging and TE results and the different histologic stages are shown in Figure 3. Spearman correlation coefficients (ρ) for the correlations between histologic fibrosis stage and the results of ARFI imaging, TE, FibroTest scoring, and APRI scoring indicated significant correlations: 0.71, 0.73, 0.66, and 0.45, respectively ($P < .001$). When the patients infected with hepatitis B virus were excluded—and, thus, the data of only

Figure 3

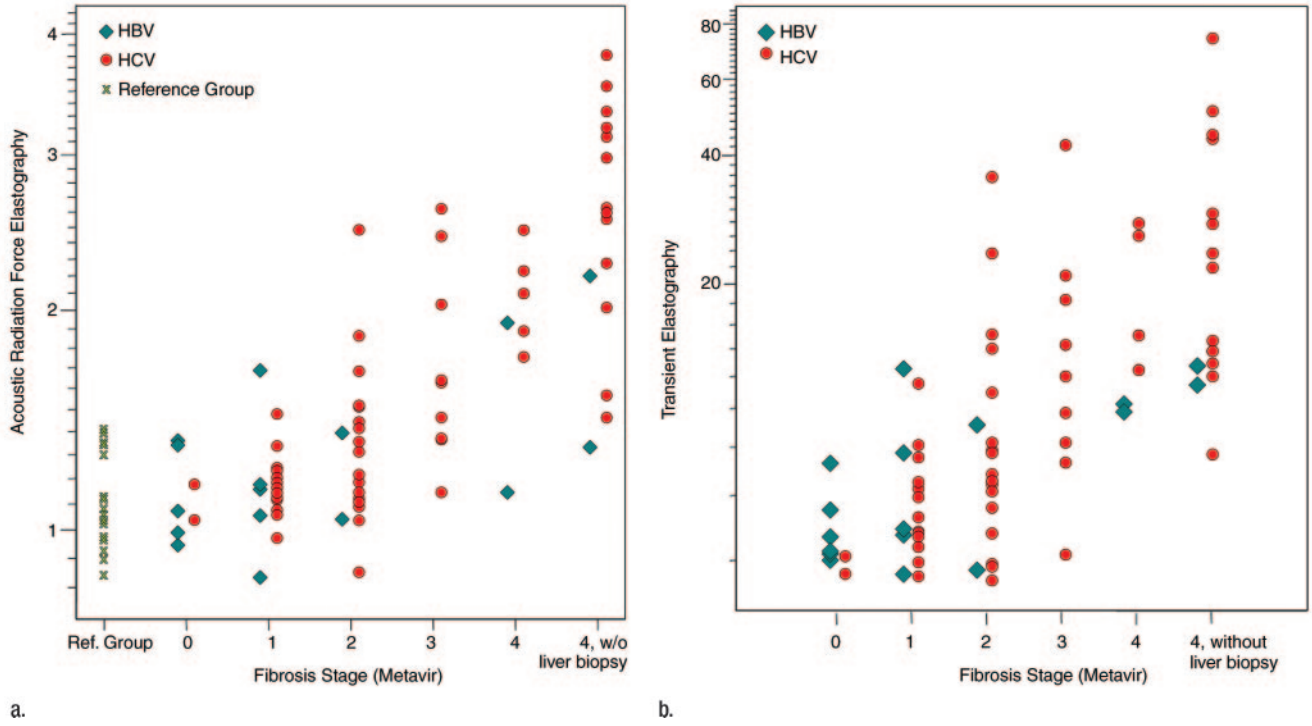

Figure 3: Scatterplots of **(a)** ARFI imaging and **(b)** TE results for determination of each fibrosis stage. Stage F4 group is divided into patients who had recently undergone liver biopsy and patients with proved liver cirrhosis who had not recently undergone liver biopsy. ARFI measurements in the healthy volunteers (Reference *[Ref.]* Group) are included in **a**.

the 64 patients with HCV infection were analyzed—ρ values for the correlations between histologic fibrosis stage and the results of ARFI imaging, TE, FibroTest scoring, and APRI scoring improved to 0.77, 0.74, 0.72, and 0.53, respectively.

ARFI imaging, TE, and FibroTest scoring yielded comparable A_z values for the diagnosis of moderate fibrosis (stage ≥ F2), severe fibrosis (stage ≥ F3), and cirrhosis (stage F4): 0.82–0.84, 0.90–0.91, and 0.82–0.91, respectively (P = .15 with adjustment for multiple tests). No significant differences in A_z were observed when the patients with hepatitis B virus infection were excluded (Table 2, Fig 4). Optimal cutoff ARFI imaging and TE values, with respective sensitivity, specificity, and positive and negative predictive values, are cited in Tables 3 and 4, respectively.

Interexaminer Agreement and Factors Influencing Measurements

Agreement between the two examiners in determining each fibrosis stage was estimated by using the calculated cutoff values (Tables 3, 4) for the 61 patients infected with HCV. There was 87% (53 of 61 patients) agreement regarding ARFI imaging–derived stages and 85% (52 of 61 patients) agreement regarding TE-derived stages. For the differentiation between Metavir fibrosis stage F2 or greater and stage lower than F2, interobserver agreement was 90% (55 of 61 patients) with ARFI imaging and 85% (52 of 61 patients) with TE. The histologic steatosis grade had no significant influence on measurement results. Exclusion of the eight 10–15-mm biopsy specimens did not change the results.

The 49 (61%) patients with elevated ALT levels had higher TE values overall, especially after Bonferroni correction for multiple tests (P = .01) was applied to the data of those with fibrosis stages F3 and F4 (Table 5). However, the difference was not significant for ARFI imaging results (P = .065). A similar nonsignificant trend was observed when we discriminated the necroinflammatory marker (ActiTest) results (P = .095 after correction for TE and ARFI imaging results) (Table E1, *http://radiology.rsnajnls.org/cgi/content/full/252/2/595/DC1*).

Table 2

A_z Values for Diagnostic Accuracy of ARFI Imaging, TE, FibroTest Scoring, and APRI Scoring in Patients with Different METAVIR Fibrosis Stages

Fibrosis Assessment Method	Stage ≥ F2 (F2, F3, F4)	Stage ≥ F2 (Adjusted)*	Stage ≥ F3 (F3, F4)	Stage F4
All patients				
ARFI imaging	0.82 (0.73, 0.91)	0.84 (0.75, 0.93)	0.91 (0.85, 0.98)	0.91 (0.84, 0.98)
TE	0.84 (0.75, 0.93)	0.86 (0.77, 0.95)	0.90 (0.83, 0.97)	0.91 (0.84, 0.97)
FibroTest	0.82 (0.75, 0.93)	0.84 (0.77, 0.95)	0.91 (0.84, 0.97)	0.82 (0.73, 0.92)
APRI	0.75 (0.64, 0.86)	0.79 (0.66, 0.88)	0.76 (0.64, 0.87)	0.76 (0.64, 0.87)
Only patients with HCV				
ARFI imaging	0.84 (0.74, 0.94)	0.86 (0.76, 0.96)	0.93 (0.87, 0.99)	0.95 (0.89, 0.996)
TE	0.85 (0.75, 0.95)	0.87 (0.77, 0.97)	0.90 (0.81, 0.98)	0.91 (0.84, 0.979)
FibroTest	0.84 (0.74, 0.95)	0.86 (0.76, 0.97)	0.93 (0.87, 0.99)	0.84 (0.74, 0.934)
APRI	0.79 (0.68, 0.90)	0.81 (0.70, 0.92)	0.80 (0.69, 0.92)	0.73 (0.59, 0.868)

Note.—Numbers in parentheses are 95% confidence intervals.

* A_z values adjusted for differences in mean advanced fibrosis stage versus mean nonadvanced fibrosis stage (DANA) according to method of Poynard et al (22), for a uniform DANA value of 2.5.

Discussion

In chronic viral hepatitis, the stage of liver fibrosis is an important parameter in the evaluation to determine the appropriate antiviral treatment. TE and FibroTest scoring are two noninvasive methods that have been evaluated in multiple studies and yielded comparable results for the determination of liver fibrosis (6,7,23). In our pilot study, the results of US-based ARFI imaging for the noninvasive measurement of liver fibrosis were comparable to those of TE and FibroTest scoring. After these preliminary results, a large performance study to establish that ARFI imaging is not clinically inferior to TE seems justified.

To our knowledge, this is the first study in which the value of ARFI imaging for assessment of liver fibrosis was evaluated. Nightingale et al (10), in a preliminary quantitative in vivo study of ARFI imaging, reported markedly lower displacement magnitudes induced in cirrhotic liver tissue relative to those induced in noncirrhotic liver tissue. Lower displacements were associated with a faster shear-wave velocity. In our study, a significantly higher median shear-wave velocity (2.29 m/sec) was recorded for patients with cirrhosis compared with that for patients without fibrosis (1.18 m/sec). In addition, we were able to diagnose moderate or severe fibrosis with high diagnostic accuracy. Nevertheless, although the healthy volunteers had a mean ARFI velocity comparable to that of the patients with Metavir fibrosis stage F0, individual measurements in the healthy volunteers ranged from the velocities documented in patients without histologic fibrosis to the velocities measured in patients with liver cirrhosis. However, the laboratory data of the healthy volunteers were not available, so no statement can be made about which factors were associated with high velocities. Future studies with large numbers of healthy subjects are needed to address these coherences.

One advantage of ARFI imaging is that it is integrated into a conventional US system and thus can be performed with conventional US probes. Therefore, ARFI imaging can be performed during standard US examinations of the liver, which are routinely performed in patients with chronic liver disease. In addition, with TE, only an M-mode image is obtained to localize the optimal measurement site. However, with ARFI imaging, the measurement site can be chosen on a conventional B-mode image of the liver and measurement of nearby interfering structures such as blood vessels can be prevented systematically. Another

ARFI mode that is available with the Acuson S2000 US system, virtual touch tissue imaging, enables one to acquire sonoelastographic images similar to those obtained with conventional sonoelastography. This mode is used especially to characterize and visualize lesions within tissue. However, it was not used in the present study.

Results for the diagnostic accuracy of TE in our study are comparable to those reported in previous studies (6,7). Two (2%) of 86 patients had to be excluded owing to failed TE. This TE failure rate is slightly lower than that reported in previous studies (24,25). An association between TE failure and a fatty thoracic belt has been suggested in previous studies and is supported by the results of our present study. In both patients in whom TE was not successful, 10 valid ARFI imaging measurements could be obtained. Interexaminer agreement was comparable with both methods and in accordance with previous studies of TE (25,26).

Excellent results have been reported for the noninvasive assessment of liver fibrosis with MR elastography, the advantage being that a much larger area of the liver can be examined with this method (27–29). In a comparative study, MR elastography was superior to TE in the assessment of liver fibrosis, yielding accuracies higher than 98% in the diagnosis of all fibrosis categories (28). However, MR elastography is more expensive and time consuming than US-based elastography methods, and its applicability in the work-up of patients with chronic liver disease needs to be further evaluated.

Histologic analysis, in addition to facilitating liver fibrosis staging, also yields information about the necroinflammatory activity in the liver, which is associated with progression of liver disease. Necroinflammatory activity cannot be quantified with sonoelastography, and this is a limitation of the technique. Inflammation in the liver influences the accuracy of liver fibrosis staging. Wong et al (30) reported that among patients with the same fibrosis stage, those with elevated ALT levels tended to have higher TE values than did those with normal ALT levels. We made the same observation regarding TE values in our study; however, our ARFI imaging findings were not significantly different between the two ALT level groups. Similar results have been observed when the influence of necroinflammatory activity markers (ActiTest) (14,31) on liver stiffness measurements was analyzed. Again, our results for correlations with ActiTest results were not significant; however, this may have been due to the relatively small number of patients.

Thresholds for fibrosis and cirrhosis assessment increased slightly when patients with hepatitis B virus infection were excluded. The reasons for this might be the higher prevalence of macronodular cirrhosis and the more patchy distribution of fibrous tissue in the patients infected with hepatitis B.

To compare sensitivity and specificity between TE and ARFI imaging, optimal cutoff values for both methods were calculated. The cutoff TE values for the diagnosis of severe fibrosis and cirrhosis were very similar—most

Figure 4

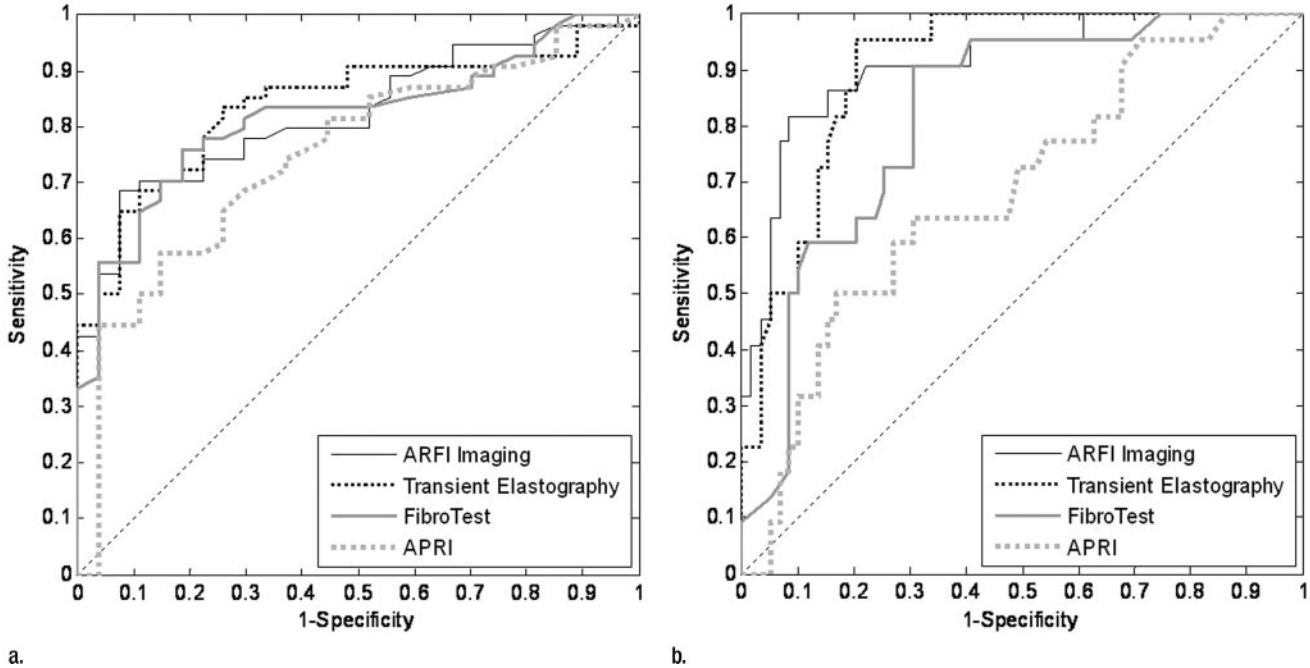

Figure 4: Receiver operating characteristic curves for ARFI imaging–, TE-, FibroTest-, and APRI-based diagnoses of **(a)** moderate fibrosis (stage ≥ F2) and **(b)** cirrhosis (stage F4).

likely because of the small number of patients with stage F3 fibrosis in this study.

FibroTest is currently the best evaluated noninvasive serum fibrosis marker panel that is commercially available (14). In our study, the diagnostic accuracy of FibroTest scoring was comparable to that of sonoelastography methods. APRI scoring has been shown to be inferior to FibroTest scoring and TE (23,32); this was also shown in our study. Nevertheless, it is the least expensive and easiest to perform fibrosis marker examination, and it might supplement the other noninvasive methods.

One limitation of our study was that the liver biopsies were performed up to 15 months before ARFI imaging. However, because the mean rate of liver fibrosis progression per year in untreated patients, expressed in stage-specific transition probability values, has been estimated to be 0.085–0.120 for fibrosis stages determined according to the Metavir scoring system (11), the changes during the 15-month period were expected to be minimal. Another limitation was the inclusion of biopsy specimens shorter than the standard length of 15 mm (if at least six portal tracts are present). Nevertheless, excluding biopsy specimens this short had no significant effect on our study results. Furthermore, the majority of our patients with cirrhosis had overt clinical signs of cirrhosis. However, this was a comparative study of different noninvasive fibrosis assessment methods, in which the inclusion of patients with proved liver cirrhosis affected the results for all methods equally. Patients with ascites were excluded from the study. However, the presence of ascites is a strong indicator of cirrhosis that makes noninvasive staging of fibrosis unnecessary. Finally, the relatively small study population was another limitation. However, this was a pilot study to evaluate ARFI imaging.

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Table 3

ARFI Imaging Cutoff and Performance Values for Diagnosis of Metavir Fibrosis Stage

Value	Stage ≥ F2 (F2, F3, F4)	Stage ≥ F3 (F3, F4)	Stage F4
All patients			
Cutoff ARFI velocity (m/sec)	1.37	1.45	1.75
Sensitivity (%)	68.5 (54.4, 80.5)	83.9 (66.3, 94.5)	81.8 (59.7, 94.8)
Specificity (%)	92.6 (75.7, 99.1)	86.0 (73.3, 94.2)	91.5 (81.3, 97.2)
PPV (%)	94.9 (82.7, 99.4)	78.8 (61.1, 91.0)	78.3 (56.3, 92.5)
NPV (%)	59.5 (43.3, 74.4)	89.6 (77.3, 96.5)	93.1 (83.3, 98.1)
Only patients with HCV			
Cutoff ARFI velocity (m/sec)	1.35	1.55	1.75
Sensitivity (%)	72.9 (58.2, 84.7)	81.5 (61.9, 93.7)	88.9 (65.3, 98.6)
Specificity (%)	93.8 (69.8, 99.8)	91.9 (78.1, 98.3)	89.1 (76.4, 96.4)
PPV (%)	97.2 (85.5, 99.9)	88.0 (68.8, 97.5)	76.2 (52.8, 91.8)
NPV (%)	53.6 (33.9, 72.5)	87.2 (72.6, 95.7)	95.3 (84.2, 99.4)

Note.—Numbers in parentheses are 95% confidence intervals. NPV = negative predictive value, PPV = positive predictive value.

Table 4

TE Cutoff and Performance Values for Diagnosis of Metavir Fibrosis Stage

Value	Stage ≥ F2 (F2, F3, F4)	Stage ≥ F3 (F3, F4)	Stage F4
All patients			
Cutoff TE value (kPa)	6.3	9.5	9.8
Sensitivity (%)	83.3 (70.7, 92.1)	87.1 (70.2, 96.4)	90.9 (70.8, 98.9)
Specificity (%)	74.1 (53.7, 88.9)	86.0 (73.3, 94.2)	79.7 (67.2, 89.0)
PPV (%)	86.5 (74.2, 94.4)	79.4 (62.1, 91.3)	62.5 (43.7, 78.9)
NPV (%)	69.0 (49.2, 84.7)	91.5 (79.6, 97.6)	95.9 (86.0, 99.5)
Only patients with HCV			
Cutoff TE value (kPa)	6.3	11.5	11.75
Sensitivity (%)	83.3 (69.8, 92.5)	81.5 (61.9, 93.7)	94.4 (72.7,)
Specificity (%)	75.0 (47.6, 92.7)	89.2 (74.6, 97.0)	80.4 (66.1, 90.6)
PPV (%)	90.9 (78.3, 97.5)	84.6 (65.1, 95.6)	65.4 (44.3, 82.8)
NPV (%)	60.0 (36.1, 80.9)	86.8 (72.0, 95.6)	97.4 (86.2, 99.9)

Note.—Numbers in parentheses are 95% confidence intervals. NPV = negative predictive value, PPV = positive predictive value.

Table 5

Median ARFI Imaging and TE Values at Different Histologic Fibrosis Stages and ALT Levels

	ARFI Velocity (m/sec)		TE Value (kPa)	
Metavir Fibrosis Stage*	ALT/ULN ≤ 1	ALT/ULN > 1	ALT/ULN ≤ 1	ALT/ULN > 1
F0	1.08 (0.95, 1.35)	1.18 (1.00, 1.27)	4.2 (4.0, 7.3)	4.2 (3.65, 4.7)
F1	1.19 (1.13, 1.49)	1.14 (0.84, 1.70)	4.9 (4.3, 7.6)	5.0 (3.6, 12.6)
F2	1.13 (0.86, 1.42)	1.42 (1.04, 2.50)	6.6 (3.5, 8.2)	7.2 (3.9, 35.6)
F3	1.55 (1.47, 1.63)	1.65 (1.15, 2.63)	9.7 (7.3, 12.0)	14.3 (4.2, 42.3)
F4	2.07 (1.15, 2.64)	2.74 (1.57, 3.83)	12.6 (7.7, 23.6)	28.6 (10.3, 74.3)

Note.—Numbers in parentheses are 95% confidence intervals of median values. Normal ALT values for female and male patients are less than 35 U/L and less than 50 U/L, respectively.

* Among the 81 patients included in the analysis, eight had fibrosis stage F0: In five, the quotient for ALT level divided by upper limit of normal ALT value (ALT/ULN) was less than or equal to 1, and in three, the ALT/ULN was greater than 1. Nineteen patients had stage F1: five with an ALT/ULN of less than or equal to 1 and 14 with an ALT/ULN of greater than 1. Twenty-three patients had stage F2: nine with an ALT/ULN of less than or equal to 1 and 14 with an ALT/ULN of greater than 1. Nine patients had stage F3: three with an ALT/ULN of less than or equal to 1 and six with an ALT/ULN of greater than 1. Twenty-two patients had stage F4 (cirrhosis): 10 with an ALT/ULN of less than or equal to 1 and 12 with an ALT/ULN of greater than 1.

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