AJR FOCUS ON:

Performance of Real-Time Strain Elastography, Transient Elastography, and Aspartate-to-Platelet Ratio Index in the Assessment of Fibrosis in Chronic Hepatitis C

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OBJECTIVE. The purpose of this article is to evaluate the diagnostic performance of transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index in assessing fibrosis in patients with chronic hepatitis C by using histologic Metavir scores as reference standard.

SUBJECTS AND METHODS. Consecutive patients with chronic hepatitis C scheduled for liver biopsy were enrolled. Liver biopsy was performed on the same day as transient elastography and real-time strain elastography. Transient elastography and real-time strain elastography were performed in the same patient encounter by a single investigator using a medical device based on elastometry and an ultrasound machine, respectively. Diagnostic performance was assessed by using receiver operating characteristic curves and area under the receiver operating characteristic curve (AUC) analysis.

RESULTS. One hundred thirty patients (91 men and 39 women) were analyzed. The cutoff values for transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index were 6.9 kPa, 1.82, and 0.37, respectively, for fibrosis score of 2 or higher; 7.3 kPa, 1.86, and 0.70, respectively, for fibrosis score of 3 or higher; and 9.3 kPa, 2.33, and 0.70, respectively, for fibrosis score of 4. AUC values of transient elastography, real-time strain elastography, aspartate-to-platelet ratio index were 0.88, 0.74, and 0.86, respectively, for fibrosis score of 2 or higher; 0.95, 0.80, and 0.89, respectively, for fibrosis score of 3 or higher; and 0.97, 0.80, and 0.84, respectively, for fibrosis score of 4. A combination of the three methods, when two of three were in agreement, showed AUC curves of 0.93, 0.95, and 0.95 for fibrosis scores of 2 or higher, 3 or higher, and 4, respectively.

CONCLUSION. Transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index values were correlated with histologic stages of fibrosis. Transient elastography offered excellent diagnostic performance in assessing severe fibrosis and cirrhosis. Real-time elastography does not yet have the potential to substitute for transient elastography in the assessment of liver fibrosis.

Fibrosis is the feature most strictly associated with progression of chronic hepatitis. Liver fibrosis is the result of a complex dynamic process that includes inflammation and necrosis, which is responsible for hepatocyte lysis, as well as reparative tissue response. Assessment of fibrosis is a relevant issue not only in terms of liver illness prognosis but also for starting targeted treatment [1, 2]. Thus far, liver biopsy represents the best elective procedure to assess liver fibrosis. In addition to fibrosis and its structural shape, liver biopsy also provides useful information about necrosis, inflammation grading, and iron storage, if any. On the other hand, it is an invasive procedure, with some associated morbility and mortality, though those risks are extremely low [3]. Patients are reluctant to undergo the procedure, and, what is more relevant, its significance is limited by a number of factors, such as variability among pathologist readings, uneven changes in liver tissue (implying potential different findings according to the biopsy site), the needle gauge, and the sample length, which affects histologic workup [4]. Fernández-Salazar et al. [5] concluded that one of six patients would rather choose a less-aggressive technique, even though it provided less information. Hence, a good substitute for liver biopsy has long been sought.

Actually, interest in surrogate fibrosis markers—either blood tests or noninvasive

imaging techniques—maintains a high profile because it implies avoiding liver biopsy, with its costs in terms of patient compliance, risks, and, not least, money. Furthermore, combining surrogate markers with liver biopsy could offer a better data yield when biopsy fails [6–13]. Among surrogate markers, the aspartate-to-platelet ratio index has proved to be relatively reliable in terms of sensitivity and specificity [10, 14]. Results of several studies have shown that transient elastography, which is based on tissue elasticity changes related to liver fibrosis, has good performance in the detection and measurement of liver fibrosis [6–8, 12, 13, 15–17]. Real-time elastography is a new method for the assessment of liver elasticity [18–21]. It uses ultrasound equipment with an embedded elastography module. Real-time strain elastography evaluates the degree of liver fibrosis through a slight compression of body tissues that induces a strain into the tissues. Harder tissues show less strain than do softer tissues. Real-time strain elastography can be performed during routine ultrasound examination of the liver.

The aim of our study was to evaluate the diagnostic performance of transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index in the assessment of fibrosis in patients with chronic hepatitis C by using histologic Metavir scores as the reference standard.

Subjects and Methods

Design Overview and Participants

This was a single-center study with prospective acquisition of data after informed consent. From June 17, 2009, through December 7, 2010, all consecutive patients with chronic hepatitis C scheduled for liver biopsy at the outpatient ward of our infectious diseases department were enrolled into the study. Moreover, patients followed up because of a diagnosis of compensated hepatitis C virus (HCV) liver cirrhosis based on previous histologic evidence of liver biopsy performed at our institution were also included. Inclusion criteria were the presence of HCV RNA in serum and, at least transiently, elevated serum alanine aminotransferase level. Exclusion criteria were HCV-HIV coinfection and decompensated liver cirrhosis. As a rule, patients with clinically overt cirrhosis were not scheduled for liver biopsy. Epidemiologic data, serum aminotransferase level, and platelet count were determined. Liver biopsy was performed on the same day as transient elastography and real-time strain elastography, as a same-day case procedure. A single physician with more than 30 years of experience in ultrasound examinations and 2 years of experience in real-time strain elastography consecutively performed transient elastography and real-time strain elastography in a randomized order before liver biopsy.

The study protocol was approved by the institutional ethics committee. Participants gave their informed written consent.

Transient Elastography

Transient elastography was performed by using FibroScan (Echosens), a medical device based on elastometry. The physician performing all the examinations had experience with at least 50 transient elastography procedures, as previously recommended [8]. Measurements of liver stiffness were performed on the right lobe of the liver through intercostal spaces on patients lying in the supine position with the right arm in maximal abduction, following an examination procedure described elsewhere [6]. Only patients with 10 validated measurements and interquartile range (IQR) of less than 30% of the median liver stiffness value were included. Values were expressed in kilopascal.

Real-Time Strain Elastography

Real-time strain elastography evaluates the stiffness of tissues by calculating the displacement of tissue in the axial direction of the ultrasound beam usually induced by slight mechanical compression of the transducer. Real-time strain elastography was performed by using an ultrasound system with real-time strain elastography software (EUB-8500, Hitachi Medical Systems). A linear broadband transducer (EUP-L52, Hitachi Medical Systems; frequency, 7.5–5.0 MHz) was used. The real-time strain elastography method integrated in the equipment we used is able to compute the automatic displacement of the liver determined by the heartbeat; thus, no compression with the transducer is required. Patients were examined in the supine position with the right arm in maximal abduction and were instructed to hold their breath. The examinations were performed on the right lobe of the liver through the intercostal spaces, holding firmly the transducer without applying compression on the skin. The equipment displays two images simultaneously: the conventional B-mode image and the color-coded elastography region of interest (ROI) overlaid on the B-mode image (Fig. 1). The system uses a hue color map where hard tissue areas are marked with blue, intermediate tissue areas with green, and soft tissue areas with red. To standardize the measurements, the size of the ROI was set as a rectangle of 20 × 40 mm and placed starting from 10 mm below the Glisson capsule of the liver, choosing an area of the parenchyma free of large vessels. Acquisitions were considered effective when the ROI was filled with colors and no artifacts were observed. Real-time strain elastography images were stored as moving digital images for 10–15 seconds. Three effective acquisitions were performed for each patient. The movies were stored uncompressed at maximum quality and sent to the engineers of Hitachi Medical Systems in Japan for the calculation of the liver fibrosis index, because at the time of our study, the elastography software of the machine that computes the automatic displacement of the liver determined by the heartbeat was not commercially available and was not implemented yet in our system. Thus, the operator performing real-time strain elastography was blind to liver fibrosis index measurement results.

To calculate liver fibrosis index, five frames in which the liver moved in the axial direction by the heartbeat were selected from the movie. Nine features—mean and SD of the relative strain value, complexity and ratio of the blue area in the ROI, skewness, kurtosis, entropy, inverse difference moment, and angular second moment—were extracted from each frame. The liver fibrosis index for each frame was calculated using a formula that had been previously obtained in a Japanese series [20] and that was

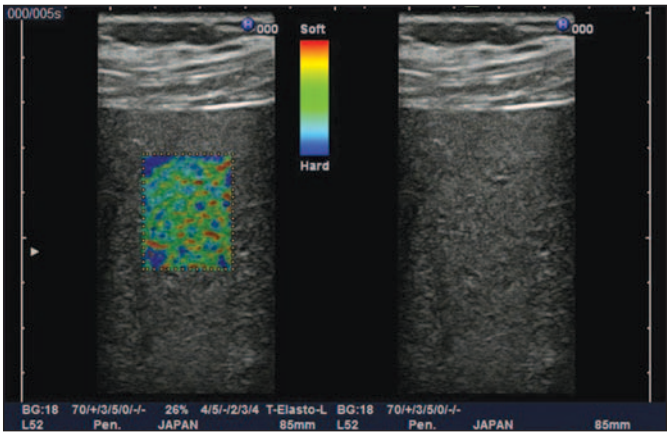

Fig. 1—44-year-old man with chronic hepatitis C and fibrosis stage F1. Intercostal scan shows conventional B-mode image and color-coded elastography region of interest overlaid on B-mode image. Red indicates that tissue is soft, and blue that it is hard.

modified on the basis of results obtained in a series of 70 patients studied by us before the current study. The formula to calculate the liver fibrosis index was as follows: (–0.0581 × mean) + (0.164 × SD) – (0.069 × percentage area) – (0.129 × complexity) + (1.97 × skewness) + (1.6 × kurtosis) – (1.68 × entropy) + (11.9 × inverse difference moment) – (488 × angular second moment) + 4.05. The liver fibrosis index of each patient was obtained from the mean value of the five- frames that were analyzed. The entire real-time strain elastography examination lasted approximately 5–10 minutes per patient.

Liver Biopsy and Histology

Ultrasound-assisted percutaneous liver biopsy was performed by two experienced physicians by using the same intercostal space chosen for transient elastography and real-time strain elastography measurements, where the skin had been previously marked. A disposable 1.4-mm-diameter modified Menghini needle (Hepafix, Braun) was used. All biopsy specimens were fixed in formalin and embedded in paraffin. The specimens were read on site by a single expert liver pathologist blind to the results of both transient elastography and real-time strain elastography but not to the clinical and biochemical data. Fibrosis was evaluated semiquantitatively and was staged on a 5-point scale from 0 to 4 according to the Metavir scoring system (F0, absent; F1, enlarged fibrotic portal tract; F2, periportal or initial portal-portal septa but intact architecture; F3, architectural distortion but no obvious cirrhosis; and F4, cirrhosis). For the purpose of this study, F0 and F1 scores were grouped in the subsequent statistical analysis. Necroinflammatory activity was evaluated by using the histologic activity index described by Knodell et al. [22] and was classified as follows: histologic activity index score of 1–5, mild; histologic activity index score of 6–9, moderate; and histologic activity index score of 10 or higher, severe.

Steatosis was expressed as a percentage of fat in the hepatocytes and was classified as absent (S0), less than 33% (S1), 33–66% (S2), and greater than 66% (S3). The length of each liver biopsy specimen (in centimeters) and the number of fragmented specimens were recorded.

Aspartate-to-Platelet Ratio Index

The aspartate-to-platelet ratio index [10] was calculated as follows: (aspartate transaminase level × upper limit of normal) × 100 / platelet count (10^9 cells/L).

Statistical Analysis

Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of patients. Medians and IQRs of values were calculated for all variables. The Spearman rank coefficient was used to test correlation between two variables. Quantile regression was used for the multivariate model to assess the association between transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index and fibrosis, histologic activity index, and steatosis. A frequency distribution was obtained, and optimal cutoff values of real-time strain elastography, transient elastography, and aspartate-to-platelet ratio index were chosen to maximize the sum of sensitivity and specificity for different fibrosis thresholds: F0–F1 versus F2–F4 ($F \geq 2$), F0–F2 versus F3–F4 ($F \geq 3$), and F0–F3 versus F4 ($F = 4$). The diagnostic performance of real-time strain elastography, transient elastography, aspartate-to-platelet ratio index, and their combinations was assessed by using receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC) analysis. The performance of paired parallel combination of transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index was assessed by using the optimal cutoff values obtained with the ROC curves.

Comparisons of AUCs were done using the method described by DeLong et al. [23] for correlated data. Data analysis was performed with STATA statistical package (release 11.1, StataCorp).

TABLE 1: Patient Demographics and Biochemical and Histologic Data at Liver Biopsy Examination

Variable	Value
Patient demographics (*n* = 130)	
Male sex	91 (70)
Age (y)	46 (39–54)
Body mass index (kg/m^2)	25.6 (22–28)
Aspartate aminotransferase level (IU/L)	45 (27–81)
Alanine aminotransferase level (IU/L)	72 (38–119)
Platelet count (10^3 cells/mm^3)	211 (171–266)
Fibrosis (Metavir) score (*n* = 130)	
F0	8 (6)
F1	62 (48)
F2	24 (18)
F3	12 (10)
F4	24 (18)
Steatosis (*n* = 124)	
S0 (0%)	85 (69)
S1 (< 33%)	23 (19)
S2 (33–66%)	7 (5)
S3 (> 66%)	9 (7)
Histologic activity index (*n* = 124)	
Mild	55 (44)
Moderate	54 (44)
Severe	15 (12)

Note—Data are median (interquartile range) or no. (%) of patients.

Results

Patients

One hundred thirty-eight patients met the inclusion criteria. Seven patients (5.1%) were excluded because of unreliable transient elastography measurements (no successful acquisitions in five patients; IQR > 30% in two patients), and one patient was excluded because both transient elastography and real-time strain elastography were unsuccessful because of narrow intercostal spaces. Thus, 130 patients were analyzed. Their characteristics are summarized in Table 1. There were 91 men (median age, 45 years; IQR, 39–50 years) and 39 women (median age, 49 years; IQR, 39–58 years). Six patients had a diagnosis of liver cirrhosis based on historical histology results of liver biopsy. The median length of the liver biopsy samples was 2.5 cm (IQR, 2.0–3.5 cm); 11 liver biopsy samples were fragmented. The fibrosis grade distribution was as follows: F0, eight patients; F1, 62 patients; F2, 24 patients; F3, 12 patients; and F4, 24 patients.

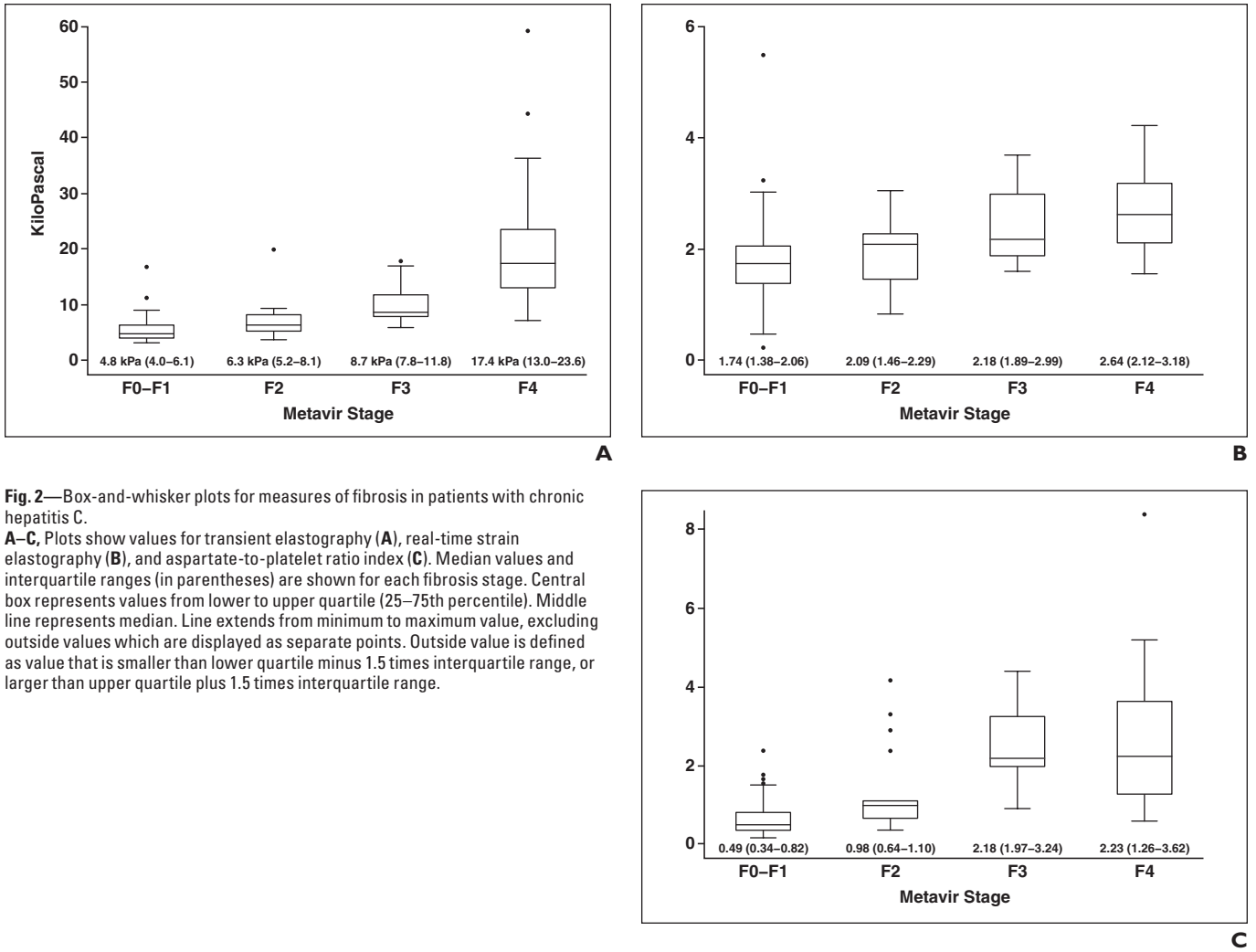

Fig. 2—Box-and-whisker plots for measures of fibrosis in patients with chronic hepatitis C.
A–C, Plots show values for transient elastography (**A**), real-time strain elastography (**B**), and aspartate-to-platelet ratio index (**C**). Median values and interquartile ranges (in parentheses) are shown for each fibrosis stage. Central box represents values from lower to upper quartile (25–75th percentile). Middle line represents median. Line extends from minimum to maximum value, excluding outside values which are displayed as separate points. Outside value is defined as value that is smaller than lower quartile minus 1.5 times interquartile range, or larger than upper quartile plus 1.5 times interquartile range.

There was good correlation between the degree of histologic activity index and Metavir score ($r = 0.60$ and $p < 0.001$) and poor correlation between the degree of steatosis and Metavir score ($r = 0.20$ and $p = 0.027$). In univariate analysis, transient elastography and aspartate-to-platelet ratio index showed a good correlation with the degree of fibrosis ($r = 0.71$ and $p < 0.0001$; and $r = 0.69$ and $p < 0.001$, respectively) and the degree of histologic activity index ($r = 0.58$ and $p < 0.0001$; and $r = 0.61$ and $p < 0.0001$, respectively) and a poor correlation with the degree of steatosis, despite being statistically significant ($r = 0.27$ and $p = 0.002$; and $r = 0.23$ and $p = 0.02$, respectively), whereas real-time strain elastography showed a good correlation with the degree of fibrosis ($r = 0.47$ and $p = 0.0001$) and a poor correlation with the degree of both histologic activity index ($r = 0.26$ and $p = 0.004$) and steatosis ($r = 0.25$ and $p = 0.006$). Multivariate regression analysis, including fibrosis stage, histologic activity index, and steatosis, confirmed the correlation with fibrosis stage and histologic activity index but not with steatosis for transient elastography and aspartate-to-platelet ratio index, whereas real-time strain elastography was correlated only with fibrosis.

Liver Stiffness by Transient Elastography

Figure 2 shows medians and IQR of transient elastography values for each fibrosis stage. ROC curve analysis identified optimal cutoff value of liver stiffness measurements as high as 6.9 kPa for F ≥ 2, 7.3 kPa for F ≥ 3, and 9.3 kPa for F = 4 (Fig. 3). Corresponding values of sensitivity, specificity, and AUCs are shown in Table 2. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR), and negative LR were 87.8%, 79.0%, 8.36, and 0.31, respectively, for F ≥ 2; 75.0%, 96.5%, 7.83, and 0.09, respectively, for F ≥ 3; and 76.7%, 99.0%, 14.5, and 0.05, respectively, for F = 4.

Liver Stiffness by Real-Time Strain Elastography

Figure 2 shows medians and IQR of real-time strain elastography values for each fibrosis stage. ROC curve analysis identified optimal cutoff value of liver fibrosis index as high as 1.82 for F ≥ 2, 1.86 for F ≥ 3, and 2.33 for F = 4 (Fig. 3). The corresponding sensitivity, specificity, and AUCs are shown in Table 2. PPV, NPV, positive LR, and negative LR were 63.6%, 79.2%, 2.04, and 0.31, respectively, for F ≥ 2; 45.2%, 94.7%, 2.15, and 0.15, for F ≥ 3; and 48.5%, 91.8%, 4.16, and 0.40, for F = 4.

Aspartate-to-Platelet Ratio Index

Figure 2 shows medians and IQR of aspartate-to-platelet ratio index values for each fibrosis stage. ROC curve analysis identified optimal cutoff value of aspartate-to-platelet ratio index greater than 0.37 for F ≥ 2; greater than 0.70 for F ≥ 3; and 0.70 or higher for F = 4 (Fig. 3). The corresponding sensitivity, specificity, and

AUCs are shown in Table 2. PPV, NPV, positive LR, and negative LR were 74.0%, 93.5%, 3.09, and 0.08, respectively, for F ≥ 2; 64.4%, 91.9%, 4.35, and 0.21, respectively, for F ≥ 3; and 44.4%, 95.9%, 3.34, and 0.18, respectively, for F = 4.

Comparison of Transient Elastography, Real-Time Strain Elastography, and Aspartate-to-Platelet Ratio Index

Pairwise comparison of ROC curves showed that transient elastography performed significantly better than real-time strain elastography in the assessment of all fibrosis stages. No significant differences were observed between real-time strain elastography and aspartate-to-platelet ratio index. With respect to aspartate-to-platelet ratio index, transient elastography performed significantly better in the assessment of liver fibrosis (Table 3).

Combination of Transient Elastography, Real-Time Strain Elastography, and Aspartate-to-Platelet Ratio Index

We evaluated the performance of paired parallel combination of transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index for the diagnosis of fibrosis stage as compared with the liver biopsy histologic results. Sensitivity, specificity, and AUCs of the combinations for each Metavir fibrosis stage are reported in Table 2.

Transient elastography plus aspartate-to-platelet ratio index combined showed PPV, NPV, positive LR, and negative LR of 71.4%, 95.2%, 2.72, and 0.05, respectively, for F ≥ 2; 58.9%, 96.8%, 3.44, and 0.08, respectively, for F ≥ 3; and 43.1%, 98.5, 3.17, and 0.06, respectively, for F = 4. Real-time strain elastography plus aspartate-to-platelet ratio index combined displayed PPV, NPV, positive LR, and negative LR of 59.4%, 100%, 1.59, and 0.00, respectively, for F ≥ 2; 43.2%, 100%, 1.83, and 0.00, respectively, for F ≥ 3; and 33.9%, 95.0%, 2.14, and 0.22, respectively, for F = 4.

The combination of transient elastography plus real-time strain elastography plus aspartate-to-platelet ratio index showed the

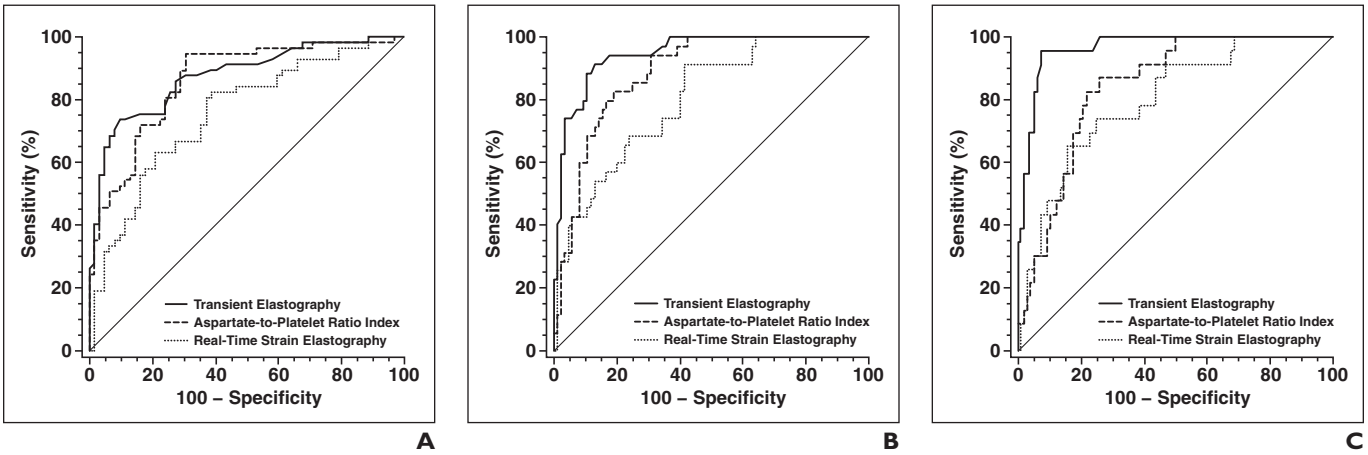

Fig. 3—Receiver operating characteristic curves.
A–C, Graphs show curves for transient elastography, aspartate-to-platelet ratio index, and real-time strain elastography for different fibrosis thresholds: F0–F1 versus F2–F4 (F ≥ 2) (**A**), F0–F2 versus F3–F4 (F ≥ 3) (**B**), and F0–F3 versus F4 (F = 4) (**C**).

TABLE 2: Sensitivity, Specificity, and Area Under the Receiver Operating Characteristic Curves (AUCs) for Transient Elastography, Real-Time Strain Elastography, and Aspartate-to-Platelet Ratio Index and Their Combinations for Each Metavir Fibrosis Stage (F)

	F ≥ 2			F ≥ 3			F = 4		
Method	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC
Transient elastography	71.7 (58.6–82.5)	91.4 (82.3–96.8)	0.88 (0.81–0.93)	91.7 (77.5–98.2)	88.3 (80.0–94.0)	0.95 (0.90–0.98)	95.8 (78.9–99.9)	93.4 (86.9–97.3)	0.97 (0.92–0.99)
Real-time strain elastography	81.7 (69.6–90.5)	60.0 (47.6–71.5)	0.74 (0.66–0.81)	91.7 (77.5–98.2)	57.5 (46.8–67.6)	0.80 (0.72–0.87)	66.7 (44.7–84.4)	84.0 (75.6–90.4)	0.80 (0.72–0.87)
Aspartate-to-platelet ratio index	94.7 (85.4–98.9)	69.4 (56.3–80.4)	0.86 (0.79–0.92)	82.9 (66.4–93.4)	81.0 (70.9–88.7)	0.89 (0.81–0.94)	87.0 (66.4–97.2)	74.0 (64.0–82.4)	0.84 (0.76–0.90)
Transient elastography plus aspartate-to-platelet ratio index	96.5 (87.9–99.6)	64.5 (51.3–76.3)	0.81 (0.72–0.87)	94.3 (80.8–99.3)	72.6 (61.8–81.8)	0.84 (0.75–0.90)	95.7 (78.1–99.9)	69.8 (59.6–78.7)	0.83 (0.75–0.89)
Real-time strain elastography plus aspartate-to-platelet ratio index	100.0 (93.7–100.0)	37.1 (25.2–50.3)	0.69 (0.67–0.84)	100.0 (90.0–100.0)	45.2 (34.3–56.5)	0.73 (0.64–0.80)	87.0 (66.4–97.2)	59.4 (48.9–69.3)	0.73 (0.64–0.81)
Real-time strain elastography plus transient elastography plus aspartate-to-platelet ratio index[a]	87.7 (76.3–94.9)	83.9 (72.3–92.0)	0.93 (0.86–0.97)	71.4 (53.7–85.4)	97.6 (91.7–99.7)	0.95 (0.89–0.98)	95.7 (78.1–99.9)	81.3 (72.0–88.5)	0.95 (0.90–0.98)

Note—Ranges in parentheses are 95% CIs.
[a]The best sensitivity, specificity, and AUCs were obtained with combination of two of the three methods.

best diagnostic performance when two of the three methods were in agreement. In this case, AUC values were higher than those of transient elastography alone, but this difference did not reach statistical significance. PPV, NPV, positive LR, and negative LR were 83.3%, 88.1%, 5.44, 0.15, respectively, for F ≥ 2; 71.7%, 97.3%, 6.09, 0.07, respectively, for F ≥ 3; and 55.0%, 98.7%, 5.10, and 0.05, respectively, for F = 4.

Discussion

The results of this study show that transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index values were directly and linearly correlated with the stages of fibrosis as determined by histology. Transient elastography and aspartate-to-platelet ratio index also showed a good correlation with the degree of necroinflammatory activity, suggesting that the liver might show changes in elasticity related to inflammation [24–27]. Multiple regression analysis in earlier studies did not find a relationship between elasticity measurements and necroinflammatory score [6–8]. This dissimilarity could be explained by differences in the study design. In both the present study and the study by Fraquelli et al. [27], liver biopsy was performed on the same day as transient elastography measurements; thus, the results were not affected by the interval of time between procedures. Moreover, only patients with chronic hepatitis C were enrolled; thus, bias due to histologic differences of hepatitis B virus infection or other coinfections was avoided.

Measurements of transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index were not influenced by the degree of steatosis, and these findings are in agreement with previous reports [28, 29]. The results of our study show that, using a cutoff value of 6.9 kPa, transient elastography is able to accurately assess significant fibrosis (F ≥ 2). The cutoff value obtained in our study is slightly lower than that observed by Castéra et al. [8], but the specificity is higher (91.4% vs 89%). Unlike that observed in the study of Castéra et al., the distribution of patients in our study was not equal through Metavir scores. Indeed, 54% of subjects were in the F0–F1 stage. We enrolled consecutive patients undergoing liver biopsy for potential antiviral therapy, and we think that the uneven distribution of patients over fibrosis stage reflects what is normally observed in clinical practice.

Transient elastography offered an excellent diagnostic performance in the assessment of severe fibrosis and cirrhosis. A cutoff value of 9.3 kPa excluded cirrhosis with an NPV of 99%. These findings are similar to those reported in previous studies [8, 16]. In assessing liver fibrosis, compared with liver biopsy, performance of either transient elastography, real-time strain elastography, and aspartate-to-platelet ratio index or their combinations, as measured by AUC, was good. Focusing on differentiating nonsignificant from significant fibrosis (F ≥ 2), transient elastography and aspartate-to-platelet ratio index, with an overlapping AUC, seem to perform better than real-time strain elastography. In particular, aspartate-to-platelet ratio index showed the highest performance, with an NPV of 97.2%. The aspartate-to-platelet ratio index cutoff value of 0.37 obtained in our series is lower than that reported by other studies [10, 14], and this difference might explain the better diagnostic performance observed in our study. The lower threshold for significant fibrosis of aspartate-to-platelet ratio index value could be due to the higher prevalence of nonsignificant fibrosis (F0–F1) in our cohort of patients. Aspartate-to-platelet ratio index values less than 0.37 and real-time strain elastography values of liver fibrosis index less than 1.82 would confidently indicate nonsignificant fibrosis with an NPV of 100%, but the specificity is very low (37.1%). We decided to use aspartate-to-platelet ratio index instead of other available biomarkers [11, 13] because it is inexpensive and routinely available; thus, it is an interesting tool for first-line evaluation of liver fibrosis [14].

Even though it is still considered the reference standard, liver biopsy may fail in the assessment of the degree of liver fibrosis because it is subject to intra- and interobserver variability and to sampling errors, even when the biopsy length is adequate [4]. Moreover, the Metavir scoring system takes into account not only fibrosis but also architectural changes in the liver, without reference to quantitative changes in liver collagen [4].

A limitation of our study is that a computer-assisted digital image analysis of liver sample to obtain a quantitative and continuous measure of fibrosis was not performed. This analysis would have given a better comparison with noninvasive markers of fibrosis, as suggested by Calvaruso et al. [30]. Another limitation is that the same physician performed both transient elastography and real-time strain elastography. Nonetheless, the operator was blind to measurement results of real-time strain elastography. The effects of body mass index on transient elastography or real-time strain elastography measurements were not assessed because obesity was not observed in our series of patients.

Even though it correlated with the stages of fibrosis by histology, real-time strain elastography was not able to accurately predict stepwise progression of fibrosis. Our data do not confirm the promising results obtained in other studies conducted using real-time strain elastography [18–20], but are in agreement with the results of the study of Friedrich-Rust et al. [31]. Combined with aspartate-to-platelet ratio index, real-time strain elastography may be eligible to be an adjunct ultrasound tool to exclude the presence of significant liver fibrosis, but it does not yet have the potential to substitute for transient elastography in the assessment of liver fibrosis.

TABLE 3: Pairwise Comparison of Receiver Operating Characteristic Curves: Differences Between Areas Under the Curve (AUC) for Fibrosis Scores (F)

Fibrosis Score, Parameter	Transient Elastography and Real-Time Strain Elastography	Real-Time Strain Elastography and Aspartate-to-Platelet Ratio Index	Transient Elastography and Aspartate-to-Platelet Ratio Ibndex
F ≥ 2			
AUC (95% CI)	0.14 (0.04–0.23)	0.11 (-0.06 to 0.22)	0.02 (-0.05 to 0.08)
p	0.004	0.06	0.69
F ≥ 3			
AUC (95% CI)	0.15 (0.05–0.25)	0.08 (-0.02 to 0.19)	0.06 (0.002–0.12)
p	0.003	0.10	0.04
F = 4			
AUC (95% CI)	0.17 (0.06–0.27)	0.04 (-0.07 to 0.16)	0.12 (0.06–0.19)
p	0.004	0.46	< 0.001

Few meta-analysis of already published series using transient elastography are available so far [32–35]. We think that multicenter studies with the same design of this study to achieve larger cohort of patients are strongly needed to establish optimal cutoff values of noninvasive imaging techniques or biochemical markers of liver fibrosis for each fibrosis stage.

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