Assessment of Biliary Fibrosis by Transient Elastography in Patients With PBC and PSC

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Noninvasive measurement of liver stiffness with transient elastography has been recently validated for the evaluation of hepatic fibrosis in chronic hepatitis C. The current study assessed the diagnostic performance of liver stiffness measurement (LSM) for the determination of fibrosis stage in chronic cholestatic diseases. One hundred one patients with primary biliary cirrhosis (PBC, n = 73) or primary sclerosing cholangitis (PSC, n = 28) were prospectively enrolled in a multicenter study. All patients underwent liver biopsy (LB) and LSM. Histological and fibrosis stages were assessed on LB by two pathologists. LSM was performed by transient elastography. Efficiency of LSM for the determination of histological and fibrosis stages were determined by a receiver operating characteristics (ROC) curve analysis. Analysis failed in six patients (5.9%) because of unsuitable LB (n = 4) or LSM (n = 2). Stiffness values ranged from 2.8 to 69.1 kPa (median, 7.8 kPa). LSM was correlated to both fibrosis (Spearman's $\rho = 0.84$, $P < .0001$) and histological (0.79, $P < .0001$) stages. These correlations were still found when PBC and PSC patients were analyzed separately. Areas under ROC curves were 0.92 for fibrosis stage (F) ≥2, 0.95 for F ≥ 3 and 0.96 for F = 4. Optimal stiffness cutoff values of 7.3, 9.8, and 17.3 kPa showed F ≥ 2, F ≥ 3 and F = 4, respectively. LSM and serum hyaluronic acid level were independent parameters associated with extensive fibrosis on LB. In conclusion, transient elastography is a simple and reliable noninvasive means for assessing biliary fibrosis. It should be a promising tool to assess antifibrotic therapies in PBC or PSC. (HEPATOLOGY 2006;43:1118-1124.)

Transient elastography is a new tool for assessing the extent of liver fibrosis. The method has been recently validated in chronic hepatitis C.[1,2] However, its accuracy to detect extensive fibrosis or cirrhosis in other chronic liver diseases remains to be demonstrated. The aim of the current study was to assess the diagnostic performance of transient elastography for the evaluation of fibrosis and histological stages in chronic cholestatic diseases.

Patients and Methods

Patients. One hundred one consecutive patients with primary biliary cirrhosis (PBC, n = 73) or primary sclerosing cholangitis (PSC, n = 28) who underwent a liver biopsy (LB) at the hepato-gastroenterology departments of Saint-Antoine Hospital (Paris, France; n = 71), Jean Verdier Hospital (Bondy, France; n = 13), Haut-Lévêque Hospital (Pessac, France; n = 13), Henri Mondor Hospital (Créteil, France; n = 3) or Beaujon Hospital (Clichy, France; n = 1) between February 2003 and September 2005 were included in the study. PBC was defined by at least two of the following criteria: serum alkaline phosphatase more than 1.5 times the upper limit of normal, a positive antimitochondrial antibody (>1:40), and compatible liver histology. PSC was diagnosed according

Abbreviations: PBC, primary biliary sclerosis; PSC, primary sclerosing cholangitis; LB, liver biopsy; LSM, liver stiffness measurement; ROC, receiver operating characteristics.

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to accepted criteria, including typical findings of bile duct irregularities, strictures, and dilatations at cholangiography or lesions of fibro-obliterative cholangitis at liver histology. Exclusion criteria were ascites, hepatocellular carcinoma, a positive serology for hepatitis B or C viruses, a history of alcoholic abuse, and all other causes of chronic liver injuries except PBC and PSC. Blood liver tests (*i.e.,* serum bilirubin and albumin levels, gamma-glutamyl transpeptidase, alkaline phosphatase, and alanine aminotransferase activities, platelet count, prothrombin index and serum hyaluronic acid level) and transient elastography were performed the same day. Serum hyaluronic acid level was evaluated using a sequential radiometric assay (HA-test, Pharmacia Diagnostics, Uppsala, Sweden). The study protocol conformed to the ethical guidelines of the Helsinski Declaration and was approved by the institutional review board of each hospital that participated in this study. Patients were enrolled after giving their written informed consent.

Liver Stiffness Measurements. Measurement of liver stiffness by transient elastography was performed using a Fibroscan (EchoSens, Paris, France) as described in previous studies.[1,2] Ten validated measurements were made on each patient. The results were expressed in kilopascals (kPa). Only procedures with 10 validated measurements and a success rate of at least 60% (ratio of the number of successful acquisitions over the total number of acquisitions) were considered reliable. The median value was considered representative of the liver elastic modulus.

Liver Histology and Quantification of Liver Fibrosis. Liver biopsy specimens were fixed in formalin and paraffin embedded. Four-micron-thick sections were stained with hematoxylin-eosin-saffron and picrosirius red. All biopsy specimens were analyzed by two experienced pathologists blinded to the results of transient elastography and clinical data. Histological stage was determined according to the Ludwig's classification.[3] Liver fibrosis and necroinflammatory activity were evaluated semiquantitatively according to the METAVIR scoring system.[4] Fibrosis was staged on a 0-4 scale as follows: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis. Activity was graded as follows: A0 = none; A1 = mild; A2 = moderate; A3 = severe. In case of discrepancies, histological sections were simultaneously reviewed using a multi-pipe microscope to reach a consensus. The length of each LB specimen (in millimeters) and the number of fragments were recorded.

Statistical Analysis. Patients were divided according to their consensus fibrosis stage. F0 and F1 categories were grouped because of a too-small number of F0 patients. The groups were compared by the Kruskal-Wallis nonparametric test, and the trend between liver stiffness measurements and ordinate fibrosis stages was estimated by the Spearman's ρ coefficient. The diagnostic performance of transient elastography was determined in terms of sensitivity, specificity, positive and negative predictive values, likelihood ratio, and area under receiver operating characteristics (ROC) curves. Optimal cutoff values between fibrosis categories were determined at the maximum total sensitivity and specificity. Internal validation was performed by the jackknife method. Logistic regression analysis was performed to assess the relationship between fibrosis, biochemical markers, and liver stiffness measurement. All tests were two-sided with a significance level of 5%. Statistical analyses were performed with JMP statistical software v5.1. (SAS Institute Inc., Cary, NC).

Table 1. Characteristics of Patients

	PBC (n = 69)	PSC (n = 26)	Total (n = 95)
Female sex	84%	46%	74%
Age (y)	59 (29-77)	46 (18-73)	57 (18-77)
Serum bilirubin (μmol/L)	12 (4-491)	14 (5-78)	13 (4-491)
AST (×ULN)	1.3 (0.5-6.4)	1.3 (0.4-7.9)	1.3 (0.4-7.9)
ALT (×ULN)	1.6 (0.5-7.8)	1.4 (0.4-24.3)	1.5 (0.4-24.3)
Alkaline phosphatase (×ULN)	1.5 (0.6-8.2)	2.0 (0.6-6.9)	1.5 (0.6-8.2)
GGT (×ULN)	5.3 (0.9-43.9)	7.4 (0.3-41.3)	6.6 (0.3-43.9)
Serum albumin (g/L)	41 (26-48)	42 (30-52)	41 (26-52)
Prothrombin index (%)	99 (49-132)	99 (72-108)	99 (49-132)
Platelet count (10^3/mm^3)	251 (62-435)	263 (48-481)	255 (48-481)
Hyaluronic acid (μg/L)	49 (12-373)	46 (9-228)	49 (9-373)
Histological stage [n (%)]			
I	16 (23%)	11 (42%)	27 (28%)
II	16 (23%)	4 (15%)	20 (21%)
III	24 (35%)	9 (35%)	33 (35%)
IV	13 (19%)	2 (8%)	15 (16%)
Activity grade [n (%)]			
A0	16 (23%)	15 (58%)	31 (33%)
A1	32 (46%)	8 (31%)	40 (42%)
A2	19 (28%)	3 (11%)	22 (23%)
A3	2 (3%)	0 (0%)	2 (2%)
Fibrosis stage [n (%)]			
F0-F1	25 (36%)	13 (50%)	38 (40%)
F2	16 (23%)	6 (23%)	22 (23%)
F3	15 (22%)	5 (19%)	20 (21%)
F4	13 (19%)	2 (8%)	15 (16%)

NOTE. Quantitative variables are expressed as median (range).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; GGT, gamma-glutamyltransferase.

Results

Among the 101 patients enrolled, four patients with PBC and two with PSC were *a posteriori* excluded because of unsuitable LB (n = 4) or defective liver stiffness measurement (n = 2). Data analysis was performed on the basis of the 95 remaining patients (69 PBC, 26 PSC). Their characteristics are shown in Table 1. The median length of LB was 17 mm (range, 8-40 mm) and the me-

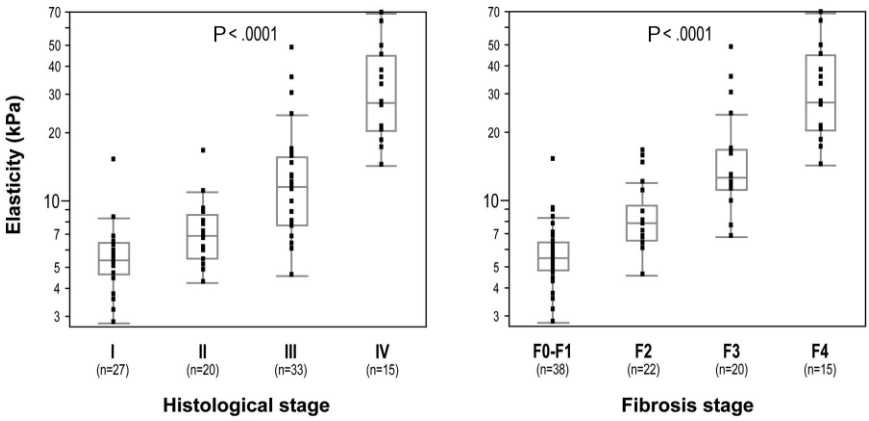

Fig. 1. Box plots of liver stiffness values for each histological (left) and fibrosis (right) stage (PBC and PSC data are combined). The vertical axis is in logarithmic scale. The *top* and *bottom* of the boxes are the first and third quartiles, respectively. The length of the box thus represents the interquartile range within which 50% of the values were located. The *line* through the middle of each box represents the median. Upper and lower *error bars* are computed as upper quartile + 1.5* (interquartile range) and lower quartile − 1.5* (interquartile range), respectively. The *P* values are those obtained by the Kruskall-Wallis test. PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

dian number of fragments was 2. The mean interval between LB and transient elastography was 2 months (range, 0-12 months). Most of the patients (76%) had the two procedures within the same month. The mean success rate of liver stiffness measurement per patient was 87% (range, 60%-100%).

The distribution of liver stiffness values according to histological and fibrosis stages is shown in Fig. 1. Values ranged from 2.8 to 69.1 kPa (median, 7.8 kPa). The median interquartile (*i.e.,* the range within which 50% of the values from a given patient were located) was 1.9 kPa. Liver stiffness was positively correlated to both histological ($\rho = 0.79$; $P < .0001$) and fibrosis ($\rho = .84$; $P < .0001$) stages. Significant correlations were still observed when PBC and PSC patients were studied separately (PBC histological stage: $\rho = .81$, $P < .0001$; PBC fibrosis stage: $\rho = .86$, $P < .0001$; PSC histological stage: $\rho = .75$, $P < .0001$; PSC fibrosis stage: $\rho = .79$, $P < .0001$) (Fig. 2). Liver stiffness was correlated to activity

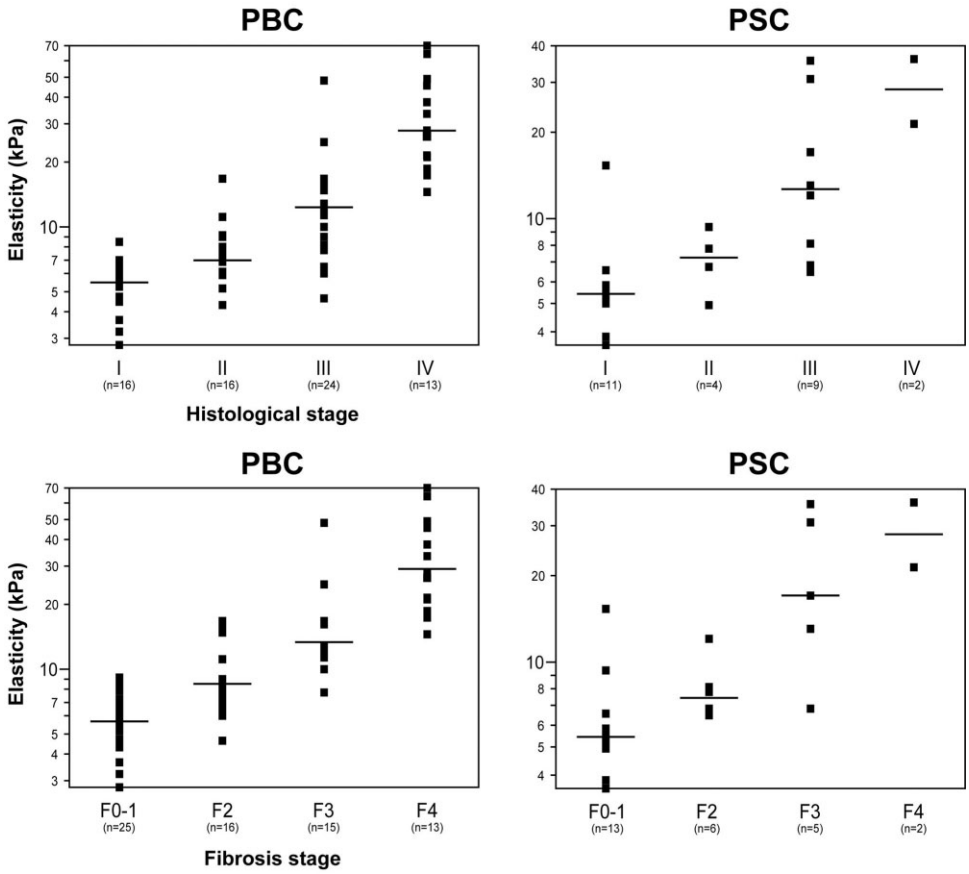

Fig. 2. Distribution of liver stiffness values according to the cholestatic disease (PBC at left, PSC at right) and the histological (top) or fibrosis (bottom) stage. The vertical axis is in logarithmic scale. Horizontal bars are medians. PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

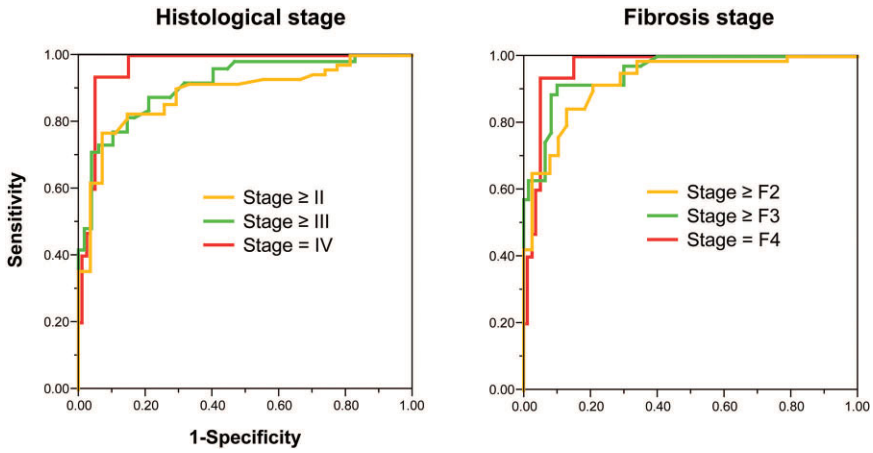

Fig. 3. Receiver operator characteristics (ROC) curves for liver stiffness measurement for different thresholds of histological (left) and fibrosis (right) stage.

grade, but to a lesser extent than to fibrosis stage ($\rho = 0.36$, $P < .001$).

ROC curve analysis was performed on overall PBC and PSC patients (Fig. 3). Areas under curves (95% CI) were 0.88 (0.81-0.95), 0.91 (0.85-0.97), and 0.96 (0.93-1.00) for histological stage ≥ II, ≥ III and = IV, respectively, and 0.92 (0.87-0.98), 0.95 (0.91-0.99), and 0.96 (0.93-1.00) for fibrosis stage ≥ 2, ≥ 3 and = 4, respectively. Optimal cutoff values were 7.1 kPa, 11.1 kPa, and 17.3 kPa for histological stage ≥ II, ≥ III, and = IV, respectively, and 7.3 kPa, 9.8 kPa, and 17.3 kPa for fibrosis stage ≥ 2, ≥ 3, and = 4, respectively. The diagnostic performance of transient elastography for histological and fibrosis staging are summarized in Tables 2 and 3, respectively. Comparisons between observed and predicted fibrosis stages are shown in Table 4. Accurate prediction of fibrosis stage was made in 69 of the 95 patients (72.6%).

Univariate analysis of parameters associated with extensive fibrosis on LB (*i.e.,* fibrosis stages 3 or 4) was performed on overall PBC and PSC patients (Table 5). The variables significantly associated with the extent of fibrosis were (by decreasing level of significance) liver stiff-

Table 2. Performance of Transient Elastography for the Determination of Histological Stage

	Performance	Cross-validation
Histological stage ≥ II		
AUROC	0.88	
Optimal cutoff (kPa)	7.10	7.09
Sensitivity	0.76	0.75
Specificity	0.93	0.85
Positive predictive value	0.96	0.93
Negative predictive value	0.61	0.58
Likelihood ratio	10.86	5.06
Histological stage ≥ III		
AUROC	0.91	
Optimal cutoff (kPa)	11.10	10.90
Sensitivity	0.71	0.69
Specificity	0.96	0.81
Positive predictive value	0.94	0.79
Negative predictive value	0.76	0.72
Likelihood ratio	16.63	3.59
Histological stage = IV		
AUROC	0.96	
Optimal cutoff (kPa)	17.30	17.31
Sensitivity	0.93	0.87
Specificity	0.95	0.95
Positive predictive value	0.78	0.76
Negative predictive value	0.99	0.97
Likelihood ratio	18.67	17.40

Table 3. Performance of Transient Elastography for the Determination of Fibrosis Stage

	Performance	Cross-validation
Fibrosis stage ≥ 2		
AUROC	0.92	
Optimal cutoff (kPa)	7.30	7.29
Sensitivity	0.84	0.82
Specificity	0.87	0.79
Positive predictive value	0.91	0.85
Negative predictive value	0.79	0.75
Likelihood ratio	6.40	3.90
Fibrosis stage ≥ 3		
AUROC	0.95	
Optimal cutoff (kPa)	9.80	9.81
Sensitivity	0.91	0.89
Specificity	0.90	0.90
Positive predictive value	0.84	0.84
Negative predictive value	0.95	0.93
Likelihood ratio	9.14	8.90
Fibrosis stage = 4		
AUROC	0.96	
Optimal cutoff (kPa)	17.30	17.31
Sensitivity	0.93	0.87
Specificity	0.95	0.95
Positive predictive value	0.78	0.76
Negative predictive value	0.99	0.97
Likelihood ratio	18.67	17.40

Table 4. Observed and Predicted Fibrosis Stages

	Predicted Stage According to Liver Stiffness			
Observed stage on LB	F0-1	F2	F3	F4
F0-1 (38)	33	4	1	0
F2 (22)	8	9	5	0
F3 (20)	1	2	13	4
F4 (15)	0	0	1	14
	(42)	(15)	(20)	(18)

Table 6. Multivariate Analysis of Parameters Associated With Extensive Fibrosis on Liver Biopsy

	Estimate ± SE	Odds Ratio (95% CI)	*P*
Liver stiffness ≥ 9.8 kPa	2.1 ± 0.6	72.7 (11.0-1488.2)	.0002
Serum hyaluronic acid ≥ 50 μg/L	1.6 ± 0.6	24.0 (3.5-493.2)	.0058

Abbreviation: SE, standard error.

ness, serum hyaluronic acid level, serum bilirubin and albumin levels, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase activities, and platelet count. Among them, liver stiffness and serum hyaluronic acid level were independent variables associated with extensive fibrosis according to a multivariate logistic regression analysis (Table 6).

Discussion

We prospectively assessed the diagnostic performance of transient elastography for the evaluation of histological and fibrosis stages in a cohort of 101 patients with chronic cholestatic diseases, including 73 patients with PBC and 28 patients with PSC. Liver stiffness measurement failed in only two patients (2%). We found a significant positive relationship between liver stiffness values and histological and fibrosis stages on LB. The diagnostic performance of the test was similar to, or even better than, that previously reported in patients with chronic hepatitis C.[1,2] Areas under ROC curves were 0.92 for F ≥ 2, 0.95 for F ≥ 3 and 0.96 for F = 4. Optimal cutoff values allowed us to accurately predict fibrosis stage on LB in 72.6% of the patients. Despite the relatively small number of patients, these results suggest that transient elastography is an efficient and simple method for assessing biliary fibrosis in patients with chronic cholestatic diseases.

Table 5. Univariate Analysis of Parameters Associated With Extensive Fibrosis on Liver Biopsy

	F0-F1-F2 (n = 60)	F3-F4 (n = 35)	*P*
Female sex	77%	69%	.4704
Age (y)	56 (18-76)	59 (19-77)	.3939
Serum bilirubin (μmol/L)	11 (5-26)	21 (4-491)	.0001
AST (×ULN)	1.1 (.4-3.7)	1.7 (.8-7.9)	.0029
ALT (×ULN)	1.4 (.3-5.9)	1.7 (.5-24.3)	.0925
ALP (×ULN)	1.3 (.6-4.6)	2.0 (.9-8.2)	.0117
GGT (×ULN)	3.6 (.3-41.3)	7.1 (.9-43.9)	.0178
Serum albumin (g/L)	42 (34-52)	39 (26-49)	.0006
Prothrombin index (%)	100 (62-132)	96 (49-120)	.0807
Platelet count (μ^{-3})	263 (128-435)	229 (48-481)	.0300
Cholesterol (mmol/L)	5.5 (3.7-10.2)	6.1 (2.2-14.3)	.1256
Hyaluronic acid (μg/L)	34 (9-93)	102 (23-373)	<.0001
Liver stiffness (kPa)	6.4 (2.8-16.5)	17.3 (6.8-69.1)	<.0001

NOTE. Quantitative variables are expressed as median (range). *P* value for the Fisher's exact test or the Mann-Whitney test.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

The prognosis of chronic cholestatic diseases depends at least in part on the extent of fibrosis in the liver parenchyma.[5,6] Until now, liver needle biopsy remained the most usual method for assessing liver damage in these diseases. However, LB is an invasive procedure that precludes repeated and multiple assessments in the same patient. Furthermore, the accuracy of LB for the evaluation of fibrosis in PBC and PSC patients remains debatable. Indeed, there is large variation in the degree of fibrosis within a single liver. Fibrosis areas in parenchyma are often patchy in distribution and may not be sampled in small needle biopsy specimens. This has been well shown by the examination of hepatectomy specimens obtained at transplantation. Only 20% of PBC hepatectomy specimens obtained at liver transplantation had a consistent degree of fibrosis throughout the liver.[7] When these specimens were examined with a simulated liver needle biopsy method, a discrepancy of one or two fibrosis stages was seen in 64% of the samples. Similar data have been reported in patients with PSC.[8] This suggests that histological staging may not be appropriate in clinical practice for the assessment of disease progression in individual patients, although it may still be relevant in clinical trials in which the large number of specimens overcomes some of the problems associated with sampling variation.

Several serum markers of connective tissue have been proposed as an alternative to liver biopsy for the evaluation of fibrosis in PBC. Hyaluronic acid and type III procollagen peptide were the most studied.[9-11] These are components or split products of the extracellular matrix that are released into the systemic circulation. The sensitivity and specificity of these markers for detection of extensive fibrosis do not exceed 60% and 80%, respectively.[11,12] Serum bilirubin level is also a surrogate marker of liver fibrosis in PBC.[12,13] However, bilirubinemia can be increased even in early-stage disease, in particular in florid and rapidly ductopenic forms of PBC, or in case of "flare" of associated-autoimmune hepatitis (overlap syndrome), or during episodes of angiocholitis in PSC. We recently assessed the diagnostic performance of a fibrosis score calculated from the serum bilirubin and hyaluronic

acid levels of 153 UDCA-treated patients with PBC.[12] This score had acceptable positive predictive value (76%) but poor sensitivity (65%) for the diagnosis of extensive fibrosis. Finally, most serum fibrosis scores developed in chronic hepatitis C are not appropriate to assess PBC or PSC patients because parameters such as gamma-glutamyltransferase (FibroTest,[14] Forns[15]), cholesterol (Forns), or apolipoprotein A1 (FibroTest) are markedly influenced by cholestasis.

Transient elastography constitutes a new approach in noninvasive measurement of liver fibrosis. It is a simple and rapid method that measures a quantitative physical parameter directly on the liver with no possible interference with extrahepatic disorders. It measures liver stiffness of a volume of parenchyma that is approximately 100 times bigger than a needle biopsy specimen. Obesity, ascites, and tight intercostal spaces are the only physical limitations of the technique. Transient elastography has been prospectively evaluated in two large series of patients with chronic hepatitis C.[1,2] Both studies have reported good diagnostic performance for detection of extensive fibrosis or cirrhosis with areas under ROC curves above 90% and specificity above 85%, suggesting that transient elastography can be used in clinical practice as a reliable tool to assess severity and probably progression of fibrosis in chronic hepatitis C. In a large series of patients with various causes of chronic liver diseases, transient elastography was shown to detect cirrhosis with both negative and positive predictive values of 90%.[16] A preliminary report about 170 patients with chronic hepatitis B showed that the accuracy of transient elastography for assessing fibrosis was similar to that observed in chronic hepatitis C.[17] Finally, in a recent series of 245 alcohol consulting outpatients, the method was found to have a positive predictive value of 97% for the diagnosis of cirrhosis.[18] To our knowledge, no published data exist on the assessment of transient elastography in patients with nonalcoholic steatohepatitis or hemochromatosis.

The current study provides data about the accuracy and reliability of transient elastography for the assessment of histological stage and fibrosis extent in chronic cholestatic diseases. PBC and PSC patients were included in the same analysis because of the small number of patients. This limitation must be taken into account in the interpretation of the results. Further studies from specific and larger populations are needed, especially to assess whether the optimal cutoff values differ between the two cholestatic diseases. The correlations obtained from the whole patients were confirmed when PBC and PSC patients were analyzed separately. Liver stiffness was strongly correlated to both fibrosis and histological stages but the diagnostic performances were better for staging fibrosis, as shown by the comparison of area under the ROC curve. Liver stiffness and serum hyaluronic acid level were independently related to the extent of biliary fibrosis. Among these two variables, liver stiffness was the most strongly linked. These results suggest that transient elastography is more accurate and reliable than any serum fibrosis markers validated until now in PBC. It is also, to our knowledge, the first noninvasive fibrosis test reported in PSC.

In conclusion, the current data obtained in patients with chronic cholestatic diseases are consistent with those reported in chronic hepatitis C, confirming the accuracy and simplicity of transient elastography for the assessment of liver fibrosis in a different disease setting. Transient elastography appears as a simple and reliable noninvasive method for evaluating fibrosis and histological stage in PBC and PSC and should be a promising tool to assess antifibrotic therapies in these diseases. Larger studies are needed to confirm these results.

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