

Noninvasive Assessment of Liver Fibrosis by Measurement of Stiffness in Patients With Chronic Hepatitis C

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Liver fibrosis is the main predictor of the progression of chronic hepatitis C, and its assessment by liver biopsy (LB) can help determine therapy. However, biopsy is an invasive procedure with several limitations. A new, noninvasive medical device based on transient elastography has been designed to measure liver stiffness. The aim of this study was to investigate the use of liver stiffness measurement (LSM) in the evaluation of liver fibrosis in patients with chronic hepatitis C. We prospectively enrolled 327 patients with chronic hepatitis C in a multicenter study. Patients underwent LB and LSM. METAVIR liver fibrosis stages were assessed on biopsy specimens by 2 pathologists. LSM was performed by transient elastography. Efficiency of LSM and optimal cutoff values for fibrosis stage assessment were determined by a receiver-operating characteristics (ROC) curve analysis and cross-validated by the jack-knife method. LSM was well correlated with fibrosis stage (Kendall correlation coefficient: 0.55; $P < .0001$). The areas under ROC curves were 0.79 (95% CI, 0.73-0.84) for $F \geq 2$, 0.91 (0.87-0.96) for $F \geq 3$, and 0.97 (0.93-1) for $F = 4$; for larger biopsies, these values were, respectively, 0.81, 0.95, and 0.99. Optimal stiffness cutoff values of 8.7 and 14.5 kPa showed $F \geq 2$ and $F = 4$, respectively. **In conclusion**, noninvasive assessment of liver stiffness with transient elastography appears as a reliable tool to detect significant fibrosis or cirrhosis in patients with chronic hepatitis C. (HEPATOLOGY 2005;41:48–54.)

Quantification of liver fibrosis by noninvasive means is a major challenge that has stimulated the search for new approaches. The prognosis and clinical management of chronic liver dis-

eases are highly dependent on the extent of liver fibrosis, as complications mainly occur in patients in the advanced stages.¹ This is particularly true in patients with chronic hepatitis C (CHC), which is the leading cause of cirrhosis in western countries. Liver biopsy (LB), the reference method for assessing liver fibrosis, is an invasive and expensive procedure that is not well accepted by patients,² especially when repeated examinations are needed. Moreover, its accuracy in assessing fibrosis is questionable, as reproducibility is poor due to sampling errors, and even in adequately sized specimens, intraobserver and interobserver discrepancies are seen.^{3–7} Transient elastography is a new technique that rapidly and noninvasively measures mean tissue stiffness.⁸ The purpose of this prospective, multicenter study was to compare liver stiffness measurement (LSM) obtained with a new medical device (Fibroscan), based on ultrasound transient elastography, with the available gold standard, which is fibrosis stage assessed on a biopsy sample. To minimize the drawbacks of this reference method, histological sections were read blindly using the validated METAVIR scoring system,⁹ and the comparison between both methods was performed in the whole population of patients

Abbreviations: CHC, chronic hepatitis C; LB, liver biopsy; LSM, liver stiffness measurement; ROC, receiver-operating characteristics.

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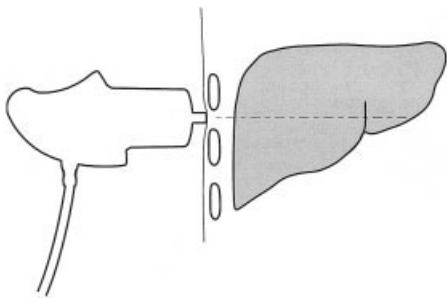


Fig. 1. Fibroscan probe and its positioning on patient during examination.

with interpretable hepatic biopsy and stiffness measurement as well as in patients with the largest biopsy samples.

Patients and Methods

Patients. Three hundred twenty-seven consecutive patients with CHC who underwent LB at the hepatogastroenterology departments of Jean Verdier Hospital (Bondy, France; $n = 214$), Haut-Lévêque Hospital (Pessac, France; $n = 54$), Beaujon Hospital (Clichy, France; $n = 38$), or Henri Mondor Hospital (Créteil, France; $n = 21$) between November 2002 and September 2003 were included in the study. Inclusion criteria were the presence of HCV RNA in serum and at least transiently elevated serum alanine aminotransferase level. Patients with ascites were excluded from the study. LSM was performed within 6 months after LB. The protocol was in accordance with the Helsinki Declaration and was approved by an independent ethics committee. Patients fulfilling these criteria were enrolled after providing their written and informed consent. Blood parameters were evaluated on the same day that LSM was performed.

Transient Elastography Principle. LSM was performed with a Fibroscan (EchoSens, Paris, France), a new medical device based on elastometry (or one-dimensional transient elastography). Details of the technical description and examination procedure have been previously described.^{8,10} Briefly, this system is equipped with a probe including an ultrasonic transducer mounted on the axis of a vibrator (Fig. 1). A vibration of mild amplitude and low frequency is transmitted from the vibrator toward the tissue by the transducer itself. This vibration induces an elastic shear wave that propagates through the tissue. In the meantime, pulse-echo ultrasound acquisitions are performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness (or elastic modulus). Results are expressed in kilopascal. The harder the tissue, the faster the shear wave propagates.

Liver Stiffness Measurements. Measurements were performed in the right lobe of the liver through the intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction (Fig. 1). The tip of the probe transducer was covered with coupling gel and placed on the skin, between the ribs at the level of the right lobe of the liver. The operator, assisted by ultrasound time-motion and A-mode images provided by the system, located a portion of the liver that was at least 6 cm thick and free of large vascular structures. Once the area of measurement had been located, the operator pressed the probe button to begin an acquisition. The measurement depth was between 25 and 45 mm. Ten successful acquisitions were performed on each patient. The success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions. The median value was kept as representative of the liver elastic modulus. The entire examination lasted less than 5 minutes. Only results of LSM obtained with 10 successful acquisitions and a success rate of at least 60% were considered reliable.

Liver Histology and Quantification of Liver Fibrosis. Liver biopsy specimens were fixed in formalin and paraffin embedded. Four-micrometer-thick sections were stained with hematoxylin-eosin-safran and picrosirius red. All biopsy specimens were analyzed by 2 experienced hepatopathologists (M.Z. and A.H.L.) blinded to the results of LSM and clinical data. Liver biopsy specimens that contained fewer than 10 portal tracts (except for cirrhosis) or that obviously showed liver lesions unrelated to CHC infection such as alcohol-induced hepatitis or cholestasis were excluded from the histological analysis. Liver fibrosis and necro-inflammatory activity were evaluated semi-quantitatively according to the METAVIR scoring system.⁹ Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. The fibrosis stage was assessed independently on each histological section by both pathologists. Thereafter, in case of discrepancies, histological sections were simultaneously reviewed using a multi-pipe microscope to reach a consensus. Activity and steatosis were evaluated only by one pathologist. Activity was graded as: A0, none; A1, mild; A2, moderate; and A3, severe. Steatosis was categorized by visual assessment as: 0, none; 1, steatosis in 1% to 10% of hepatocytes; 2, in 10% to 30%; and 3, 30% to 100% of hepatocytes. The length of each LB specimen was also established in millimeters.

Statistical Analysis. Interobserver agreement for the ordinate fibrosis stages was determined by the quadratic-weighted kappa coefficient of Cohen. The rating bias between both pathologists was evaluated by the generalized McNemar chi-square. Because only one patient had a fibrosis stage of F0, we grouped F0 and F1 categories in the con-

sensus fibrosis stage for the procedures that followed. The proportion of patients excluded because of failure of stiffness measurement in each center was compared using the chi-square test. Even though this study was conducted in four centers, 65% of the included patients came from a single center. However, there were no significant differences among centers for the relationship between stiffness measurements and fibrosis stages ($P = .13$) or for the mean level of stiffness adjusted for the fibrosis stage ($P = .27$), allowing results from the four centers to be pooled together. Stiffness measurements were not normally distributed. Therefore, we compared the results of this test with the categories of the consensus fibrosis stage using the Kruskal-Wallis nonparametric analysis of variance. Unless otherwise mentioned, results were given as the median and 25th to 75th percentile values. The correlation coefficient of Kendall estimated the trend between the test results and the ordinate fibrosis stages. The receiver-operating characteristics (ROC) curves were computed, and areas under the curves as well as 95% CI were calculated with the Mann-Whitney statistic as described by Hanley and McNeil.^{12,13} Efficiency of LSM for the prediction of fibrosis stages was evaluated in the whole studied population. Sensitivity, specificity, likelihood ratios, positive and negative predictive values were computed for the stiffness value at the maximum total sensitivity and specificity. Internal validation was performed by the jack-knife method¹⁴: the fibrosis stage in one patient was predicted by the liver stiffness cutoffs obtained from the whole included population minus this subject. The procedure was repeated for all the patients to establish a cross-validated performance of the test. To investigate the effect of biopsy length on the diagnostic performances of LSM, the median biopsy length for each fibrosis stage was used to split the studied population into small and large biopsy populations. The areas under the ROC curves were then computed for both populations. All tests were two-sided with a significance level of 5%. Statistical analyses were performed with StatsDirect statistical software v2.31 (StatsDirect Ltd. 2003, Cheshire, England) and NCSS 2004 (Statistical Systems, Kayville, UT).

Results

Patients. *A posteriori* exclusion criteria were the following: LB unsuitable for fibrosis staging (49 patients with less than 10 portal tracts and no obvious cirrhosis, 4 patients with lesions unrelated to CHC) or unreliable LSM with less than 10 successful acquisitions or a success rate of less than 60% (23 patients). The proportion of excluded patients was not significantly different between centers ($P = .41$). Thus, the statistical analysis was performed on 251 patients (Fig. 2). Among the 251 patients included in the statistical analysis, 13 had a human immunodeficiency virus co-infection, 5 had

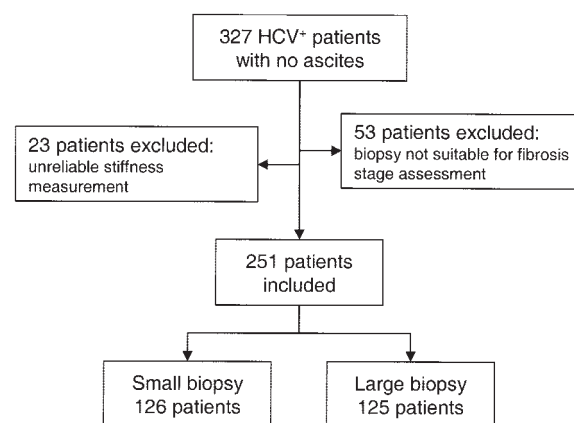


Fig. 2. Trial profile.

a hepatitis B virus co-infection, 18 had a current daily alcohol intake of at least 60 g/d, and 2 had undergone a liver transplantation. LB was performed by the transperitoneal route on 188 patients and by the transjugular route on 63 patients. Table 1 summarizes the general characteristics of included patients. Most (225) of the 251 patients included in the statistical analysis had LB and LSM within the same week and less than 6 months in all cases (mean delay, 8 ± 26 days).

Histology. In the studied population, the median biopsy length was 18 (range, 13-25) mm. Patient distribution for METAVIR fibrosis stage, activity grade, and steatosis are presented in Table 2. Pathologists were initially in agreement for 196 of the 251 liver biopsy specimens analyzed (quadratic-weighted kappa coefficient of Cohen, 0.90; 95% CI, 0.77-1.02) with no significant rating bias ($P = .38$).

Relationship Between Liver Stiffness and Histological Parameters. Figure 3 shows the median value (95% CI) of liver stiffness compared with consensus METAVIR fibrosis stage: F0-1: 5.5 (4.1-7.1) kPa; F2: 6.6 (4.8-9.6) kPa; F3: 10.3 (7.6-12.9) kPa; and F4: 30.8 (16.3-48) kPa. Liver stiffness was significantly different between patients according to their fibrosis stages ($P < .0001$) and positively correlated to the fibrosis stages (tau beta of Kendall, 0.55; $P < .0001$). In univariate analysis, liver stiffness was correlated to activity (tau beta, 0.21; $P = 0.0003$) and steatosis (tau beta, 0.19; $P = 0.0008$), but fibrosis stage was also correlated to activity (tau beta, 0.36; $P < .0001$) and steatosis (tau beta: 0.19; $P = .008$). Finally, in multivariate analysis including fibrosis, activity, and steatosis, fibrosis was the only parameter significantly correlated to liver stiffness.

Receiver Operator Characteristics (ROC) Curves. Figure 4 shows the ROC curves determined for the whole population according to three different fibrosis stage thresholds: F0 and F1 patients versus F2, F3, and F4 patients ($F \geq 2$); F0, F1, and F2 patients versus F3 and F4

Table 1. Characteristics of Included Patients

Characteristics	Included (n = 251)
Sex (male)	155 (61.8)
Age (years)	47.5 ± 13.0
BMI (kg/m ²)	23.9 ± 3.4
Alcohol (g/d)	13.8 ± 37.9
ALT (× upper limit normal)	2.0 ± 2.0
Serum albumin (g/L)	43.8 ± 5.1
Platelet count (10 ³ /mm ³)	207.6 ± 69.8
Prothrombin time (%)	92.0 ± 11.6
Total bilirubin (μM/L)	13.2 ± 15.2
Gamma-glutamyl transferase (IU/L)	104.3 ± 131.3
Gamma-globulins (g/L)	14.7 ± 6.5

NOTE. Results are given as mean ± standard deviation or n (%).
Abbreviations: BMI, body mass index; ALT, alanine aminotransferase.

patients (F ≥ 3); and F0, F1, F2, and F3 patients versus F4 patients (F = 4). The areas under the ROC curves (95% CI) were 0.79 (0.73-0.84) for F ≥ 2, 0.91 (0.87-0.96) for F ≥ 3 and 0.97 (0.93-1.00) for F = 4.

Determination of Liver Stiffness Cutoff Values.

Table 3 shows the optimal liver stiffness cutoff values obtained for the entire included population with cross-validation analysis as well as corresponding sensitivity, specificity, and likelihood ratios. Apparent cutoff values for F ≥ 2 (8.8 kPa) and F ≥ 3 (9.6 kPa) were close but with a greater total sensitivity and specificity for F ≥ 3 (1.71) than for F ≥ 2 (1.47). A clear cutoff value (14.6 kPa) was obtained for F = 4 with a total sensitivity and specificity of 1.82. The cross-validation performances were close to the apparent performances except for likelihood ratios.

Considering the detection of patients with a fibrosis stage F ≥ 2 generally eligible for antiviral treatment, the number of patient for whom LSM would have preclude the need for LB was evaluated using two liver stiffness cutoff values. The optimized cutoff value of 8.74 kPa given by the cross-validation analysis can be used to detect patients who need to be treated without requiring the need for LB. Indeed, among the 251 included patients, 101 had a liver stiffness superior or equal to 8.74 kPa. Of these 101 patients, only 9 were F1 and none were F0. The choice of a cutoff value to detect patients who do not need to be treated without using LB was im-

Table 2. Patient Distribution for METAVIR Fibrosis Stage, Activity Grade, and Steatosis

Stage	Fibrosis		Activity		Steatosis	
	n (%)	Grade	n (%)	Grade	Category	n (%)
0	1 (0.4)	0	1 (0.4)	0	116 (46.2)	
1	87 (34.7)	1	167 (66.5)	1	77 (30.7)	
2	87 (34.7)	2	76 (30.3)	2	34 (13.5)	
3	27 (10.8)	3	7 (2.8)	3	24 (9.6)	
4	49 (19.5)					

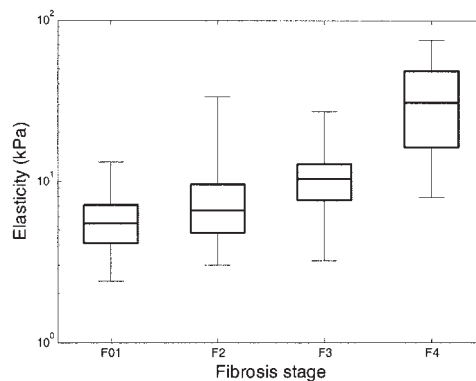


Fig. 3. Liver stiffness values for each fibrosis stage. The vertical axis is in logarithmic scale. The top and bottom of the boxes are the 1st and 3rd quartiles. The length of the box thus represents the interquartile range (IQR) within which are located 50% of the values. The lines through the middle of the boxes represent the median. The error bars are the minimum and maximum values (measurement range).

paired by the lack of F0 patients within the studied population. The optimized cutoff would be 3 kPa. Within the studied population, 5 patients had a liver stiffness lower than 3 kPa, and all were F1. Thus, LB could have been avoided on 106 patients with liver stiffness either lower than 3 kPa or superior or equal to 8.74 kPa, who represent 42% (106 of 251) of the included population. Finally, when patients for whom LSM failed were included, the percentage of patients in whom LB can be avoided would be 39% (106 of [251 + 23]).

Effect of the Biopsy Specimen Length. The median lengths of biopsy specimens were 18.5 (13-27) mm, 18 (14-23) mm, 19 (10-27) mm, and 13 (9-22) mm for F0-1, F2, F3, and F4, respectively. Sixty-seven biopsy specimens were longer than 25 mm. The areas (95% CI) under the ROC curves for the smaller specimens (shorter than the median value in each category) were 0.76 (0.67-

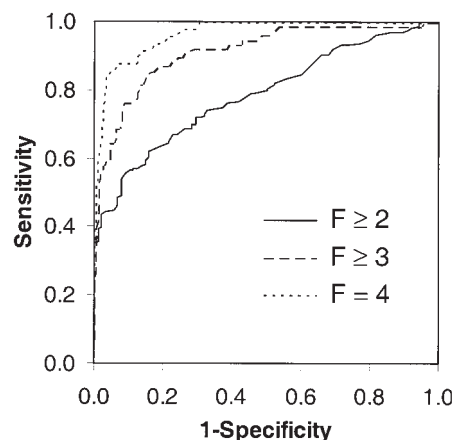


Fig. 4. Receiver Operator Characteristics (ROC) curves on the entire population (251 patients).

Table 3. Liver Stiffness Values for the Determination of METAVIR F \geq 2, F \geq 3, and F = 4

	Apparent Performance	Cross-validation Performance
F \geq 2 (F0-1 vs. F2-3-4)		
Optimal cutoff* (kPa)	8.80	8.74 (8.66-8.81)
Sensitivity	0.56 (0.49-0.64)	0.55 (0.48-0.63)
Specificity	0.91 (0.84-0.97)	0.84 (0.76-0.91)
Likelihood ratio	6.63 (3.10-15.83)	3.47 (2.30-5.23)
Positive predictive value	0.88 (0.81-0.93)	0.87 (0.79-0.93)
Negative predictive value	0.56 (0.47-0.64)	0.51 (0.42-0.59)
F \geq 3 (F0-1-2 vs. F3-4)		
Optimal cutoff* (kPa)	9.60	9.56 (9.49-9.64)
Sensitivity	0.86 (0.78-0.93)	0.84 (0.75-0.92)
Specificity	0.85 (0.79-0.91)	0.85 (0.79-0.91)
Likelihood ratio	5.76 (3.94-8.42)	5.67 (3.87-8.29)
Positive predictive value	0.71 (0.61-0.80)	0.71 (0.61-0.80)
Negative predictive value	0.93 (0.88-0.97)	0.93 (0.87-0.96)
F = 4 (F0-1-2-3 vs. F4)		
Optimal cutoff* (kPa)	14.60	14.52 (14.41-14.64)
Sensitivity	0.86 (0.76-0.94)	0.84 (0.73-0.94)
Specificity	0.96 (0.93-0.99)	0.94 (0.90-0.97)
Likelihood ratio	23.05 (10.77-56.20)	13.00 (7.54-22.43)
Positive predictive value	0.78 (0.65-0.98)	0.76 (0.62-0.85)
Negative predictive value	0.97 (0.93-0.99)	0.96 (0.92-0.98)

NOTE. Results are given with 95% confidence intervals in parentheses.

*The optimal cutoff value is the one that gives the higher total sensitivity and specificity.

0.84) for F \geq 2, 0.87 (0.79-0.95) for F \geq 3, and 0.93 (0.86-1.00) for F = 4. For the larger specimens (longer than the median value in each category), the areas under the ROC curves were 0.81 (0.74-0.89) for F \geq 2, 0.95 (0.90-1.00) for F \geq 3, and 0.99 (0.97-1.00) for F = 4.

Discussion

We found a significant positive correlation between LSM and fibrosis stages in patients with CHC. This observation is consistent because stiffness of tissues largely depends on their molecular building blocks (collagen) and on the microscopic structural organization of these blocks (septa).¹⁵ Significant areas under the ROC curves for F = 4 and F \geq 3 (0.97 and 0.91 for the whole studied population and 0.95 and 0.99 for the larger biopsy specimens, respectively), distinct cutoff values (14.5 kPa and 9.6 kPa) with high total sensitivity and specificity, and high likelihood ratios (confirmed by the cross-validation) suggest that liver elastometry is a reliable method for the diagnosis of cirrhosis (F = 4) and extensive fibrosis (F \geq 3). Rapid and noninvasive detection of fibrosis in these patients is of major clinical interest because they have a high risk of developing complications such as portal hypertension or hepatocellular carcinoma and require specific follow-up. As well, identification of patients with significant fibrosis (F \geq 2) is also of importance because they are eligible for antiviral therapy. Box plots (Fig. 3) clearly indicate that even if F4 patients are well separated from other stages, over-

laps are observed between F0-1 and F2 and F3 groups. The increase in liver stiffness is more important between stages F2 (6.6 kPa) and F3 (10.3 kPa) than between stages F1 (5.5 kPa) and F2 (6.6 kPa), which is consistent with the fact that the increase in fibrous tissue is more important between stages F2 and F3 than between stages F1 and F2.³ However, LSM correctly detected F \geq 2 (area under ROC curve 0.79 for the whole studied population and 0.81 for the larger biopsy specimens) with a cutoff value of 8.7 kPa. These results are in good agreement with those of a pilot study in 67 patients¹⁰; however, in community practice, where the proportion of patients with F4 may be lower than in referral centers, LSM accuracy in predicting patients with F2 or more METAVIR fibrosis stage might be lower.

The current study also confirms that in CHC, the correlation between liver stiffness and fibrosis stage is not affected by steatosis or activity grade. Indeed, activity was not expected to modify liver stiffness, whereas steatosis could have been expected to soften the liver because it consists of fat deposits in the liver parenchyma. Within the studied population, the bivariate correlations showed that no patient had massive steatosis without an important stage of fibrosis, and the multivariate analysis showed that the potential effect of steatosis on liver stiffness was hidden by the strong effect of fibrosis. Further studies are required to investigate the effect of pure steatosis (without fibrosis) on liver stiffness. These findings support a study on elastic modulus measurements of *ex vivo* human liver samples that reported a correlation between liver stiffness and fibrosis but did not show any obvious correlation between steatosis and elastic modulus.¹⁶

LB was considered the gold standard in this study because it is the only reference method for the moment. However, this technique is known to have serious limitations. First, the biopsy procedure results in pain in 24.6% of patients¹⁷ and has a risk of severe complications of 3.1 per 1,000.¹⁸ It is therefore not well accepted by patients. A French survey recently showed that approximately half of hepatitis C virus-infected patients refuse to be referred to hepatologists for fear of LB.² The major advantage of liver elastometry compared with LB is that it is painless, rapid, has no risk of complications, and is therefore very well accepted. Second, it has been shown that there is a high interobserver variation among pathologists for the staging of liver biopsy specimens.^{5,6} To minimize this bias, we selected pathologists with extensive experience in METAVIR staging, histological sections with at least 10 portal tracts or obvious cirrhosis, and we used blinded readings. Therefore, our study showed a fair agreement between pathologists. Third, histological staging is based on a biopsy specimen that represents at most 1/50,000 of the total liver mass.¹⁹ This, in addition to the fact that distribution of fibrosis in the liver parenchyma is heteroge-

neous, results in a nonnegligible sampling error. A recent study by Bedossa et al.³ indicated that only 75% of LB with specimens at least 25 mm long (67 biopsy specimens in our study) were correctly classified for METAVIR fibrosis stage. Using the Batts and Ludwig classification,²⁰ Regev et al.⁵ showed that 33% (124) of studied patients had at least 1 fibrosis stage of difference between the right and left lobe of the liver. Nearly 10% were classified F0-2 in one lobe and F3 or F4 in the other. Similarly, Siddique et al.²¹ found that 45% (29) of studied patients had a difference of at least 1 fibrosis stage between 2 specimens (at least 15 mm long) taken at the same puncture site. Conversely, the Fibroscan measures liver stiffness of a volume that is approximately a cylinder of 1-cm diameter and 2 cm long, which is 100 times bigger than the biopsy specimen and is thus much more representative of the entire hepatic parenchyma. To further investigate the effect of biopsy length on the diagnostic performance of the LSM, areas under the ROC curves were calculated in patients with small biopsy specimens and in patients with large biopsy specimens. Results show that the diagnostic performances of LSM were better in the larger specimens than in the smaller. This suggests that the real diagnostic performance of liver elastometry may be underestimated because of the sampling error of the biopsy. Moreover, in this study, the area of measurement was chosen between 25 and 45 mm, but this could presumably be increased to 65 mm, thus doubling the volume of liver that is explored.

Alternatives to LB have been investigated, such as fibrosis markers (procollagen III peptide, laminin, hyaluronic acid),²²⁻²⁶ which are products of degradation or synthesis of extra cellular matrix. Fibrosis is not specific to the liver, however. An impaired metabolism (renal failure, cholestasis) could influence blood levels of these markers. Moreover, they reflect dynamic processes such as fibrogenesis or fibrolysis rather than existent fibrosis. More recently, different authors have developed scoring systems using biochemical parameters that have no direct relationship to fibrosis and are constructed to predict fibrosis stages provided by the biopsy based on a purely statistical approach. The main drawback to these tests is that certain parameters can be influenced by extrahepatic diseases and others, such as serum bilirubin or gamma glutamyl transpeptidase, are genetically heterogeneous. Wai et al.²⁷ compared the ratio of the aspartate aminotransferase to platelet ratio and found areas under the ROC curves of 0.88 and 0.94 for the prediction of significant fibrosis (Ishak fibrosis score of 3 and more) and cirrhosis (Ishak fibrosis score of 5 and 6), respectively. Forns et al.²⁸ proposed a combination of age and 3 biochemical parameters with an area under the ROC curve of 0.81 for patients with significant fibrosis (Scheuer's classification stage 2 or

more). For the more widely validated predictive index Fibrotest,²⁹⁻³¹ the area under the ROC curve for the detection patients with significant fibrosis (METAVIR F2 or more) varied from 0.73 to 0.84. Thus, the diagnostic performance of liver elastometry appears to be equivalent to that of the best biochemical scores for patients with significant fibrosis ($F \geq 2$) and appears to be better than this test for the diagnosis of extensive fibrosis ($F \geq 3$) and cirrhosis ($F = 4$). However, a direct comparison of LSM with predictive blood tests and indexes on the same population sample needs to be performed to reliably compare the performances of these new noninvasive methods. The main advantage of liver elastometry compared with fibrosis markers and biochemical scores is that it measures a quantitative physical parameter directly on the liver and there is no interference from extrahepatic disorders. It represents a totally different approach and therefore could be complementary of the fibrosis markers and biochemical scores to better assess liver fibrosis without using LB.

The limitations to liver elastometry also should be mentioned. Elastometry cannot be applied in patients with ascites, even if clinically undetected. Ascites is a physical limitation to the technique because elastic waves do not propagate through liquids. However, the presence of ascites generally indicates by itself cirrhosis. In addition, liver elastometry is unsuccessful in patients with narrow intercostal spaces and in patients with morbid obesity. Probes with smaller size and elongated shape transducer tips are currently available for these patients. In obese patients, the fatty thoracic belt attenuates both elastic waves and ultrasound, rendering LSM more difficult or even impossible. In these cases of failure, no results were obtained with the Fibroscan, preventing the risk of false measurements. Specific probes also are being developed for obese patients. Despite these limitations, the number of LSM failures was nearly half the number of noninterpretable biopsy samples. However, the number of obese patients in the studied population was rather small, reflecting the situation in France. One can expect a larger rate of failure in a population where morbid obesity is more frequently encountered.

The current results suggest that LSM could be used instead of LB in many cases for the purpose of quantifying fibrosis in patients with CHC. Because the present technique is completely noninvasive and because stiffness is a continuous variable, repeated measurements could show changes in the amount of fibrosis and help follow-up in these patients.

In summary, the increase in the incidence of hepatitis C worldwide in the last few decades has resulted in an increase in the number of patients requiring diagnosis, evaluation, and treatment. Thus, the use of LB as the

recommended technique for the repeated assessment of fibrosis in patients with CHC is increasingly a matter of debate. Even though the results presented here need to be confirmed by independent validation studies, the simple, noninvasive, and well-accepted technique used in this multicenter study may prove particularly beneficial in detecting patients with advanced fibrosis or cirrhosis and more generally in assessing fibrosis in patients with CHC.

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