SAFE Biopsy: A Validated Method for Large-Scale Staging of Liver Fibrosis in Chronic Hepatitis C

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The staging of liver fibrosis is pivotal for defining the prognosis and indications for therapy in hepatitis C. Although liver biopsy remains the gold standard, several noninvasive methods are under evaluation for clinical use. The aim of this study was to validate the recently described sequential algorithm for fibrosis evaluation (SAFE) biopsy, which detects significant fibrosis (≥F2 by METAVIR) and cirrhosis (F4) by combining the AST-to-platelet ratio index and Fibrotest-Fibrosure, thereby limiting liver biopsy to cases not adequately classifiable by noninvasive markers. Hepatitis C virus (HCV) patients (2035) were enrolled in nine locations in Europe and the United States. The diagnostic accuracy of SAFE biopsy versus histology, which is the gold standard, was investigated. The reduction in the need for liver biopsies achieved with SAFE biopsy was also assessed. SAFE biopsy identified significant fibrosis with 90.1% accuracy (area under the receiver operating characteristic curve = 0.89; 95% confidence interval, 0.87-0.90) and reduced by 46.5% the number of liver biopsies needed. SAFE biopsy had 92.5% accuracy (area under the receiver operating characteristic curve = 0.92; 95% confidence interval, 0.89-0.94) for the detection of cirrhosis, obviating 81.5% of liver biopsies. A third algorithm identified significant fibrosis and cirrhosis simultaneously with high accuracy and a 36% reduction in the need for liver biopsy. The patient's age and body mass index influenced the performance of SAFE biopsy, which was improved with adjusted Fibrotest-Fibrosure cutoffs. Two hundred two cases (9.9%) had discordant results for significant fibrosis with SAFE biopsy versus histology, whereas 153 cases (7.5%) were discordant for cirrhosis detection; 71 of the former cases and 56 of the latter cases had a Fibroscan measurement within 2 months of histological evaluation. Fibroscan confirmed SAFE biopsy findings in 83.1% and 75%, respectively. *Conclusion:* SAFE biopsy is a rational and validated method for staging liver fibrosis in hepatitis C with a marked reduction in the need for liver biopsy. It is an attractive tool for large-scale screening of HCV carriers. (HEPATOLOGY 2009;49:1821-1827.)

Liver fibrosis is the hallmark of disease progression in chronic hepatitis C.[1] Its staging by liver biopsy represents the gold standard for prognostic assessment and indication to initiate antiviral therapy.[2] Liver biopsy, however, has a number of limitations, being invasive, costly, difficult to standardize, and disliked by many patients.[3-6] Its universal use in hepatitis C is unpractical because of the huge number of chronically infected and often asymptomatic hepatitis C virus (HCV) carriers.[7,8] For these reasons, increasing interest has been directed in recent years towards the identification of noninvasive tools able to accurately assess the stage of liver fibrosis in hepatitis C. Many of such markers have been described, using a variety of single or combined biochemical param-

Abbreviations: APRI, AST-to-platelet ratio index; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SAFE, sequential algorithm for fibrosis evaluation; SD, standard deviation.

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eters, but their implementation in clinical practice is still debated and controversial because of unsatisfactory accuracy or limited large-scale validation.[9,10] Recently, we and others have reported that a combination of different noninvasive markers of liver fibrosis may represent a rational approach to improve the diagnostic accuracy of the single markers and to markedly reduce rather than completely abolish the need for liver biopsy.[11,12] We report here the results of an international, multicenter study aimed at large-scale clinical validation of sequential algorithms that combine a simple noninvasive marker of liver fibrosis, the AST-to-platelet ratio index (APRI), and a commercialized method (Fibrotest-Fibrosure) for the identification of significant fibrosis, cirrhosis, or both in chronic hepatitis C.[13,14]

Patients and Methods

Study Design. This was an international, multicenter retrospective study of patients with chronic hepatitis C seen between January 2003 and January 2007 in nine clinical centers across Europe and the United States. The aim was to validate the recently described algorithms that sequentially combine two noninvasive markers for liver fibrosis (APRI and Fibrotest-Fibrosure)[13,14] in chronic hepatitis C.

Participants. Of 2441 consecutive untreated patients with chronic hepatitis C who had a liver biopsy and APRI and Fibrotest-Fibrosure performed on the same day, we included 2035 patients monoinfected with HCV. All patients were positive for serum HCV-RNA by polymerase chain reaction (Amplicor HCV Monitor Test, Roche Diagnostics, Indianapolis, IN) and had well-compensated chronic HCV infection. Information on patient demographics [gender, age, and body mass index (BMI)], HCV genotype, and liver biopsy features (length and number of portal tracts) was recorded in each center on the day of biopsy. Patients coinfected with hepatitis B virus (101) or human immunodeficiency virus (142) or with alcohol abuse (163) were excluded. Informed consent was obtained from all patients at the time of liver biopsy, and the study was conducted according to the Declaration of Helsinki.

Outcome Measures. The aim of this study was to validate the recently described algorithms that sequentially combine two noninvasive markers (APRI and Fibrotest-Fibrosure)[13,14] to detect significant fibrosis (≥F2 according to the METAVIR classification) and cirrhosis (F4) in patients with chronic hepatitis C. These thresholds were selected because the first is generally considered an indication for antiviral therapy and the second requires specific management and follow-up.[7]

Histological Assessment. Liver biopsies were analyzed in each center by the local pathologist, and the stage of fibrosis was reported according to the METAVIR classification.[15] Significant fibrosis was defined as a METAVIR score ≥ F2. A random sample of 363 liver biopsies from four centers was re-evaluated by a single pathologist (M.G.) to assess interobserver variability.

Noninvasive Markers of Liver Fibrosis. APRI was calculated with the published formula.[13] Fibrotest-Fibrosure values were obtained through Biopredictive (Paris, France; Fibrotest) or Labcorp (Burlington, NC; Fibrosure) or by courtesy of Professor Thierry Poynard.

Sequential Algorithm for Fibrosis Evaluation (SAFE) Biopsy. Two distinct algorithms for the detection of significant fibrosis and cirrhosis based on the sequential use of APRI, Fibrotest-Fibrosure, and liver biopsy were applied to the 2035 patients, and the results were compared with the histological diagnosis of liver biopsy, which was used as the reference standard. The two algorithms have been recently described and use APRI as the initial screening test, followed by Fibrotest-Fibrosure as the second step, to limit liver biopsy to those patients in which the noninvasive markers have reduced accuracy.[11] Figure 1A,B describes the two algorithms, including the cutoff values for APRI and Fibrotest-Fibrosure and the related decisional tree. A third algorithm, developed to detect simultaneously significant fibrosis and cirrhosis, is described in Fig. 1C. For the purpose of this study, the coordinating center (Venetian Institute of Molecular Medicine, Padova, Italy) received the results of APRI and

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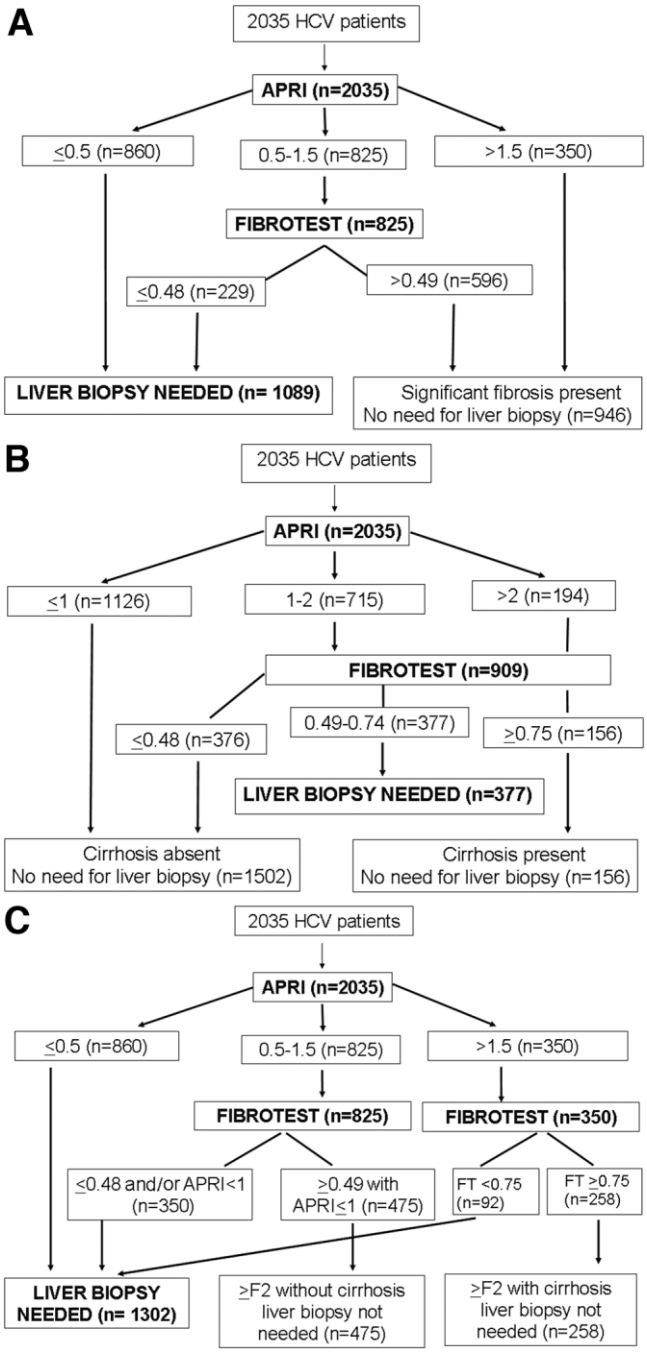

Fig. 1. (A) The SAFE biopsy algorithm for significant fibrosis (⩾F2 by METAVIR). The figure reports the cutoffs used for APRI and Fibrotest-Fibrosure in the decisional tree and also the distribution of patients in the different directions when the algorithm was applied to the 2035 HCV patients of this study. (B) The SAFE biopsy algorithm for cirrhosis (F4 by METAVIR). The figure reports the cutoffs used for APRI and Fibrotest-Fibrosure in the decisional tree and also the distribution of patients in the different directions when the algorithm was applied to the 2035 HCV patients of this study. (C) The SAFE biopsy for simultaneous detection of significant fibrosis (⩾F2 by METAVIR) and cirrhosis (F4 by METAVIR). The figure reports the cutoffs used for APRI and Fibrotest-Fibrosure in the integrated decisional tree and also the distribution of patients in the different directions when the algorithm was applied to the 2035 HCV patients of this study. Abbreviations: APRI, AST-to-platelet ratio index; HCV, hepatitis C virus; SAFE, sequential algorithm for fibrosis evaluation.

Fibrotest-Fibrosure, blinded to any information about liver histology. One member of the coordinating center (G.S.) applied the SAFE biopsy algorithms and sent back the results to the different centers. Only at this point the participating centers communicated the results of liver biopsy for all patients to the coordinating center, allowing a comparison of the diagnosis made by SAFE biopsy to that made by liver histology.

Assessment of Liver Stiffness by Fibroscan. Fibroscan is a recently developed technique for noninvasive liver stiffness measurement in kilopascals and has been proposed as an indirect estimation of liver fibrosis. The following manufacturer recommendations were applied to define the results as reliable: at least 10 validated measures, an interquartile range $< 30\%$ of the median, and a $>60\%$ success rate. Cutoffs for significant fibrosis and cirrhosis were defined as 7.1 and 12.5 kPa, respectively, as previously described.[16]

Statistical Analysis. Descriptive results were expressed as the mean $\pm$ standard deviation or as the number (percentage) of patients with a condition. The *t* test or nonparametric Mann-Whitney test was used to compare quantitative data, and the chi-square test was applied for the comparison of frequency data. All tests were two-tailed, and P values < 0.05 were considered significant. Kappa statistics were used to measure interobserver agreement in the histopathological evaluation of the degree of fibrosis and intercenter reproducibility. The performance of the noninvasive methods for liver fibrosis was measured with the following: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and positive and negative likelihood ratios. Sensitivity, specificity, PPV, NPV, and accuracy were expressed as percentages. The diagnostic value of the noninvasive methods was expressed with the area under the receiver operating characteristic curve (AUROC) and its corresponding 95% confidence intervals (CIs). AUROCs including noninvasive marker quantitative values were calculated with an empirical nonparametric method according to DeLong et al.[17] and compared with the method of Hanley and McNeil.[18]

Results

Demographic, Laboratory, and Histological Features of the 2035 HCV Patients. There were 1140 males and 895 females with a mean age of 46.9 (11.9) years. All patients were treatment-naïve. The main demographic, laboratory, and histological features are summarized in Table 1. Overall, 931 patients had significant fibrosis (45.7%). The mean length of the liver specimen was 18.0 (8.2) mm, and the mean number of portal tracts

Table 1. Demographic, Laboratory, and Histological Features of 2035 HCV Patients

Gender (%)	
Males	1140 (56)
Females	895 (44)
Age (mean years ± SD)	46.9 ± 11.9
BMI (kg/m^2 ± SD)	24.5 ± 3.7
HCV genotype (%)	
HCV-1	1383 (68)
HCV-2	240 (11.8)
HCV-3	267 (13.1)
HCV-4	114 (5.6)
HCV-5	25 (1.2)
HCV-6	6 (0.3)
Liver fibrosis according to METAVIR (%)	
F0	223 (11)
F1	881 (43.3)
F2	497 (24.4)
F3	243 (11.9)
F4	191 (9.4)

Abbreviations: BMI, body mass index; HCV, hepatitis C virus; SD, standard deviation.

was 10.6 (6.0). Interobserver agreement, assessed in 363 randomly chosen samples, was 71.98 (k = 0.42) for significant fibrosis and 85.43 (k = 0.52) for cirrhosis.

APRI in Comparison with Liver Histology. The diagnostic performance of APRI for the identification of significant fibrosis and cirrhosis is shown in Table 2. With published cutoff values, the cutoff to rule out significant fibrosis (0.5) showed an NPV of 72.6% and an AUROC of 0.70. On the other hand, the cutoff value (1.5) to rule in significant fibrosis showed a PPV of 86.3% and an AUROC of 0.62. The cutoff (1.0) to rule out cirrhosis had a high NPV (97.4%) and an AUROC of 0.80. On the other hand, the cutoff (2.0) to rule in cirrhosis had a low PPV (46.6%) and an AUROC of 0.71. When APRI alone was applied to stage fibrosis in our 2035 patients, liver biopsy was required in 1445 (71.0%).

SAFE Biopsy in Comparison with Liver Histology. The performance of two distinct SAFE biopsy algorithms that identify significant fibrosis or cirrhosis is described in Table 3. Overall, the performance of SAFE biopsy was higher than that of the single noninvasive markers (APRI and Fibrotest-Fibrosure) used separately. In the same table, the effects of different variables on SAFE biopsy performance are also reported. Overall, SAFE biopsy for significant fibrosis showed an AUROC of 0.89 (95% CI, 0.87-0.90) and 90.1% accuracy and required a liver biopsy in 1089 of 2035 patients (53.5%; see Fig. 1A). As for the detection of cirrhosis, SAFE biopsy showed an AUROC of 0.92 (95% CI, 0.89-0.94) and an accuracy of 92.5% and required liver biopsy in only 377 of 2035 cases (18.5%; see Fig. 1B). Because algorithm 1A detects significant fibrosis but does not distinguish it from cirrhosis and algorithm 1B detects cirrhosis but not significant fibrosis without cirrhosis, a third algorithm was also developed to obtain an integrated decisional tree to categorize each patient for the absence of significant fibrosis, the presence of significant fibrosis without cirrhosis, and the presence of significant fibrosis with cirrhosis without or with the need for liver biopsy (Fig. 1C). When applied to the 2035 HCV patients, this algorithm produced only 52 (2.6%) misclassified cases, with an overall accuracy of 97.4%, while requiring a liver biopsy in 1302 of 2035 cases (64.0%).

Effects of Different Variables on SAFE Biopsy Performance. As shown in Table 3, the performance of SAFE biopsy was reduced in patients > 50 years old when it was used for significant fibrosis and in the presence of a BMI > 25 kg/m^2 when it was used to identify cirrhosis, whereas the liver biopsy size, gender, and HCV genotype had no major effects. Intercenter variability was marginal, except for specificity. Indeed, 73.7% specificity was found for a single center that included only young patients, most with minimal fibrosis (F0-F1 by METAVIR). For all other centers, specificity was quite similar, ranging from 82% to 89.8%. On the basis of the AUROC analysis, the performance of SAFE biopsy for significant fibrosis was

Table 2. Performance of APRI in 2035 Hepatitis C Virus Patients Versus Liver Histology (the Gold Standard)

APRI for Significant Fibrosis (≥F2 by METAVIR)								
Cutoff	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
0.5	0.70 (0.65–0.75)	70.6	67.1	73.4	67.7	72.6	2.2	0.4
1.5	0.62 (0.59–0.65)	65.1	27.4	96.4	86.3	38.5	1.3	0.7
APRI for Cirrhosis (F4 by METAVIR)								
Cutoff	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
1	0.80 (0.77–0.83)	81.1	78.2	83.6	32.7	97.4	4.8	0.3
2	0.71 (0.69–0.73)	82.1	47.3	94.5	46.6	94.6	8.6	0.5

Abbreviations: APRI, AST-to-platelet ratio index; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Performance of SAFE Biopsy in 2035 HCV Patients with Respect to Different Variables Versus Liver Histology (the Gold Standard)

	SAFE Biopsy for Significant Fibrosis (≥F2 by METAVIR)							
	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
All cases	0.89 (0.87–0.90)	90.1	100	77.0	83.7	100	4.3	0
Males	0.88* (0.85–0.91)	89.0	100	72.6	82.1	100	3.6	0
Females	0.91* (0.89–0.94)	91.6	100	82.6	84.9	100	5.7	0
Age ≤ 50 years	0.92† (0.90–0.94)	90.9	100	83.0	83.5	100	5.9	0
Age > 50 years	0.81† (0.76–0.85)	87.2	100	61.9	83.8	100	2.6	0
BMI ≤ 25 kg/m^2	0.91* (0.87–0.94)	90.2	100	81.1	85.8	100	5.3	0
BMI > 25 kg/m^2	0.92* (0.88–0.97)	95.1	100	84.6	93.3	100	6.5	0
HCV-1	0.90* (0.87–0.92)	90.8	100	79.4	85.9	100	4.9	0
Non–HCV-1	0.89* (0.85–0.93)	89.9	100	78.2	84.2	100	4.6	0
Biopsy ≤ 15 mm	0.90* (0.88–0.93)	89.9	100	80.4	82.6	100	5.1	0
Biopsy > 15 mm	0.89* (0.87–0.92)	90.2	100	78.7	84.8	100	4.7	0
Intercenter variability range	0.87–0.95	86.5–95.9	100	73.7–89.8	80.7–87.2	100	4.0–5.1	0
	SAFE Biopsy for Cirrhosis (F4 by METAVIR)							
	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
All cases	0.92 (0.89–0.94)	92.5	90.4	92.7	55.7	99.0	16.5	0.11
Males	0.90* (0.87–0.93)	90.3	90.5	90.2	51.2	98.8	9.2	0.1
Females	0.93* (0.90–0.95)	95.3	90.1	95.7	64.6	99.1	20.9	0.1
Age ≤ 50 years	0.92* (0.88–0.96)	94.8	89.0	95.2	55.3	99.2	18.7	0.1
Age > 50 years	0.90* (0.86–0.93)	88.1	91.4	87.5	55.8	98.3	7.3	0.01
BMI ≤ 25 kg/m^2	0.93‡ (0.89–0.98)	93.6	93.2	93.7	61.1	99.2	14.7	0.07
BMI > 25 kg/m^2	0.85‡ (0.80–0.89)	87.8	82.5	91.3	64.7	96.4	9.4	0.19
HCV-1	0.91* (0.87–0.95)	91.6	89.5	91.9	59.1	99.0	11.2	0.07
Non–HCV-1	0.92* (0.87–0.97)	91.9	92.9	91.7	57.9	98.6	11.04	0.11
Biopsy ≤ 15 mm	0.88* (0.83–0.93)	90.6	84.3	91.4	53.1	98.1	9.75	0.17
Biopsy > 15 mm	0.94* (0.91–0.97)	92.1	95.9	91.7	56.5	99.5	11.6	0.04
Intercenter variability range	0.87–0.98	88.3–96.5	75.0–92.6	88.2–98.1	44.4–70	96.6–99.5	5.4–48.7	0.07–0.29

Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SAFE, sequential algorithm for fibrosis evaluation.

*P = not significant.

†P = 0.001.

‡P = 0.01.

improved to AUROC = 0.88 (95% CI, 0.85-0.91) in patients > 50 years old by the adoption of a new cutoff for Fibrotest-Fibrosure (0.57), whereas the performance for cirrhosis in patients with a BMI > 25 kg/m^2 was improved to AUROC = 0.91 (95% CI, 0.88-0.93) with a Fibrotest-Fibrosure cutoff of 0.84.

The effect of extreme stages of liver fibrosis on the performance of SAFE biopsy was evaluated by the exclusion of patients with cirrhosis from the performance analysis of SAFE biopsy for significant fibrosis and by the exclusion of patients without significant fibrosis from the performance analysis of SAFE biopsy for cirrhosis (Table 4). In this analysis, SAFE biopsy for significant fibrosis showed an AUROC of 0.90 (95% CI, 0.87-0.93) and 91% accuracy and required a liver biopsy in 1302 of 2035 patients (64.0%). As for the detection of cirrhosis, SAFE

Table 4. Performance of SAFE Biopsy Without Extreme Stages (F4 in SAFE Biopsy for Significant Fibrosis and F0-F1 in SAFE Biopsy for Cirrhosis) in 1844 and 931 Hepatitis C Virus Cases, Respectively, Versus Liver Histology (the Gold Standard)

	SAFE Biopsy for Significant Fibrosis (≥F2 by METAVIR)							
	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
All cases (n = 1844)	0.90 (0.87–0.93)	91.0	100	82.0	84.0	100	5.6	0
	SAFE Biopsy for Cirrhosis (F4 by METAVIR)							
	AUROC (95% CI)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR−
All cases (n = 931)	0.77 (0.73–0.81)	83.0	52.6	92.3	60.2	89.7	6.8	0.5

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SAFE, sequential algorithm for fibrosis evaluation.

biopsy showed an AUROC of 0.77 (95% CI, 0.73-0.81) and an accuracy of 83% and required liver biopsy in 428 of 2035 (21%).

Fibroscan Results in Discordant Cases. In four of the nine centers, a subgroup of cases having discordant results with SAFE biopsy and histological examination was evaluated for liver stiffness by Fibroscan within 2 months of inclusion in this study. Among 202 patients with discordant results for significant fibrosis, Fibroscan was available in 81 (40%) and confirmed the SAFE biopsy diagnosis in 69 of them (85.1%). Fibroscan was available in 60 of 153 cases (39.2%) with a discordant result for cirrhosis and confirmed the SAFE biopsy diagnosis in 45 (75%). Thus, in cases with discordant results between SAFE biopsy and histological findings, an independent method of evaluation of liver fibrosis such as Fibroscan was concordant with SAFE biopsy (and discordant with the histological reading) in 114 of 141 cases (81%) and was concordant with histological findings (and discordant with SAFE biopsy) in only 27 of 141 (19%). This was largely independent of alanine aminotransferase levels in individual patients at the time of Fibroscan evaluation, the mean alanine aminotransferase level being 99.3 ± 67.5 IU/L in all patients showing concordance and 115.8 ± 88.3 IU/L in those with discordance between SAFE biopsy and Fibroscan results ($P = 0.30$). The results were also independent of liver steatosis, moderate-to-severe steatosis being present in 40 of all 114 cases (35.0%) showing concordance and in 10 of 27 cases (37.0%) showing discordance between SAFE biopsy and Fibroscan results ($P = 0.85$).

Discussion

Since the discovery of HCV and the identification of its pivotal role in causing chronic progressive liver disease and cirrhosis, staging of liver fibrosis by percutaneous biopsy has been considered of paramount importance for the definition of prognosis and of urgency for antiviral therapy in patients with chronic hepatitis C infection.[1,7] However, performing liver biopsy in all HCV carriers is certainly inconceivable, and there is an urgent need for noninvasive surrogate markers for a more practical and rapid initial screening for disease stage and risk of progression. Indeed, because of the cost and invasiveness of liver biopsy and because of the large number of patients infected with HCV, liver biopsy is a diagnostic funnel for the large-scale screening of liver fibrosis in chronic hepatitis C. Several noninvasive markers of liver fibrosis have been described, including simple methods such as APRI and more elaborate combinations of markers such as Fibrotest-Fibrosure. A panel that combines proteins and proteinases of the extracellular matrix has been recently proposed by Rosenberg and colleagues, and the results are promising.[19] In clinical practice, the clinical implementation of noninvasive markers for liver fibrosis is still limited by the skepticism shared by many clinicians concerning their diagnostic accuracy as a substitute for liver histology.[9,10,20,21] The combined use of some of these markers with the aim of reducing rather than completely abolishing liver biopsy may represent a rational and more convincing approach.[10] On this line, we have here validated in a large-scale multicenter study the diagnostic accuracy of a stepwise combination of two well-studied noninvasive markers of fibrosis (APRI and Fibrotest-Fibrosure) followed by liver biopsy in only a subset of cases. This approach, called SAFE biopsy, has been developed with the double goal of identifying both significant fibrosis and cirrhosis and has here been proved to guarantee >90% diagnostic accuracy (with respect to liver histology as the gold standard) with <2% underestimation of the liver disease stage as derived from NPV values. A subgroup of cases misclassified by SAFE biopsy with respect to liver biopsy could be evaluated also by transient elastography (Fibroscan) as an independent method for liver fibrosis. In the majority of these discordant cases (81%), Fibroscan confirmed the results of SAFE biopsy. Because the vast majority of discordant cases were classified as having significant fibrosis or cirrhosis by SAFE biopsy and not by liver histology, our findings appear to be in agreement with published evidence indicating that liver biopsy may underestimate the fibrosis stage in chronic hepatitis C.[22]

In our study, the interobserver agreement among histopathologists was somehow low, and this confirmed that the staging of liver fibrosis by liver biopsy and precise distinction, stage by stage, may vary among different readers. A lack of evaluation by a single pathologist of all biopsies could be seen as a weakness of our study, but it better describes what occurs in real life. Furthermore, the diagnostic performance of SAFE biopsy was unchanged in comparison with the whole cohort when only patients having liver biopsy evaluated by a single pathologist were considered (data not shown).

The SAFE biopsy approach allowed liver biopsy to be avoided in around 50% of the patients when it was used to identify significant liver fibrosis (≥F2 by METAVIR) and in more than 80% of the cases when it was used to diagnose the presence of cirrhosis. When it was used to diagnose significant fibrosis and to simultaneously identify cases with cirrhosis, the need for liver biopsy was reduced by 36%. The SAFE biopsy algorithms may be particularly useful for screening HCV-infected individuals in whom an immediate approach with liver biopsy is particularly problematic or questionable. These cases include in primis some clinical categories that are largely

represented in the general population in many parts of the world, such as elderly HCV carriers and those with normal or minimally elevated serum liver enzymes. However, the SAFE biopsy approach may well be considered for more general use in all patients with well-compensated chronic HCV infection requiring staging of liver disease because its validated diagnostic accuracy, combined with its practicability on a large scale, improved patient acceptance and reduced the risk/cost profile in comparison with the generalized use of liver biopsy. The SAFE biopsy algorithm for significant fibrosis may be particularly indicated to screen HCV patients for indications to initiate antiviral therapy, and the SAFE biopsy algorithm for cirrhosis may be ideal for the follow-up of patients already known to have progressed to significant fibrosis on the basis of a previous histological evaluation.

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